

Efficacy and durability of immediate single-dose human papillomavirus vaccination versus delayed vaccination in persistent HPV infection among young women: a randomized, blinded, cross-over clinical trial

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Supplementary Information

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Supplementary Tables

Supplementary Table 1 | Completeness of Endpoint Swab* Collection, by Randomized Group (HPV 16/18 mITT Cohort)

Pre-Crossover												
Randomized Group	Swab 1 (Month 6)		Swab 2 (Month 12)		Swab 3 (Month 18)		Swab 4 (Month 24)		Swab 5 (Month 30 or Crossover)		Swab 6 (Month 36 or Crossover)	
	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)
Nonavalent HPV	496	496 (100.0%)	496	495 (99.8%)	496	491 (99.0%)	496	487 (98.2%)	496	463 (93.3%)	335	301 (89.9%)
Bivalent HPV	489	489 (100.0%)	489	487 (99.6%)	489	484 (99.0%)	489	479 (98.0%)	489	465 (95.1%)	325	299 (92.0%)
Control	473	473 (100.0%)	473	472 (99.8%)	473	467 (98.7%)	472	459 (97.2%)	471	441 (93.6%)	314	268 (85.4%)
All	1458	1458 (100.0%)	1458	1454 (99.7%)	1458	1442 (98.9%)	1457	1425 (97.8%)	1456	1369 (94.0%)	974	868 (89.1%)

Post-Crossover						
Randomized Group	Swab 1 (Month 36 42 - Crossover M6)		Swab 2 (Month 42 48 - Crossover M12)		Swab 3 (Month 48 54 - Crossover M18)	
	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)
Nonavalent HPV	476	472 (99.2%)	476	467 (98.1%)	476	438 (92.0%)
Bivalent HPV	465	453 (97.4%)	465	451 (97.0%)	465	420 (90.3%)
Control	449	444 (98.9%)	449	433 (96.4%)	449	405 (90.2%)
All	1390	1369 (98.5%)	1390	1351 (97.2%)	1390	1263 (90.9%)

*Endpoint swabs defined as post-Month 3 cervical or self-collected vaginal swabs at least 4 months apart.

**Pre-crossover swabs 1 through 5 are expected for all non-deceased participants. Pre-crossover swab 6 is expected for participants who either crossed over or exited at month 36. Post-crossover swabs 1 through 3 are expected for all participants who received crossover vaccine.

Supplementary Table 2 | Number of Endpoint Swabs per Participant, by Randomized Group (HPV 16/18 mITT Cohort)

Pre-Crossover: Number of Endpoint Swabs per Participant*													
Randomized Group	1		2		3		4		5		6		Total
	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	n %
Nonavalent HPV	1	0.1%	4	0.4%	4	0.4%	24	2.4%	162	16.3%	301	30.3%	496 34.0%
Bivalent HPV	2	0.2%	3	0.3%	5	0.5%	14	1.4%	166	17.0%	299	30.6%	489 33.5%
Control	1	0.1%	5	0.5%	8	0.8%	18	1.9%	173	18.3%	268	28.3%	473 32.4%
	4	0.3%	12	0.8%	17	1.2%	56	3.8%	501	34.4%	868	59.5%	1458 100.0%

Post-Crossover: Number of Endpoint Swabs per Participant*											
Randomized Group	0		1		2		3		Total		
	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	%
Nonavalent HPV	4	0.8%	5	1.1%	29	6.1%	438	92.0%	476		34.2%
Bivalent HPV	12	2.6%	2	0.4%	31	6.7%	420	90.3%	465		33.5%
Control	5	1.1%	11	2.4%	28	6.2%	405	90.2%	449		32.3%
	21		18		88		1263		1390		100.0%

*Endpoint swabs defined as post-Month 3 cervical vaginal or self-collected vaginal swabs at least 4 months apart.

Supplementary Table 3 | Completeness of Endpoint Swab* Collection, by Randomized Group (HPV 16/18/31/33/45/52/58 mITT Cohort)

Pre-Crossover												
Randomized Group	Swab 1 (Month 6)		Swab 2 (Month 12)		Swab 3 (Month 18)		Swab 4 (Month 24)		Swab 5 (Month 30 or Crossover)		Swab 6 (Month 36 or Crossover)	
	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)
Nonavalent HPV	325	325 (100.0%)	325	325 (100.0%)	325	323 (99.4%)	325	321 (98.8%)	325	306 (94.2%)	231	215 (93.1%)
Control	290	290 (100.0%)	290	289 (99.7%)	290	287 (99.0%)	290	282 (97.2%)	290	273 (94.1%)	195	167 (85.6%)
All	615	615 (100.0%)	615	614 (99.8%)	615	610 (99.2%)	615	603 (98.0%)	615	579 (94.1%)	426	382 (89.7%)

Post-Crossover						
Randomized Group	Swab 1 (Month 36 42 - Crossover M6)		Swab 2 (Month 42 48 - Crossover M12)		Swab 3 (Month 48 54 - Crossover M18)	
	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)	Expected (n)**	Completed, n (%)
Nonavalent HPV	314	311 (99.0%)	314	308 (98.1%)	314	290 (92.4%)
Control	279	275 (98.6%)	279	267 (95.7%)	279	250 (89.6%)
All	593	586 (98.8%)	593	575 (97.0%)	593	540 (91.1%)

*Endpoint swabs defined as post-Month 3 cervical or self-collected vaginal swabs at least 4 months apart.

