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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

This online publication has been corrected. The corrected version first appeared at thelancet.com on December 17, 2020.

Supplement to: Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* 2020; published online Nov 19. http://dx.doi.org/10.1016/S0140-6736(20)32466-1.

Supplementary Materials

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Figure S1 Solicited local adverse reactions in the 7 days after priming and boosting with low dose vaccinations as recorded in participant symptom e-diaries. Participants shown are those randomised to receive 2 doses (LD/LD).

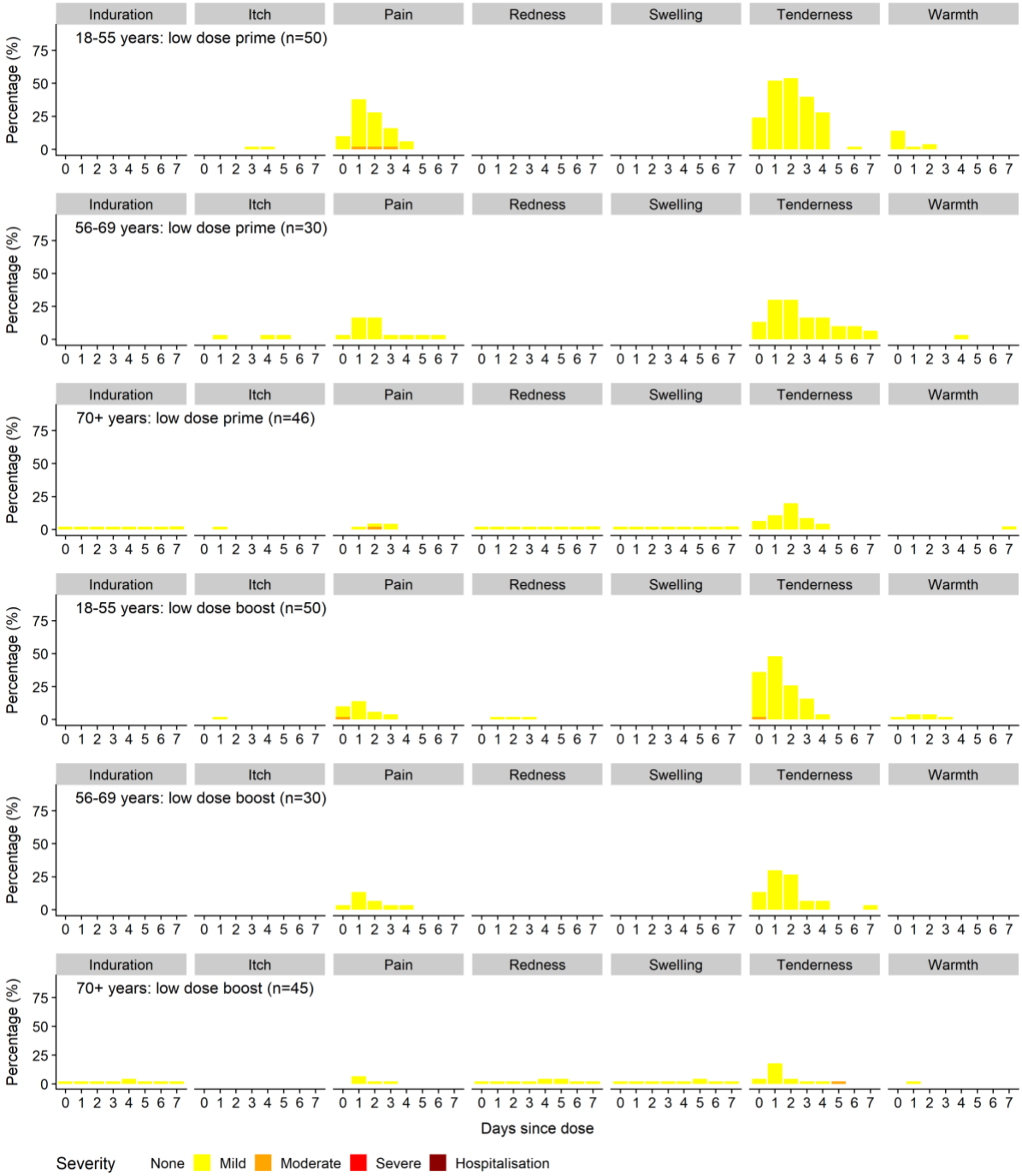
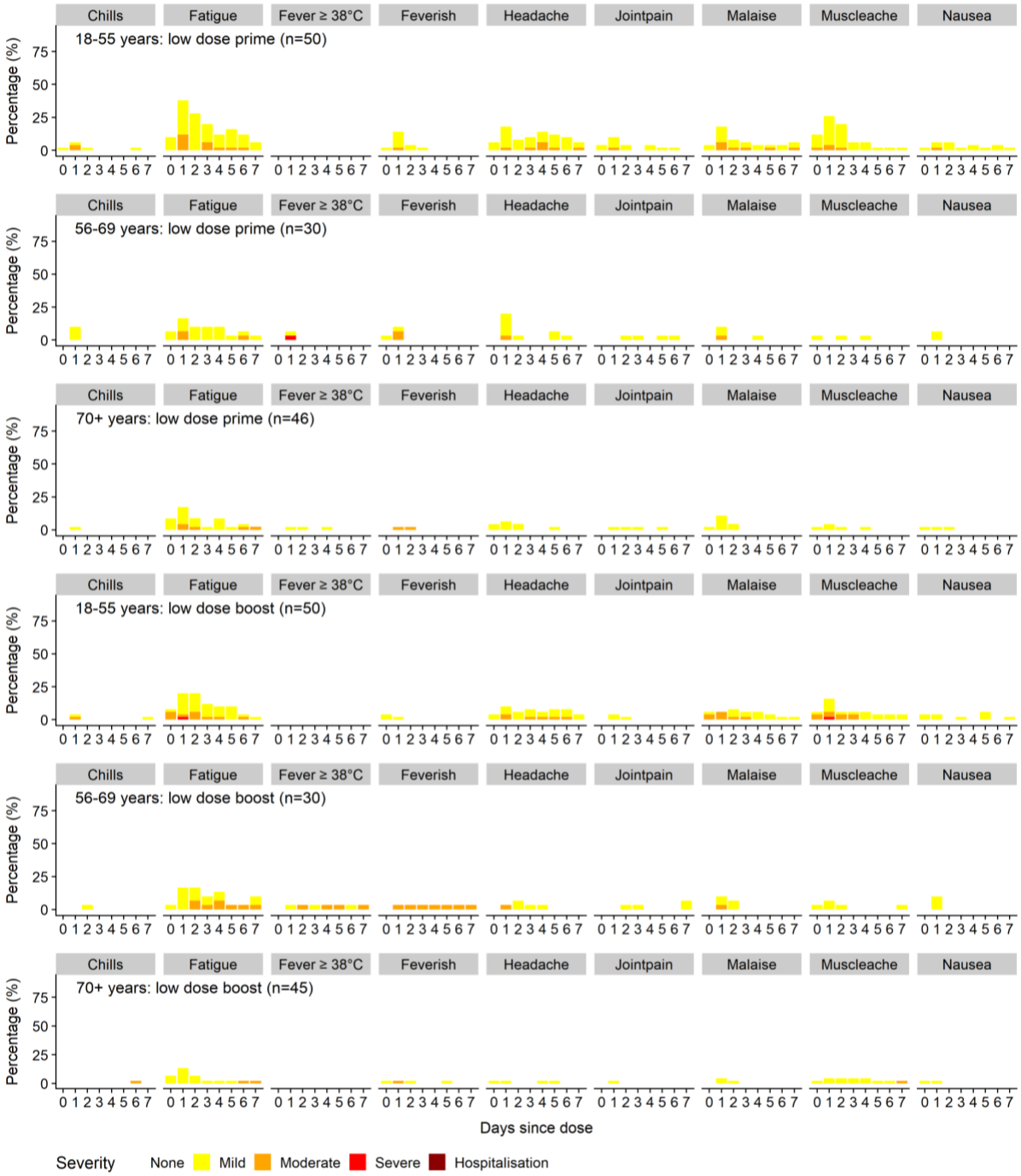


