Supplementary Online Content

Ogilvie GS, van Niekerk D, Krajden M, et al. Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.7464

eTable 1. High-Grade CIN Rates per 1000 (95% CI) Detected at Round 1 and 48-Month Exit Round, All Results

eTable 2. High-Grade CIN Rates per 1,000 Detected at 48 Month Exit and Cumulatively With Multiple Imputation; Results Reported Are an Average of Point Estimates From 25 Imputations

eFigure. FOCAL Study Overall Flowchart

This supplementary material has been provided by the authors to give readers additional information about their work.

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eTable 1. High-Grade CIN Rates per 1000 (95% CI) Detected at Round 1 and 48-Month Exit Round, All Results

			Round 1					48 month exit round only					Round 1 and 48 mo. exit round combined				
	Pathology outcome	Age at baseline	Intervention (HPV)	Control (LBC)*	Risk Ratio (HPV vs LBC)	P-value	Absolute Difference (HPV - LBC)	Intervention (HPV)	Control (LBC)*	Risk Ratio (HPV vs LBC)	P-value	Absolute Difference (HPV - LBC)	Intervention (HPV)	Control (LBC)	Risk Ratio (HPV vs LBC)	P-value	Absolute Difference (HPV - LBC)
All participants attending 48 month screening	CIN3+ Primary Objective	25-29	20/826 (24.2; 15.7, 37.1)	14/828 (16.9; 10.1, 28.2)	1.43 (0.73, 2.82)	0.30	7.30 (0.00,21.99)	6/826 (7.3; 3.3,15.8)	15/828 (18.1; 11.0,29.7)	0.40 (0.16, 1.02)	0.05	-10.85 (-23.22,-0.06)	26/826 (31.5; 21.6,45.7)	29/828 (35.0; 24.5,49.8)	0.90 (0.53, 1.51)	0.69	-3.55 (-21.43,14.16)
		30+	47/8714 (5.4; 4.1, 7.2)	27/8580 (3.1; 2.2, 4.6)	1.71 (1.07, 2.74)	0.02	2.25 (0.31,4.29)	16/8714 (1.8; 1.1,3.0)	37/8580 (4.3; 3.1,5.9)	0.43 (0.24, 0.76)	0.003	-2.48 (-4.27,-0.86)	63/8714 (7.2; 5.7,9.2)	64/8580 (7.5; 5.8,9.5)	0.97 (0.69, 1.37)	0.86	-0.22 (-2.82,2.35)
		All	67/9540 (7.0; 5.5, 8.9)	41/9408 (4.4; 3.2, 5.9)	1.61 (1.09, 2.37)	0.01	2.67 (0.53,4.88)	22/9540 (2.3; 1.5,3.5)	52/9408 (5.5; 4.2,7.2)	0.42 (0.25, 0.69)	<.001	-3.22 (-5.12,-1.48)	89/9540 (9.3; 7.6,11.5)	93/9408 (9.8; 8.1,12.1)	0.94 (0.71, 1.26)	0.69	-0.55 (-3.37,2.24)
	CIN2+ Secondary Objective	25-29	45/826 (54.5; 41.0, 72.1)	26/828 (31.4; 21.5, 45.6)	1.73 (1.08, 2.78)	0.02	23.08 (3.62,43.47)	14/826 (16.9; 10.1,28.2)	27/828 (32.6; 22.5,47.0)	0.52 (0.27, 0.98)	0.04	-15.66 (-31.78,-0.70)	59/826 (71.4; 55.8, 91.0)	53/828 (64.0; 49.3,82.8)	1.11 (0.78, 1.60)	0.54	7.42 (-17.02,32.03)
		30+	102/8714 (11.7; 9.7, 14.2)	64/8580 (7.5; 5.8, 9.5)	1.57 (1.15, 2.14)	0.004	4.25 (1.36,7.22)	34/8714 (3.9; 2.8,5.4)	73/8580 (8.5; 6.8,10.7)	0.46 (0.31, 0.69)	<.001	-4.61 (-7.07,-2.31)	136/8714 (15.6; 13.2,18.4)	137/8580 (16.0; 13.5,18.8)	0.98 (0.77, 1.24)	0.85	-0.36 (-4.11,3.37)
		All	147/9540 (15.4; 13.1, 18.1)	90/9408 (9.6; 7.8, 11.7)	1.61 (1.24, 2.09)	<.001	5.84 (2.70,9.07)	48/9540 (5.0; 3.8,6.7)	100/9408 (10.6; 8.7,12.9)	0.47 (0.34, 0.67)	<.001	-5.60 (-8.21,-3.13)	195/9540 (20.4; 17.8,23.5)	190/9408 (20.2; 17.5,23.2)	1.01 (0.83, 1.23)	0.90	0.24 (-3.79,4.28)
Baseline screen negative (Cytology or HPV negative)	CIN3+ Primary Objective	25-29						4/635 (6.3; 2.5,16.1)	15/758 (19.8; 12.0,32.4)	0.32 (0.11,0.95)	0.03	-13.49 (-26.89,-1.46)					
		30+						8/8134 (1.0; 0.5,1.9)	34/8316 (4.1; 2.9,5.7)	0.24 (0.11,0.52)	<.001	-3.10 (-4.82,-1.65)					
		All						12/8769 (1.4; 0.8,2.4)	49/9074 (5.4; 4.1,7.1)	0.25 (0.13,0.48)	<.001	-4.03 (-5.88,-2.41)					
	CIN2+ Secondary Objective	25-29						10/635 (15.7; 8.6,28.7)	25/758 (33.0; 22.4,48.2)	0.48 (0.23,0.99)	0.04	-17.23 (-34.33,-0.79)					
		30+						22/8134 (2.7; 1.8,4.1)	66/8316 (7.9; 6.2,10.1)	0.34 (0.21,0.55)	<.001	-5.23 (-7.59,-3.07)					
		All						32/8769 (3.6; 2.6,5.1)	91/9074 (10.0; 8.2,12.3)	0.36 (0.24,0.54)	<.001	-6.38 (-8.91,-4.02)					