**Pre-crossover swabs 1 through 5 are expected for all non-deceased participants. Pre-crossover swab 6 is expected for participants who either crossed over or exited at month 36. Post-crossover swabs 1 through 3 are expected for all participants who received crossover vaccine.

Supplementary Table 4 | Number of Endpoint Swabs per Participant, by Randomized Group (HPV 16/18/31/33/45/52/58 mITT Cohort)

Pre-Crossover: Number of Endpoint Swabs per Participant*														
Randomized Group	1		2		3		4		5		6		Total	
	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	n	%
Nonavalent HPV	0	0.0%	2	0.3%	2	0.3%	15	2.3%	91	14.0%	215	33.1%	325	52.8%
Control	1	0.2%	2	0.3%	5	0.9%	9	1.6%	106	18.3%	167	28.8%	290	47.2%
	1	0.2%	4	0.7%	7	1.1%	24	3.9%	197	32.0%	382	62.1%	615	100.0%

Post-Crossover: Number of Endpoint Swabs per Participant*											
Randomized Group	0		1		2		3		Total		
	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	%
Nonavalent HPV	3	1.0%	3	1.0%	18	5.7%	290	92.4%	314		53.0%
Control	4	1.4%	8	2.9%	17	6.1%	250	89.6%	279		47.0%
	7		11		35		540		593		100.0%

*Endpoint swabs defined as post-Month 3 cervical vaginal or self-collected vaginal swabs at least 4 months apart.

Supplementary Table 5 | Incidence of persistent combined non-vaccine HPV types Pre- and Post-participant Crossover Vaccine Receipt, by group (non-vaccine type DNA negative subgroup of HVP 16/18 mITT cohort)

Pre-participant Crossover											
Arm	HPV 16/18 naive at baseline (mITT) (n)	Non-vaccine HPV type DNA negative at baseline(n)	Number at risk (n)	Incident persistent non-vaccine HPV(n)	Woman-years of Follow-up [†]	Incidence of persistent non-vaccine HPV per 100 Woman-years	95% Confidence Interval*		Incidence Rate Difference [§] (95% CI)		p-value [§]
							Lower Bound	Upper Bound			
Delayed HPV Vaccine	473	203	203	97	417.56	23.23	18.84	28.34	-2.56 (-8.39, 3.26)		0.388
Immediate HPV Vaccine	985	397	397	203	786.98	25.79	22.37	29.60			
All	1458	600	600	300	1204.53	24.91	22.17	27.89			

Post-participant Crossover											
Arm	HPV 16/18 naive at baseline (mITT)(n)	Non-vaccine HPV type DNA negative at baseline (mITT) (n)	Number at risk (n)	Incident persistent non-vaccine HPV (n)	Woman-years of Follow-up [‡]	Incidence of persistent non-vaccine HPV per 100 Woman-years	95% Confidence Interval*		Incidence Rate Difference [§] (95% CI)		p-value [§]
							Lower Bound	Upper Bound			
Delayed HPV Vaccine	473	203	98	23	113.98	20.18	12.79	30.28	-2.47 (-12.9, 7.97)		0.643
Immediate HPV Vaccine	985	397	182	48	211.94	22.65	16.70	30.03			
All	1458	600	280	71	325.92	21.78	17.01	27.48			

*Exact 95% confidence interval for incidence rate computed using the Poisson distribution.

[†] Follow-up time among participants HPV 16/18 naïve and non-vaccine HPV type negative at baseline, from enrollment to first positive result of consecutive positive HPV DNA results for participants with an endpoint, or from enrollment to last HPV DNA result not meeting endpoint criteria prior to crossover vaccine receipt for participants with no endpoint. For participants with an endpoint, result day is set to the mid-point between the first positive result defining the endpoint and the previous endpoint swab collection date for the calculation of follow-up time.

[‡] Follow-up time among participants HPV 16/18 naïve and non-vaccine HPV type negative at baseline who received crossover vaccine and who were still at risk for incident non-vaccine type HPV (not previously censored and contributed at least one post-crossover swab), from date of crossover vaccine receipt to first positive result of consecutive positive HPV DNA results for participants with an endpoint, or from date of crossover vaccine receipt to last HPV DNA result not meeting endpoint criteria for participants with no endpoint. For participants with an endpoint, result day is set to the mid-point between the first positive result defining the endpoint and the previous endpoint swab collection date for the calculation of follow-up time.

[§] Incidence rate difference ($IR_{\text{Delayed}} - IR_{\text{Immediate}}$) computed using separate Poisson regression models for pre- and post-participant crossover, with an offset of log woman-years and randomized group as the only predictor. The difference in rates, 95% CIs, and two-sided p-values were obtained by estimating a nonlinear function of the Poisson model parameters on the mean scale. No adjustments for multiple comparisons were made.

NOTE: The HPV 16/18 mITT cohort is comprised of participants HPV 16/18 DNA negative at month 0 and month 3, and HPV 16/18 antibody negative at month 0. The non-vaccine HPV type DNA negative subgroup is comprised of participants additionally HPV type negative for HPV 26/35/39/40/42/43/44/51/53/54/56/59/61/66/68/69/70/73/82 at month 0 and month 3. One participant in the HPV 16/18 mITT cohort is excluded from this analysis because the Luminex back up assay does not include HPV 43/44.