Figure S2 Solicited systemic adverse reactions in the 7 days after priming and boosting with low dose vaccinations as recorded in participant symptom e-diaries. Participants shown are those randomised to receive 2 doses (LD/LD).



Day 0 is the day of vaccination. Feverish: Self-reported feeling of feverishness, Fever: objective fever measurements, mild: >= 38·ºC, moderate: >=38·5ºC, severe: >=39·0ºC.

Figure S3 Solicited local adverse reactions in the 7 days after priming and boosting with MenACWY as recorded in participant symptom e-diaries. Participants shown are those randomised to receive 2 doses of MenACWY.

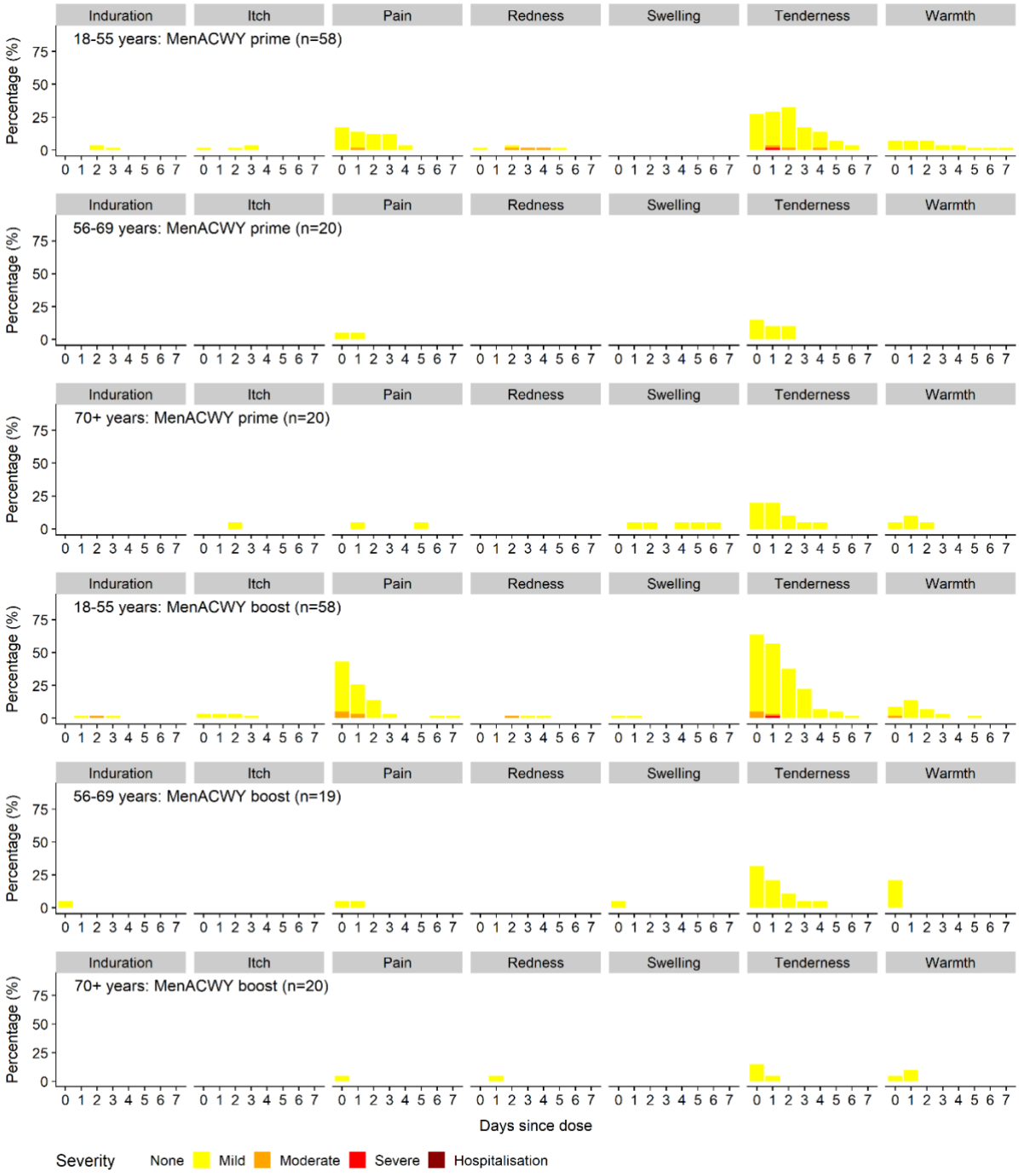
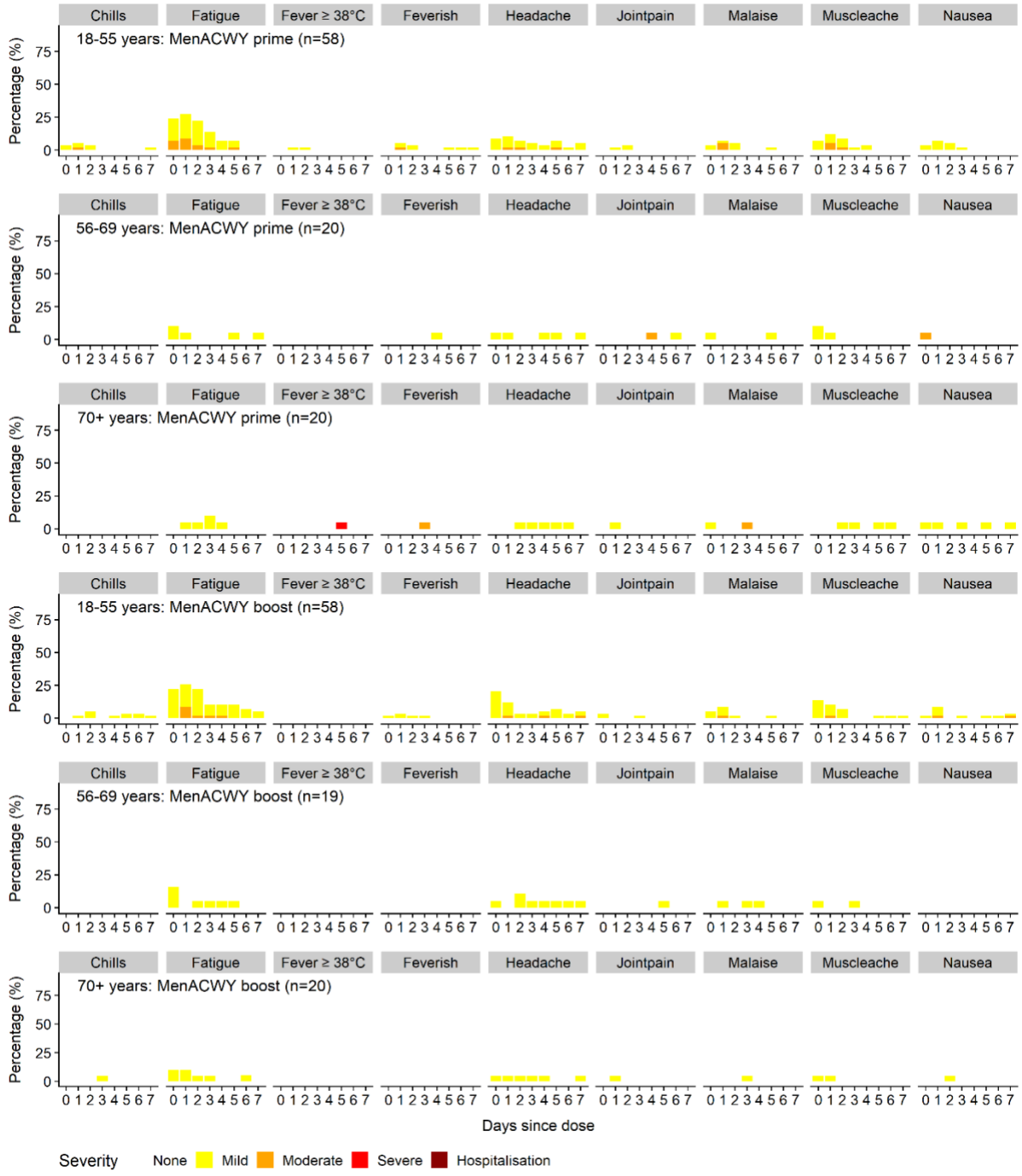
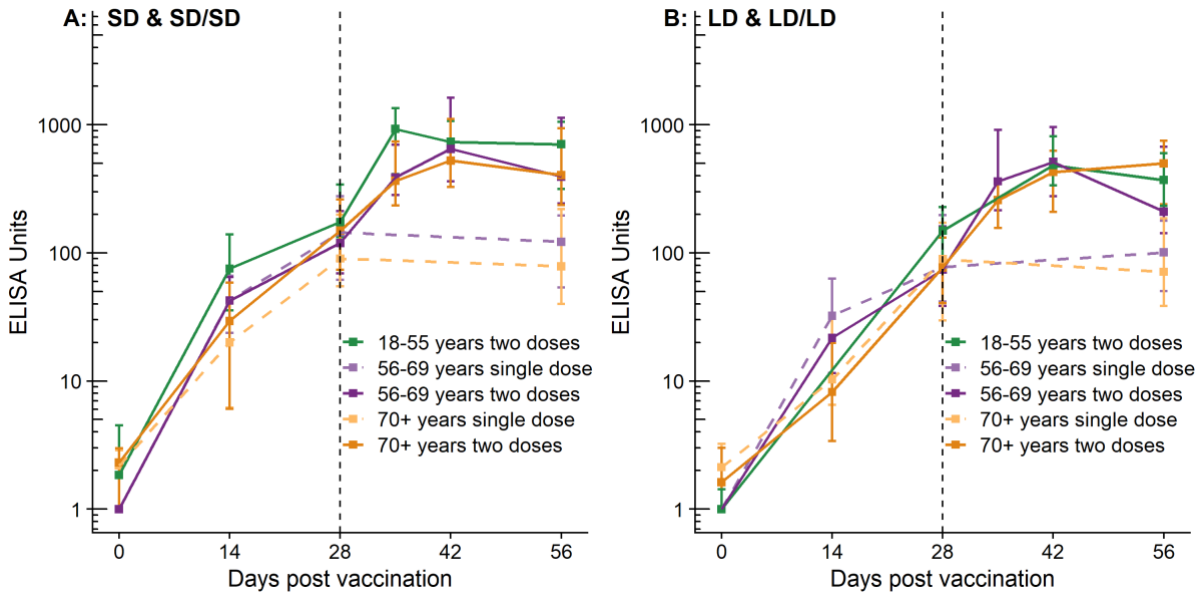


Figure S4 Solicited systemic adverse reactions in the 7 days after priming and boosting with MenACWY as recorded in participant symptom e-diaries. Participants shown are those randomised to receive 2 doses of MenACWY.