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eTable 2:

Assuming all participants that missed exit screen had a similar chance of having a negative screen (that does not recommended them for colposcopy) as well as of disease detection, we imputed the outcome based on the observed data (Age at recruitment and initial screen results). For imputation, enrollment screen results were dichotomized to be either negative (HPV- or Cytology negative) or positive (HPV+ or Cytology positive (ASCUS+)). Multiple imputation was based on logistic regression with total number of imputations set to 25.

eTable 2 below shows the outcome of multiple imputation. It is evident that the observed difference of CIN2+ rates between HPV and LBC arms persist, with similar scale as calculated from initial unimputed data.

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eTable 2. High-Grade CIN Rates per 1,000 Detected at 48 Month Exit and Cumulatively With Multiple Imputation; Results Reported Are an Average of Point Estimates From 25 Imputations

			48 month Exit round results only					Round 1 and 48 month exit results combined			
	Pathology outcome	**Age at baseline**	**Intervention (HPV)**	**Control (LBC)***	**Risk Ratio (HPV vs LBC)**	**Absolute Difference (HPV - LBC)**		**Intervention (HPV)**	**Control (LBC)**	**Risk Ratio (HPV vs LBC)**	**Absolute Difference (HPV - LBC)**
All participants attending 48 month screening	**CIN3+ Primary Outcome**	**25-29**	10.56	20.26	0.50	-10.70		34.69	38.23	0.91	-3.57
		30+	2.41	4.72	0.51	-2.31		7.81	9.03	0.86	-1.23
		All	3.11	6.18	0.50	-3.06		10.14	10.54	0.96	-0.39
	CIN2+ Secondary Outcome	**25-29**	23.7	39.3	0.60	-13.7		78.21	70.72	1.11	7.48
		30+	5.19	9.43	0.55	-4.3		16.90	16.90	1.00	0.00
		All	6.80	12.07	0.56	-5.3		22.2	21.6	1.03	0.57
Baseline screen negative (Cytology or HPV negative)	**CIN3+ Primary Outcome**	**25-29**	7.56	21.58	0.35	-14.02					
		30+	1.29	4.48	0.29	-3.19					
		All	1.75	5.91	0.30	-4.16					
	CIN2+ Secondary Outcome	**25-29**	18.83	40.05	0.47	-21.22					
		30+	3.48	8.81	0.40	-5.33					
		All	4.59	11.42	0.40	-6.82					