**Supplementary Table 6 | Summary of mITT Endpoint HPV Types by Randomized Group
Pre- and Post-participant Crossover (HPV 16/18 mITT Cohort)**

Pre-participant Crossover				
Randomized Group				
	Nonavalent HPV	Bivalent HPV	Control	Total
HPV Type	n	n	n	n
16	1	2	60	63
16,18	0	0	1	1
18	0	1	28	29
All	1	3	89	93

Post-participant Crossover				
Randomized Group				
	Nonavalent HPV	Bivalent HPV	Control	Total
HPV Type	n	n	n	n
16	2	0	3	5
18	1	1	4	6
All	3	1	7	11

Supplementary Table 7 | Summary of HPV 16/18/31/33/45/52/58 mITT Endpoint HPV Types by Randomized Group Pre-and Post-participant Crossover (HPV 16/18/31/33/45/52/58 mITT Cohort)

Pre-participant Crossover			
Randomized Group			
	Nonavalent HPV	Control	Total
HPV Type	n	n	n
16	1	22	23
16,52	0	2	2
16,52,58	0	1	1
16,58	0	1	1
18	0	12	12
18,58	0	2	2
31	1	6	7
31,58	0	1	1
33	0	3	3
33,52	0	1	1
45	0	10	10
45,52	0	2	2
52	0	15	15
52,58	0	1	1
58	3	19	22
	5	98	103

Post-participant Crossover			
Randomized Group			
	Nonavalent HPV	Control	Total
HPV Type	n	n	n
16	2	2	4
18	1	1	2
33	0	2	2
45	1	0	1
52	1	3	4
58	0	1	1
	5	9	14

Supplementary Table 8 | Sensitivity Analysis - Post-Participant Crossover Incidence Excluding Participants with Evidence of Current or Past HPV Infection at Crossover or 3 Months post-Crossover, by Randomized Group

a. HPV 16/18

Arm	Received Crossover Vaccine (n)	HPV 16/18 naive at baseline and crossover (n)	Incident persistent HPV 16/18 (n)	Woman-years of Follow-up**	Incidence of persistent HPV 16/18 per 100 Woman-years	95% Confidence Interval*	
						Lower Bound	Upper Bound
Nonavalent HPV	710	449	2	601.82	0.33	0.04	1.20
Bivalent HPV	707	427	1	577.67	0.17	0.00	0.97
Control	707	322	0	426.15	0.00	0.00	0.87
All	2124	1198	3	1605.63	0.19	0.04	0.55

*Exact 95% confidence interval for incidence rate computed using the Poisson distribution.

**Follow-up time amongst women HPV 16/18 antibody-negative at month 0, DNA-negative at month 0, month 3, crossover, and crossover month 3, and who did not have a HPV 16/18 endpoint prior to crossover. For non-endpoint participants, follow-up time is computed from crossover month 3 to the date of the last negative test, and for endpoint participants follow-up time is computed from crossover month 3 to the mid-point between the first positive result of the endpoint and the previous result.

b. HPV 16/18/31/33/45/52/58

Arm	Received Crossover Vaccine (n)	HPV 16/18/31/33/45/52/58 naive at baseline and crossover (n)	Incident persistent HPV 16/18/31/33/45/52/58 (n)	Woman-years of Follow-up**	Incidence of persistent HPV 16/18/31/33/45/52/58 per 100 Woman-years	95% Confidence Interval*	
						Lower Bound	Upper Bound
Nonavalent HPV	710	272	3	359.41	0.83	0.17	2.44
Control	707	142	1	183.61	0.54	0.01	3.03
All	1417	414	4	543.03	0.74	0.20	1.89

*Exact 95% confidence interval for incidence rate computed using the Poisson distribution.

**Follow-up time amongst women HPV 16/18/31/33/45/52/58 antibody-negative at month 0, DNA-negative at month 0, month 3, crossover, and crossover month 3, and who did not have a HPV 16/18/31/33/45/52/58 endpoint prior to crossover. For non-endpoint participants, follow-up time is computed from crossover month 3 to the date of the last negative test, and for endpoint participants follow-up time is computed from crossover month 3 to the mid-point between the first positive result of the endpoint and the previous result.