Day 0 is the day of vaccination. Feverish: Self-reported feeling of feverishness, Fever: objective fever measurements, mild: >= 38·ºC, moderate: >=38·5ºC, severe: >=39·0ºC.

Figure S5 SARS-CoV-2 IgG response to spike protein by standardised ELISA by age and vaccine dose



Error bars show median and interquartile range [IQR]. Participants in boost group received their second dose at day 28 (vertical dotted line). Lower limit of quantification is 1 EU. SD = standard dose, LD= low dose.

Table S1 Summary statistics for SARS-CoV-2 IgG response to the spike protein by multiplex immunoassay (Mesoscale platform, AU/mL).

Vaccine	Day	N	18-55 yrs, LD/LD	N	56-69 yrs, LD	N	56-69 yrs, LD/LD	N	70+ yrs, LD	N	70+ yrs, LD/LD	56-69 years combined	70+ year combined	KW test p value
	0	49	58 [27, 89]	30	44 [27, 84]	30	38 [15, 67]	49	40 [19, 100]	44	48 [16, 90]			
ChAdOx1														
	28	**49**	**6439 [4338, 10640]**	30	5032 [2753, 9578]	30	4040 [2537, 12567]	49	4103 [1507, 9288]	44	3168 [1495, 5257]	**4553 [2657 12462]**	**3565 [1507, 6345]**	0.0037†
Low dose														
	42	47	19507 [12793, 31376]			28	19103 [11807, 31347]			44	19498 [8749, 36513]			
	56	**48**	**15114 [9996, 22084]**	29	4645 [2155, 6145]	**28**	**19156 [8919, 26348]**	48	2576 [1430, 5595]	**45**	**17439 [7785, 29259]**			0.7485£
			18-55 yrs, SD/SD		**56-69 yrs, SD**		**56-69 yrs, SD/SD**		**70+ yrs, SD**		**70+ yrs, SD/SD**			
	0	25	32 [22, 85]	30	31 [19, 56]	29	44 [29, 94]	49	44 [22, 78]	49	40 [20, 70]			
ChAdOx1														
Standard	28	**43**	**9807 [5847, 17220**]	28	6693 [2814, 13730]	27	4474 [2256, 8486]	49	3454 [1974, 11702]	48	4603 [2321, 13322]	**5496 [2548, 12061]**	**4156 [2122 12595]**	0.0044†
dose														
	42	45	26251 [16453, 36643]			26	20617 [12869, 53507]			48	19414 [12054, 35867]			
	56	**39**	**20713 [13898, 33550]**	29	4938 [1868, 11935]	**26**	**16170 [10233, 40353]**	48	2954 [1546, 7305]	**47**	**17561 [9705, 37796]**			0.6834£
			18-55 yrs, LD/LD		**56-69 yrs, LD**		**56-69 yrs, LD/LD**		**70+ yrs, LD**		**70+ yrs, LD/LD**			
	0	47	48 [25, 105]	10	25 [18, 34]	10	60 [27, 92]	10	42 [26, 71]	10	68 [48, 83]			
MenACWY														
Low dose	28	47	50 [27, 88]	10	27 [19, 33]	10	73 [26, 99]	10	37 [21, 52]	10	55 [40, 147]			
control														
	42	44	45 [24, 71]			8	54 [23, 67]			10	67 [40, 121]			
	56	44	47 [32, 128]	10	25 [15, 34]	10	53 [26, 97]	9	38 [17, 44]	10	58 [46, 87]			
			18-55 yrs, SD/SD		**56-69 yrs, SD**		**56-69 yrs, SD/SD**		**70+ yrs, SD**		**70+ yrs, SD/SD**			
Men ACWY	0	5	32 [30, 71]	10	36 [12, 111]	10	34 [15, 83]	10	35 [24, 87]	10	44 [15, 55]			
Standard	28	7	31 [23, 57]	9	42 [15, 105]	10	35 [14, 64]	10	37 [24, 106]	10	48 [21, 68]			
dose control														
	42	9	34 [20, 70]			9	26 [11, 59]			10	36 [14, 50]			
	56	7	45 [22, 64]	9	61 [17, 103]	8	28 [15, 72]	10	38 [25, 79]	10	48 [20, 65]			

Median and interquartile range [IQR] shown. SD = standard dose, LD= low dose. † p value comparing 18-55 years with those 56-69 years and 70+ years at day 28 (highlighted in bold). £ p value from Kruskal Wallis test comparing those 18-55 years with those 56-69 years and 70+ years at day 56 (highlighted in bold). Data are presented for participants eligible for inclusion in the analysis – see Figure S1 for reasons for exclusion.

Table S2 Summary statistics for SARS-CoV-2 IgG response to spike protein by standardised ELISA