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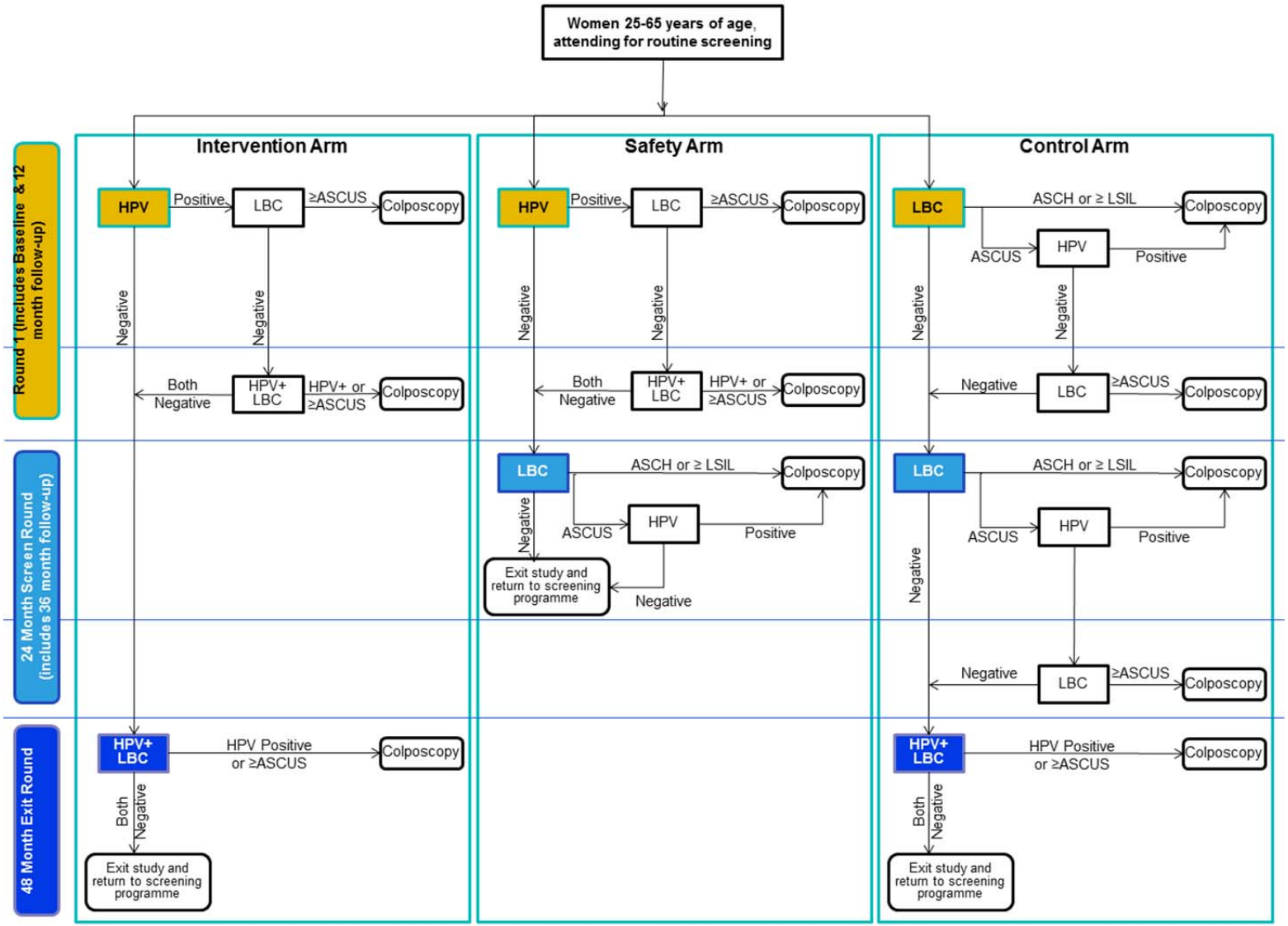
eFigure. FOCAL Study Overall Flowchart



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