Supplementary Table 9 | Baseline Characteristics of the ITT population

		Nonavalent HPV	Bivalent HPV	Control	All
Characteristic	Category	758	760	757	2275
Age group (years)	15-17	453 (59.8%)	424 (55.8%)	424 (56.0%)	1301 (57.2%)
	18-20	305 (40.2%)	336 (44.2%)	333 (44.0%)	974 (42.8%)
Age (years)	Median (IQR)	17 (16, 18)	17 (16, 19)	17 (16, 19)	17 (16, 19)
Marital status	Never married	728 (96.0%)	713 (93.8%)	712 (94.1%)	2153 (94.6%)
	Married	25 (3.3%)	39 (5.1%)	32 (4.2%)	96 (4.2%)
	Previously Married	4 (0.5%)	6 (0.8%)	13 (1.7%)	23 (1.0%)
	Other	1 (0.1%)	2 (0.3%)	0 (0.0%)	3 (0.1%)
Education (highest level)	No schooling	1 (0.1%)	3 (0.4%)	3 (0.4%)	7 (0.3%)
	Primary school, some or complete	52 (6.9%)	47 (6.2%)	61 (8.1%)	160 (7.0%)
	Secondary school, some or complete	553 (73.0%)	551 (72.5%)	550 (72.7%)	1654 (72.7%)
	Post-secondary school	152 (20.1%)	159 (20.9%)	143 (18.9%)	454 (20.0%)
Earns an income of her own	No	665 (87.7%)	653 (85.9%)	656 (86.7%)	1974 (86.8%)
	Yes	93 (12.3%)	107 (14.1%)	101 (13.3%)	301 (13.2%)
Has a current main or steady sexual partner	No	209 (27.6%)	222 (29.2%)	211 (27.9%)	642 (28.2%)
	Yes	549 (72.4%)	538 (70.8%)	546 (72.1%)	1633 (71.8%)
Age when first had vaginal intercourse (years)	<15	190 (25.1%)	180 (23.7%)	170 (22.5%)	540 (23.7%)
	15-17	397 (52.4%)	415 (54.6%)	445 (58.8%)	1257 (55.3%)
	>=18	148 (19.5%)	155 (20.4%)	130 (17.2%)	433 (19.0%)
	Don't remember	23 (3.0%)	10 (1.3%)	12 (1.6%)	45 (2.0%)
Number of lifetime sexual partners	1	464 (61.2%)	484 (63.7%)	444 (58.7%)	1392 (61.2%)
	2	195 (25.7%)	176 (23.2%)	194 (25.6%)	565 (24.8%)
	>=3	99 (13.1%)	100 (13.2%)	119 (15.7%)	318 (14.0%)
Condom use with last vaginal sex	No	239 (31.5%)	244 (32.1%)	233 (30.8%)	716 (31.5%)
	Yes	358 (47.2%)	365 (48.0%)	367 (48.5%)	1090 (47.9%)
	No sex in past year	161 (21.2%)	151 (19.9%)	157 (20.7%)	469 (20.6%)
Syphilis	Negative	757 (99.9%)	760 (100.0%)	754 (99.6%)	2271 (99.8%)
	Positive	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
	Not Done	0	0	2 (0.3%)	2 (0.1%)
C. trachomatis	Negative	665 (87.7%)	663 (87.2%)	651 (86.0%)	1979 (87.0%)
	Positive	93 (12.3%)	97 (12.8%)	106 (14.0%)	296 (13.0%)
N. gonorrhoeae	Negative	745 (98.3%)	738 (97.1%)	741 (97.9%)	2224 (97.8%)
	Positive	13 (1.7%)	22 (2.9%)	16 (2.1%)	51 (2.2%)
HSV-2	Negative	616 (81.3%)	597 (78.6%)	584 (77.1%)	1797 (79.0%)
	Positive	141 (18.6%)	162 (21.3%)	173 (22.9%)	476 (20.9%)
	Indeterminate	1 (0.1%)	1 (0.1%)	0	2 (0.1%)
Bacterial vaginosis*	Negative	604 (79.7%)	576 (75.8%)	587 (77.5%)	1767 (77.7%)
	Positive	154 (20.3%)	183 (24.1%)	170 (22.5%)	507 (22.3%)
	Not Done	0	1 (0.1%)	0	1 (0.0%)
Trichomonas vaginalis	Negative	723 (95.4%)	728 (95.8%)	722 (95.4%)	2173 (95.5%)
	Positive	35 (4.6%)	32 (4.2%)	35 (4.6%)	102 (4.5%)
HPV DNA**					
HPV 16/18	Positive	112 (14.8%)	124 (16.3%)	131 (17.3%)	367 (16.1%)
HPV 16/18/31/33/45/52/58	Positive	242 (31.9%)	257 (33.8%)	261 (34.5%)	760 (33.4%)
HPV Serum Antibodies (Luminex)					
HPV 16/18	Positive	108 (14.3%)	104 (13.7%)	114 (15.1%)	326 (14.3%)
HPV 16/18/31/33/45/52/58	Positive	212 (28.0%)	212 (27.9%)	221 (29.2%)	645 (28.4%)

*BV positive defined as Nugent Score 7-10.. **Includes any DNA positive from enrollment cervical or external vaginal swabs.

Supplementary Table 10 | Sensitivity Analysis - Incidence of persistent HPV 16/18/31/33/45/52/58 infections and vaccine effectiveness within subgroups defined by enrollment cervical swab DNA positivity, by Arm (ITT cohort, Primary Endpoint Period)

						95% Confidence Interval*		Statistical Comparisons****			
Positive Cervical HPV 16/18/31/33/45/52/58 DNA at Baseline**	Arm	Enrolled (n)	Total Incident Persistent HPV 16/18/31/33/45/52/58 Infections (n)	Woman-years of Follow- up***	Incidence of persistent HPV 16/18/31/33/45/52/58 infections per 100 Woman-years	Lower Bound	Upper Bound	Comparison	Vaccine Effectiveness	95% CI	P-value
No	Nonavalent HPV	564	34	1400.15	2.43	1.68	3.39	Nonavalent HPV v. Control	87.40%	(82.0%, 91.2%)	<0.0001
	Control	539	259	1343.59	19.28	17.00	21.77				
	All	1103	293	2743.74	10.68	9.49	11.97				
Yes	Nonavalent HPV	194	16	473.61	3.38	1.93	5.49	Nonavalent HPV v. Control	80.61%	(67.0%, 88.6%)	<0.0001
	Control	218	93	533.81	17.42	14.06	21.34				
	All	412	109	1007.42	10.82	8.88	13.05				
All	All	1515	402	3751.16	10.72	9.70	11.82				

*Exact 95% confidence interval for incidence rate computed using the Poisson distribution.