Group	Visit	Single ChAdOx1			Single MenACWY			Two doses ChAdOx1			Two doses MenACWY		
		N	Median [IQR]	GMT (95% CI)	N	Median [IQR]	GMT (95% CI)	N	Median [IQR]	GMT (95% CI)	N	Median [IQR]	GMT (95% CI)
18-55 years: SD/SD	0							48	2 [1, 4]	2.54 (1.72, 3.74)	9	1 [1, 4]	1.84 (1.06, 3.18)
	14							48	75 [35, 139]	70.27 (47.00, 105.04)	9	1 [1, 3]	1.70 (0.98, 2.92)
	28							48	174 [133, 341]	214.10 (156.26, 293.36)	9	1 [1, 4]	1.80 (0.99, 3.26)
	35							47	927 [412, 1350]	784.19 (584.18, 1052.67)	9	1 [1, 1]	1.40 (0.84, 2.34)
	42							46	736 [505, 1071]	735.82 (610.53, 886.82)	9	2 [1, 4]	2.10 (1.22, 3.61)
	56							43	705 [314, 1052]	627.88 (475.82, 828.53)	7	3 [1, 4]	2.08 (0.95, 4.56)
56-69 years: SD & SD/SD	0	30	1 [1, 1]	1.23 (0.94, 1.60)	10	1 [1, 1]	1.0 (1.0, 1.0)	30	1 [1, 1]	1.05 (0.95, 1.15)	10	1 [1, 1]	1.49 (0.60, 3.70)
	14	30	42 [24, 66]	34.91 (19.24, 63.33)	10	1 [1, 1]	1.0 (1.0, 1.0)	29	42 [21, 65]	25.55 (14.63, 44.62)	10	1 [1, 1]	1.52 (0.64, 3.60)
	28	30	145 [61, 278]	123.22 (77.28, 196.46)	10	1 [1, 1]	1.0 (1.0, 1.0)	29	119 [69, 212]	115.46 (78.60, 169.62)	10	1 [1, 1]	1.51 (0.63, 3.61)
	35	0			0			29	388 [283, 698]	415.46 (299.78, 575.79)	10	1 [1, 1]	1.56 (0.70, 3.45)
	42	0			0			29	648 [360, 1622]	717.49 (526.85, 977.12)	9	1 [1, 1]	1.48 (0.60, 3.66)
	56	30	122 [54, 195]	106.24 (73.10, 154.39)	10	1 [1, 1]	1.0 (1.0, 1.0)	29	394 [243, 1130]	522.69 (368.79, 740.81)	10	3 [1, 7]	3.26 (1.23, 8.68)
70+ years: SD & SD/SD	0	49	2 [1, 3]	2.07 (1.65, 2.59)	10	1 [1, 3]	1.56 (1.00, 2.44)	49	2 [1, 3]	2.11 (1.67, 2.68)	10	1 [1, 2]	1.52 (1.03, 2.24)
	14	49	20 [6, 41]	15.93 (10.39, 24.42)	10	1 [1, 2]	1.51 (0.94, 2.40)	48	29 [6, 59]	25.89 (14.48, 46.29)	10	1 [1, 2]	1.61 (0.96, 2.70)
	28	49	90 [55, 198]	100.33 (70.71, 142.35)	10	1 [1, 1]	1.18 (0.90, 1.53)	47	149 [74, 260]	139.48 (87.17, 223.18)	10	1 [1, 1]	1.50 (0.77, 2.93)
	35	0			0			46	365 [235, 741]	427.62 (312.33, 585.46)	10	1 [1, 1]	1.43 (0.82, 2.50)
	42	0			0			48	525 [326, 1105]	533.07 (398.62, 712.87)	10	1 [1, 3]	2.06 (1.02, 4.17)
	56	48	79 [40, 220]	84.91 (61.67, 116.89)	10	3 [1, 4]	2.30 (1.44, 3.67)	48	405 [236, 940]	471.51 (344.75, 644.87)	10	1 [1, 2]	1.66 (0.84, 3.29)
18-55 years: LD/LD	0							50	1 [1, 1]	1.41 (1.13, 1.75)	49	1 [1, 1]	1.34 (1.11, 1.61)
	14							0			0		
	28							50	149 [76, 228]	119.38 (83.90, 169.86)	49	1 [1, 1]	1.31 (1.09, 1.56)
	35							0			0		
	42							49	483 [337, 810]	503.61 (410.40, 617.99)	49	1 [1, 1]	1.36 (1.14, 1.62)
	56							50	370 [224, 596]	317.38 (228.44, 440.94)	49	1 [1, 2]	1.65 (1.21, 2.25)
56-69 years: LD & LD/LD	0	30	1 [1, 1]	1.29 (1.00, 1.66)	10	1 [1, 1]	1.53 (0.80, 2.94)	30	1 [1, 1]	1.37 (1.02, 1.84)	10	1 [1, 3]	1.94 (0.97, 3.88)
	14	30	32 [10, 63]	22.37 (13.28, 37.69)	10	1 [1, 1]	1.26 (0.88, 1.81)	30	22 [11, 32]	18.73 (12.40, 28.30)	10	1 [1, 5]	2.05 (1.00, 4.21)
	28	30	78 [42, 197]	89.05 (53.40, 148.49)	10	1 [1, 2]	1.36 (0.94, 1.96)	30	74 [38, 161]	83.89 (52.73, 133.47)	10	1 [1, 2]	1.64 (1.06, 2.53)
	35	0			0			27	361 [215, 908]	415.32 (286.36, 602.38)	10	3 [1, 4]	2.79 (1.62, 4.81)
	42	0			0			29	513 [276, 962]	576.22 (392.52, 845.90)	8	1 [1, 1]	1.20 (0.78, 1.84)
	56	30	101 [50, 178]	96.68 (58.32, 160.30)	10	1 [1, 2]	1.54 (1.04, 2.29)	29	210 [142, 672]	304.62 (194.09, 478.11)	10	2 [1, 4]	2.21 (1.21, 4.04)
70+ years: LD & LD/LD	0	49	2 [1, 3]	1.88 (1.58, 2.24)	10	2 [1, 3]	1.79 (1.14, 2.83)	45	2 [1, 3]	1.79 (1.48, 2.17)	10	1 [1, 3]	1.68 (1.11, 2.56)
	14	49	10 [7, 31]	11.06 (7.60, 16.11)	10	2 [1, 3]	1.71 (1.14, 2.58)	45	8 [3, 20]	7.78 (5.17, 11.71)	10	1 [1, 3]	1.66 (1.09, 2.52)
	28	49	89 [30, 172]	87.38 (60.75, 125.69)	10	1 [1, 2]	1.86 (0.69, 5.04)	45	77 [41, 131]	64.29 (41.61, 99.33)	10	1 [1, 1]	1.10 (0.88, 1.37)
	35	0			0			45	258 [157, 380]	246.71 (187.10, 325.32)	10	1 [1, 2]	1.39 (0.95, 2.04)
	42	0			0			45	428 [209, 626]	406.04 (305.37, 539.90)	10	1 [1, 1]	1.10 (0.95, 1.26)
	56	49	71 [38, 186]	74.30 (52.35, 105.45)	9	1 [1, 1]	1.26 (0.76, 2.07)	45	500 [239, 750]	419.70 (302.14, 583.00)	10	1 [1, 1]	1.23 (0.77, 1.95)

Median and interquartile range [IQR] shown. SD = standard dose, LD= low dose.