**The enrollment cervical swab was positive for HPV 16/18/31/33/45/52/58. Two consecutive negative results of the same HPV type that was positive at enrollment were required to be evaluable for an endpoint of that HPV type.

***Follow-up time among randomized participants, from enrollment to last endpoint swab.

****Incidence rate ratios with 95% confidence intervals are estimated within subgroups using two separate Poisson regression models with a two-way class variable for vaccine arm as the only covariate, an offset of log(woman-years), and robust standard errors. Vaccine effectiveness and 95% CI computed from the incidence rate ratio as $[100 \times (1 - \text{Point Estimate})]$. Standard errors from the Poisson models were used to generate Z-scores against the null hypothesis of IRR=1.0 and compute corresponding two-sided p-values.

Supplementary Table 11 | Sensitivity Analysis – Vaccine Efficacy as a Function of Time since Vaccination (mITT Sensitivity Cohorts*)

a. HPV 16/18 mITT Sensitivity*

Randomized Group	HPV 16/18 DNA negative at baseline (n)*	Incident persistent HPV 16/18		Vaccine Efficacy at Month 54 (95% CI)†
		Pre-participant crossover (n)	Post-participant crossover (n)	
Nonavalent HPV	569	1	3	99.3% (96.2%, 99.9%)
Bivalent HPV	561	4	1	
Control	543	103	7	

b. HPV 16/18/31/33/45/52/58 mITT Sensitivity*

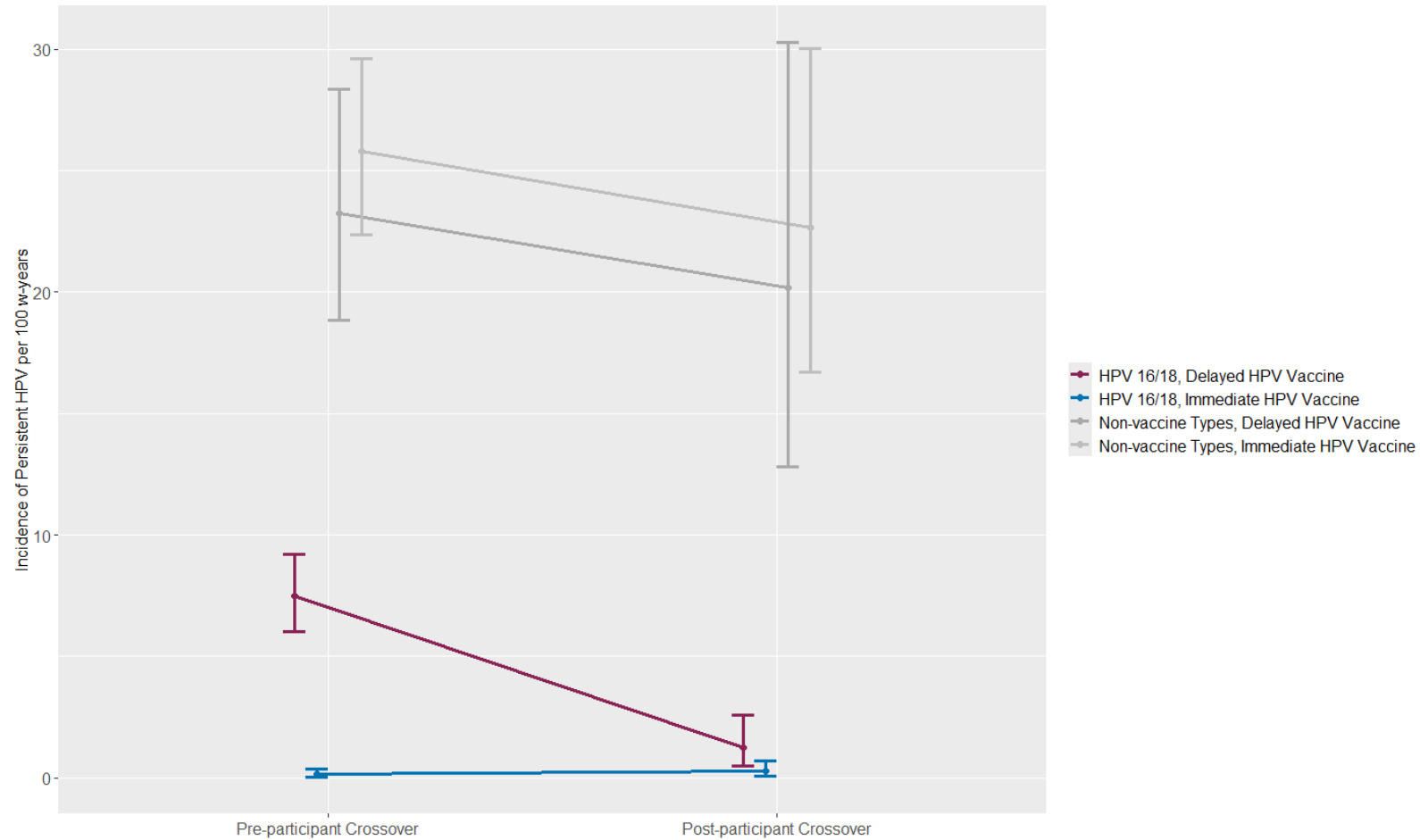
Randomized Group	HPV 16/18/31/33/45/52/58 DNA negative at baseline (n)*	Incident persistent HPV 16/18/31/33/45/52/58 (n)		Vaccine Efficacy at Month 54 (95% CI)†
		Pre-participant crossover (n)	Post-participant crossover (n)	
Nonavalent HPV	437	8	5	99.6% (97.9%, 99.9%)
Control	392	140	14	

*The mITT sensitivity cohorts include participants who were HPV DNA negative at enrollment and month 3 (enrollment serum HPV antibody results not used).

†Vaccine efficacy as a function of time since vaccination computed using a Cox regression model with time-varying covariates for HPV vaccine status and time since HPV vaccination ($VE=100*(1-HR$ at 54 months).

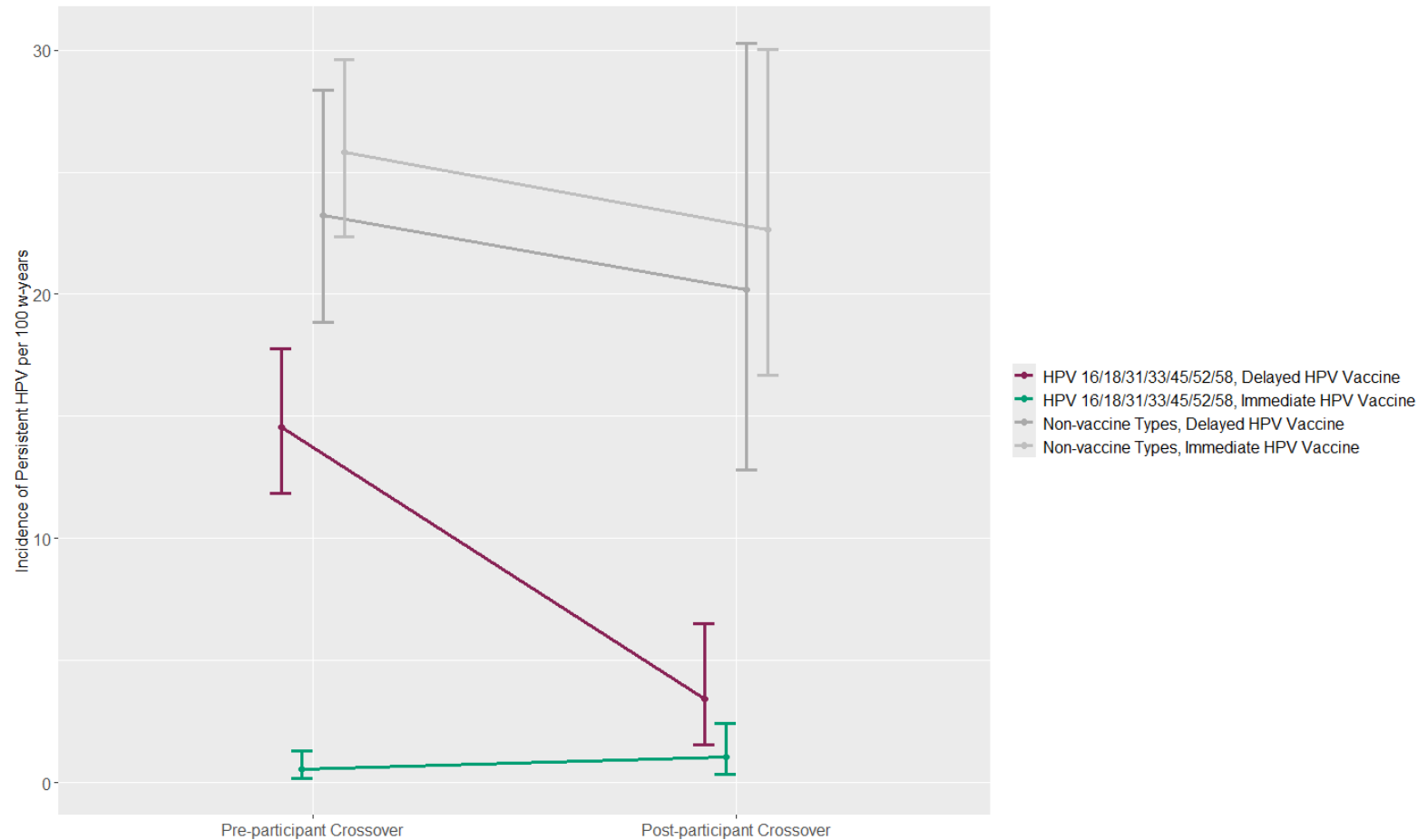
Supplementary Figures

Supplementary Figure 1 | Pre- and Post-participant Crossover Incidence of Persistent HPV 16/18 and Background Non-vaccine Types