Table S3 Summary statistics for SARS-CoV-2 live virus micro-neutralisation PHE MNA80 (normalised IC_{80} values)

Study Group	Visit	N	Single ChAdOx1	N	Two Dose ChAdOx1
18-55y LD/LD	0			47	5 [5 ,5]
	28			45	79 [47 ,127]
	42			41	**161 [99 ,233]**
	56			39	110 [74 ,184]
56-69y, LD/LD	0	30	5 [5 ,5]	27	5 [5 ,5]
	28	18	64 [41 ,93]	21	55 [25 ,79]
	42			28	**143 [79 ,220**]
	56	29	45 [27 ,67]	27	127 [74 ,183]
70+y LD/LD	0	22	5 [5 ,5]	35	5 [5 ,5]
	28	21	47 [23 ,82]	34	33 [13 ,65]
	42			34	**150 [103 ,255]**
	56	20	31 [13 ,84]	36	111 [61 ,251]
18-55y SD/SD	0			47	5 [5 ,5]
	28			43	47 [5 ,124]
	42			39	**193 [113 ,238]**
	56			37	185 [129, 359]
56-69 SD/SD	0	6	5 [5 ,5]	27	5 [5 ,5]
	28	9	76 [46 ,179]	15	72 [35 ,102]
	42			20	**144 [119 ,347]**
	56	10	32 [11 ,63]	22	178 [124 ,416]
70+y SD/SD	0	47	5 [5 ,5]	47	5 [5 ,5]
	28	49	58 [20 ,120]	42	48 [21 ,121]
	42			47	**161 [73 ,323]**
	56	47	44 [22 ,76]	43	146 [56 ,239]

Data shown are median and interquartile range.
Comparison across age groups at Day 42, from ANOVA applied to log-transformed titres: low-dose p=0·899, standard dose p=0·400
Comparison between low and standard dose at Day 42, from independent samples t-test applied to log-transformed titres: 18-55y: p=0·3287, 56-69 y: p=0·1240, 70+ y: p=0·6195

Table S4 Summary statistics for Interferon-γ ELISpot responses

Study Group	Visit	N	Single dose ChAdOx1 nCoV-19	N	Two Dose ChAdOx1 nCoV-19
56-69y, LD/LD	0	29	57 [48 ,103]	30	67 [48 ,109]
	14	30	1001 [662 ,1965]	30	1341 [536 ,2029]
	28	28	511 [264 ,790]	29	488 [255 ,1043]
	42			29	501 [253 ,905]
70+y LD/LD	0	48	48 [48 ,69]	40	48 [48 ,72]
	14	49	1009 [485 ,2265]	44	921 [400 ,1733]
	28	47	420 [232 ,721]	43	397 [203 ,715]
	42			43	285 [172 ,554]
18-55y SD/SD	0			25	58 [48 ,108]
	14			24	1187 [841 ,2428]
	28			10	292 [178 ,803]
	42			23	413 [245 ,675]
56-69y SD/SD	0	25	48 [48 ,65]	30	63 [48 ,84]
	14	21	677 [411 ,1503]	29	797 [383 ,1817]
	28	29	335 [162 ,523]	30	591 [238 ,922]
	42			28	798 [462 ,1186]
70+y SD/SD	0	47	63 [48 ,96]	47	73 [48 ,100]
	14	48	975 [442 ,1530]	48	977 [458 ,1914]
	28	47	567 [357 ,1018]	49	300 [157 ,492]
	42			47	307 [161 ,516]

Median and interquartile range [IQR] shown. SD = standard dose, LD= low dose.

Difference at day 42 across three age groups in the SD/SD recipients $p < 0{\cdot}0001$.

Table S5 Solicited local and systemic adverse reactions in the 7 days after priming and boosting with standard dose vaccine (SD/SD) in participants aged 18-55 years as recorded in participant symptom e-diaries (n=49)

	Prime dose						Boost dose					
Symptom	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**
Pain	19 (39%, 25%-54%)	22 (45%, 31%-60%)	8 (16%, 7%-30%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	30 (61%, 46%-75%)	25 (51%, 36%-66%)	19 (39%, 25%-54%)	5 (10%, 3%-22%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	24 (49%, 34%-64%)
Redness	49 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	48 (98%, 89%-100%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)
Warmth	42 (86%, 73%-94%)	7 (14%, 6%-27%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	7 (14%, 6%-27%)	43 (88%, 75%-95%)	6 (12%, 5%-25%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	6 (12%, 5%-25%)
Itch	47 (96%, 86%-100%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	2 (4%, 0%-14%)	43 (88%, 75%-95%)	5 (10%, 3%-22%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	6 (12%, 5%-25%)
Swelling	49 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	49 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)
Induration	49 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	49 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)
Tenderness	12 (24%, 13%-39%)	34 (69%, 55%-82%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	37 (76%, 61%-87%)	19 (39%, 25%-54%)	27 (55%, 40%-69%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	30 (61%, 46%-75%)
Feverish	28 (57%, 42%-71%)	8 (16%, 7%-30%)	10 (20%, 10%-34%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	21 (43%, 29%-58%)	44 (90%, 78%-97%)	5 (10%, 3%-22%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	5 (10%, 3%-22%)
Fever	37 (76%, 61%-87%)	8 (16%, 7%-30%)	3 (6%, 1%-17%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	12 (24%, 13%-39%)	48 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)
Chills	32 (65%, 50%-78%)	9 (18%, 9%-32%)	5 (10%, 3%-22%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	17 (35%, 22%-50%)	42 (86%, 73%-94%)	6 (12%, 5%-25%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	7 (14%, 6%-27%)
Joint pain	33 (67%, 52%-80%)	10 (20%, 10%-34%)	5 (10%, 3%-22%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	16 (33%, 20%-48%)	46 (94%, 83%-99%)	1 (2%, 0%-11%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	3 (6%, 1%-17%)
Muscle ache	23 (47%, 33%-62%)	13 (27%, 15%-41%)	11 (22%, 12%-37%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	26 (53%, 38%-67%)	32 (65%, 50%-78%)	11 (22%, 12%-37%)	6 (12%, 5%-25%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	17 (35%, 22%-50%)
Fatigue	12 (24%, 13%-39%)	20 (41%, 27%-56%)	13 (27%, 15%-41%)	4 (8%, 2%-20%)	0 (0%, 0%-7%)	37 (76%, 61%-87%)	22 (45%, 31%-60%)	16 (33%, 20%-48%)	11 (22%, 12%-37%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	27 (55%, 40%-69%)
Headache	17 (35%, 22%-50%)	20 (41%, 27%-56%)	10 (20%, 10%-34%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	32 (65%, 50%-78%)	34 (69%, 55%-82%)	12 (24%, 13%-39%)	2 (4%, 0%-14%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	15 (31%, 18%-45%)
Malaise	29 (59%, 44%-73%)	5 (10%, 3%-22%)	13 (27%, 15%-41%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	20 (41%, 27%-56%)	35 (71%, 57%-83%)	11 (22%, 12%-37%)	2 (4%, 0%-14%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	14 (29%, 17%-43%)
Nausea	36 (73%, 59%-85%)	11 (22%, 12%-37%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	13 (27%, 15%-41%)	45 (92%, 80%-98%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	4 (8%, 2%-20%)

*Figures in brackets reflect the proportion and 95% exact Binomial confidence interval of participants experiencing the corresponding symptom at the corresponding severity level, of those participants who provided data for that symptom.