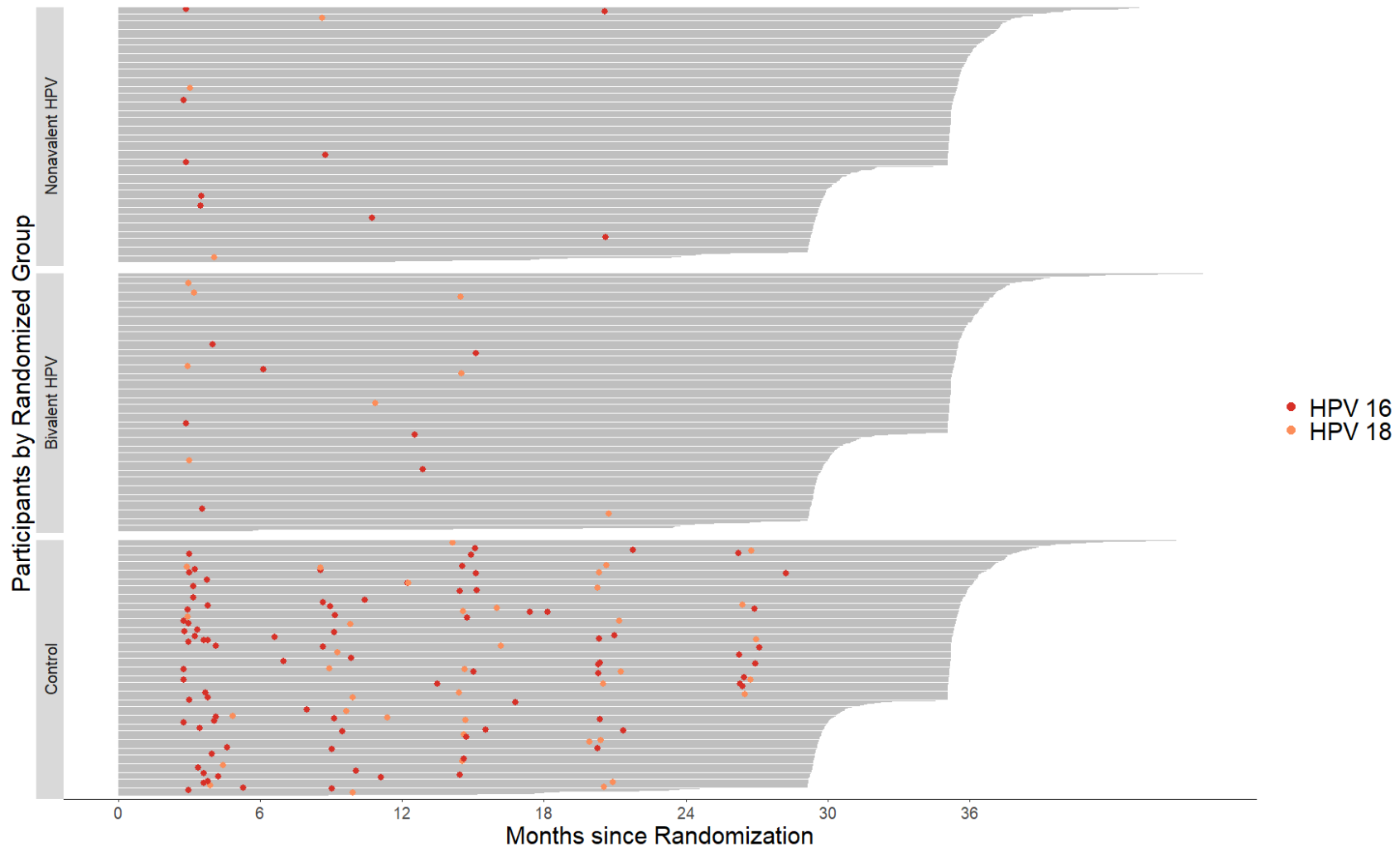
The blue and maroon lines represent the difference in pre- and post-participant crossover incidence of persistent HPV 16/18 in the HPV 16/18 modified intention-to-treat cohort (n=1,458 participants) for the immediate and delayed HPV vaccine groups, respectively. The grey lines represent the difference in incidence of non-vaccine type HPV 26/35/39/40/42/43/44/51/53/54/56/59/61/66/68/69/70/73/82 among HPV 16/18 mITT cohort participants who were also non-vaccine type negative at month 0 and month 3 (n=600 participants). Error bars represent the lower and upper bounds of the 95% confidence interval for each incidence rate, computed using the Poisson distribution.

Supplementary Figure 2 | Pre- and Post-participant Crossover Incidence of Persistent HPV 16/18/31/33/45/52/58 and Background Non-vaccine Types



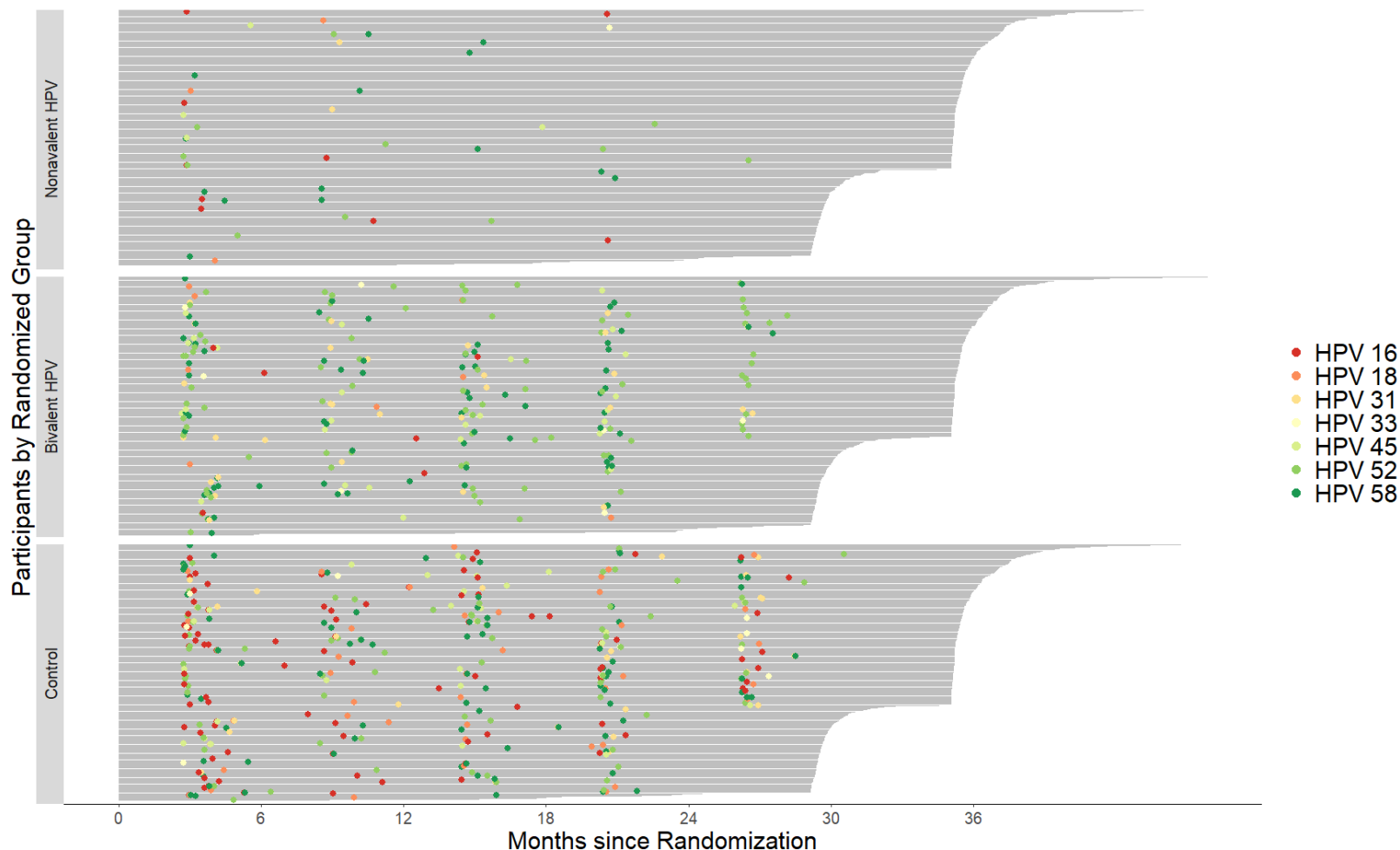
The green and maroon lines represent the difference in pre- and post-participant crossover incidence of persistent HPV 16/18/31/33/45/52/58 in the HPV 16/18/31/33/45/52/58 modified intention-to-treat cohort (n=615 participants) for the immediate and delayed HPV vaccine groups, respectively. The grey lines represent the difference in incidence of non-vaccine type HPV 26/35/39/40/42/43/44/51/53/54/56/59/61/66/68/69/70/73/82 among HPV 16/18 mITT cohort participants who were also non-vaccine type negative at month 0 and month 3 (n=600 participants). Error bars represent the lower and upper bounds of the exact 95% confidence interval for each incidence rate, computed using the Poisson distribution.

Supplementary Figure 3 | Event Plot for Incident Persistent HPV 16/18 Infections (ITT cohort, Primary Endpoint Period, n=2,275)



Recurrent event plot for incident persistent HPV 16 and HPV 18 in the intention-to-treat cohort (n=2,275 participants). The grey shaded areas represent individual participant follow-up time from randomization to the last endpoint swab at or prior to the crossover visit, and the dots represent HPV 16 and HPV 18 incident persistent type-specific infections for each participant plotted at months since randomization to the first positive swab of the incident persistent event. Participants with persistent infection at enrollment and/or during follow-up remained at risk for other HPV type infections. Two consecutive HPV negative results of the previously persistent positive HPV type were required to meet the definition of HPV clearance, at which time participants were eligible to contribute new incident persistent infections of that HPV type.

Supplementary Figure 4 | Event Plot for Incident Persistent HPV 16/18/31/33/45/52/58 Infections (ITT cohort, Primary Endpoint Period, n=2,275)



Recurrent event plot for incident persistent HPV 16, 18, 31, 33, 45, 52, and 58 in the intention-to-treat cohort (n=2,275 participants). The grey shaded areas represent individual participant follow-up time from randomization to the last endpoint swab at or prior to the crossover visit, and the dots represent HPV 16, 18, 31, 33, 45, 52, and 58 incident persistent type-specific infections for each participant plotted at months since randomization to the first positive swab of the incident persistent event. Participants with persistent infection at enrollment and/or during follow-up remained at risk for other HPV type infections. Two consecutive HPV negative results of the previously persistent positive HPV type were required to meet the definition of HPV clearance, at which time participants were eligible to contribute new incident persistent infections of that HPV type.



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	15-16
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	15
Participants	4a	Eligibility criteria for participants	16
	4b	Settings and locations where the data were collected	15
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	16-17
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	18-19
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	N/A
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	16
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	16
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	16-17
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	16-17
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	16-17

		assessing outcomes) and how	
Statistical methods	11b	If relevant, description of the similarity of interventions	16-17
	12a	Statistical methods used to compare groups for primary and secondary outcomes	19-22
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	19-22
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5, Fig. 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	5, Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	29-30
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10, 32
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	2, 15
Protocol	24	Where the full trial protocol can be accessed, if available	Suppl. Inf. 19
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	3, 26

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18. © 2010 Schulz et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.