Table S6 Solicited local and systemic adverse reactions in the 7 days after priming and boosting with standard dose vaccine (SD/SD) in participants aged 56-69 years as recorded in participant symptom e-diaries (n=30)

	Prime dose						Boost dose					
Symptom	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**
Pain	17 (57%, 37%-75%)	12 (40%, 23%-59%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	13 (43%, 25%-63%)	19 (66%, 46%-82%)	10 (34%, 18%-54%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	10 (34%, 18%-54%)
Redness	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	29 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)
Warmth	28 (93%, 78%-99%)	2 (7%, 1%-22%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	2 (7%, 1%-22%)	25 (86%, 68%-96%)	4 (14%, 4%-32%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	4 (14%, 4%-32%)
Itch	28 (93%, 78%-99%)	2 (7%, 1%-22%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	2 (7%, 1%-22%)	28 (97%, 82%-100%)	1 (3%, 0%-18%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	1 (3%, 0%-18%)
Swelling	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	29 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)
Induration	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	29 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)
Tenderness	10 (33%, 17%-53%)	19 (63%, 44%-80%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	20 (67%, 47%-83%)	12 (41%, 24%-61%)	16 (55%, 36%-74%)	1 (3%, 0%-18%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	17 (59%, 39%-76%)
Feverish	27 (90%, 73%-98%)	2 (7%, 1%-22%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	3 (10%, 2%-27%)	25 (86%, 68%-96%)	3 (10%, 2%-27%)	1 (3%, 0%-18%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	4 (14%, 4%-32%)
Fever	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	29 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)
Chills	27 (90%, 73%-98%)	1 (3%, 0%-17%)	2 (7%, 1%-22%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	3 (10%, 2%-27%)	26 (90%, 73%-98%)	2 (7%, 1%-23%)	1 (3%, 0%-18%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	3 (10%, 2%-27%)
Joint pain	25 (83%, 65%-94%)	4 (13%, 4%-31%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	5 (17%, 6%-35%)	24 (83%, 64%-94%)	4 (14%, 4%-32%)	1 (3%, 0%-18%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	5 (17%, 6%-36%)
Muscle ache	19 (63%, 44%-80%)	10 (33%, 17%-53%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	11 (37%, 20%-56%)	22 (76%, 56%-90%)	7 (24%, 10%-44%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	7 (24%, 10%-44%)
Fatigue	15 (50%, 31%-69%)	10 (33%, 17%-53%)	5 (17%, 6%-35%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	15 (50%, 31%-69%)	17 (59%, 39%-76%)	11 (38%, 21%-58%)	1 (3%, 0%-18%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	12 (41%, 24%-61%)
Headache	15 (50%, 31%-69%)	15 (50%, 31%-69%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	15 (50%, 31%-69%)	19 (66%, 46%-82%)	9 (31%, 15%-51%)	1 (3%, 0%-18%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	10 (34%, 18%-54%)
Malaise	22 (73%, 54%-88%)	6 (20%, 8%-39%)	2 (7%, 1%-22%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	8 (27%, 12%-46%)	26 (90%, 73%-98%)	2 (7%, 1%-23%)	1 (3%, 0%-18%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	3 (10%, 2%-27%)
Nausea	26 (87%, 69%-96%)	4 (13%, 4%-31%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	4 (13%, 4%-31%)	23 (79%, 60%-92%)	6 (21%, 8%-40%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	6 (21%, 8%-40%)

*Figures in brackets reflect the proportion and 95% exact Binomial confidence interval of participants experiencing the corresponding symptom at the corresponding severity level, of those participants who provided data for that symptom.

Table S7 Solicited local and systemic adverse reactions in the 7 days after priming and boosting with standard dose vaccine (SD/SD) in participants aged 70+ years as recorded in participant symptom e-diaries (n=49)

	Prime dose						Boost dose					
Symptom	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**
Pain	39 (80%, 66%-90%)	9 (18%, 9%-32%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	10 (20%, 10%-34%)	44 (90%, 78%-97%)	5 (10%, 3%-22%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	5 (10%, 3%-22%)
Redness	48 (98%, 89%-100%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)	48 (98%, 89%-100%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)
Warmth	42 (86%, 73%-94%)	7 (14%, 6%-27%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	7 (14%, 6%-27%)	47 (96%, 86%-100%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	2 (4%, 0%-14%)
Itch	47 (96%, 86%-100%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	2 (4%, 0%-14%)	48 (98%, 89%-100%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)
Swelling	47 (96%, 86%-100%)	1 (2%, 0%-11%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	2 (4%, 0%-14%)	47 (96%, 86%-100%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	2 (4%, 0%-14%)
Induration	48 (98%, 89%-100%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)	48 (98%, 89%-100%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)
Tenderness	25 (51%, 36%-66%)	24 (49%, 34%-64%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	24 (49%, 34%-64%)	26 (53%, 38%-67%)	23 (47%, 33%-62%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	23 (47%, 33%-62%)
Feverish	44 (90%, 78%-97%)	5 (10%, 3%-22%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	5 (10%, 3%-22%)	45 (92%, 80%-98%)	3 (6%, 1%-17%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	4 (8%, 2%-20%)
Fever	49 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	49 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)
Chills	47 (96%, 86%-100%)	0 (0%, 0%-7%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	2 (4%, 0%-14%)	49 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)
Joint pain	42 (86%, 73%-94%)	7 (14%, 6%-27%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	7 (14%, 6%-27%)	45 (92%, 80%-98%)	4 (8%, 2%-20%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	4 (8%, 2%-20%)
Muscle ache	40 (82%, 68%-91%)	9 (18%, 9%-32%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	9 (18%, 9%-32%)	40 (82%, 68%-91%)	9 (18%, 9%-32%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	9 (18%, 9%-32%)
Fatigue	29 (59%, 44%-73%)	17 (35%, 22%-50%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	20 (41%, 27%-56%)	33 (67%, 52%-80%)	13 (27%, 15%-41%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	16 (33%, 20%-48%)
Headache	29 (59%, 44%-73%)	17 (35%, 22%-50%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	20 (41%, 27%-56%)	39 (80%, 66%-90%)	8 (16%, 7%-30%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	10 (20%, 10%-34%)
Malaise	37 (76%, 61%-87%)	10 (20%, 10%-34%)	1 (2%, 0%-11%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	12 (24%, 13%-39%)	43 (88%, 75%-95%)	2 (4%, 0%-14%)	4 (8%, 2%-20%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	6 (12%, 5%-25%)
Nausea	45 (92%, 80%-98%)	3 (6%, 1%-17%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	4 (8%, 2%-20%)	46 (94%, 83%-99%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	3 (6%, 1%-17%)

*Figures in brackets reflect the proportion and 95% exact Binomial confidence interval of participants experiencing the corresponding symptom at the corresponding severity level, of those participants who provided data for that symptom.

Table S8 Solicited local and systemic adverse reactions in the 7 days after priming and boosting with low dose vaccine (LD/LD) in participants aged 18-55 years as recorded in participant symptom e-diaries (n=50)

	Prime dose						Boost dose					
Symptom	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**
Pain	27 (54%, 39%-68%)	22 (44%, 30%-59%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	23 (46%, 32%-61%)	42 (84%, 71%-93%)	7 (14%, 6%-27%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	8 (16%, 7%-29%)
Redness	50 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	49 (98%, 89%-100%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)
Warmth	41 (82%, 69%-91%)	9 (18%, 9%-31%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	9 (18%, 9%-31%)	47 (94%, 83%-99%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	3 (6%, 1%-17%)
Itch	48 (96%, 86%-100%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	2 (4%, 0%-14%)	49 (98%, 89%-100%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	1 (2%, 0%-11%)
Swelling	50 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	50 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)
Induration	50 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	50 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)
Tenderness	14 (28%, 16%-42%)	36 (72%, 58%-84%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	36 (72%, 58%-84%)	21 (42%, 28%-57%)	28 (56%, 41%-70%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	29 (58%, 43%-72%)
Feverish	42 (84%, 71%-93%)	7 (14%, 6%-27%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	8 (16%, 7%-29%)	47 (94%, 83%-99%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	3 (6%, 1%-17%)
Fever	50 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	50 (100%, 93%-100%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)
Chills	44 (88%, 76%-95%)	4 (8%, 2%-19%)	2 (4%, 0%-14%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	6 (12%, 5%-24%)	47 (94%, 83%-99%)	2 (4%, 0%-14%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	3 (6%, 1%-17%)
Joint pain	41 (82%, 69%-91%)	8 (16%, 7%-29%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	9 (18%, 9%-31%)	47 (94%, 83%-99%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	3 (6%, 1%-17%)
Muscle ache	33 (66%, 51%-79%)	14 (28%, 16%-42%)	3 (6%, 1%-17%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	17 (34%, 21%-49%)	39 (78%, 64%-88%)	8 (16%, 7%-29%)	2 (4%, 0%-14%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	11 (22%, 12%-36%)
Fatigue	23 (46%, 32%-61%)	17 (34%, 21%-49%)	10 (20%, 10%-34%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	27 (54%, 39%-68%)	32 (64%, 49%-77%)	11 (22%, 12%-36%)	6 (12%, 5%-24%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	18 (36%, 23%-51%)
Headache	29 (58%, 43%-72%)	15 (30%, 18%-45%)	6 (12%, 5%-24%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	21 (42%, 28%-57%)	37 (74%, 60%-85%)	8 (16%, 7%-29%)	5 (10%, 3%-22%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	13 (26%, 15%-40%)
Malaise	38 (76%, 62%-87%)	7 (14%, 6%-27%)	5 (10%, 3%-22%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	12 (24%, 13%-38%)	45 (90%, 78%-97%)	1 (2%, 0%-11%)	4 (8%, 2%-19%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	5 (10%, 3%-22%)
Nausea	45 (90%, 78%-97%)	4 (8%, 2%-19%)	1 (2%, 0%-11%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	5 (10%, 3%-22%)	45 (90%, 78%-97%)	5 (10%, 3%-22%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	0 (0%, 0%-7%)	5 (10%, 3%-22%)

*Figures in brackets reflect the proportion and 95% exact Binomial confidence interval of participants experiencing the corresponding symptom at the corresponding severity level, of those participants who provided data for that symptom.

Table S9 Solicited local and systemic adverse reactions in the 7 days after priming and boosting with low dose vaccine (LD/LD) in participants aged 56-69 years as recorded in participant symptom e-diaries (n=30)

	Prime dose						Boost dose					
Symptom	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**
Pain	22 (73%, 54%-88%)	8 (27%, 12%-46%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	8 (27%, 12%-46%)	25 (83%, 65%-94%)	5 (17%, 6%-35%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	5 (17%, 6%-35%)
Redness	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)
Warmth	29 (97%, 83%-100%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	1 (3%, 0%-17%)	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)
Itch	28 (93%, 78%-99%)	2 (7%, 1%-22%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	2 (7%, 1%-22%)	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)
Swelling	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)
Induration	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	30 (100%, 88%-100%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)
Tenderness	18 (60%, 41%-77%)	12 (40%, 23%-59%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	12 (40%, 23%-59%)	19 (63%, 44%-80%)	11 (37%, 20%-56%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	11 (37%, 20%-56%)
Feverish	26 (87%, 69%-96%)	2 (7%, 1%-22%)	2 (7%, 1%-22%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	4 (13%, 4%-31%)	29 (97%, 83%-100%)	0 (0%, 0%-12%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	1 (3%, 0%-17%)
Fever	28 (93%, 78%-99%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	2 (7%, 1%-22%)	29 (97%, 83%-100%)	0 (0%, 0%-12%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	1 (3%, 0%-17%)
Chills	27 (90%, 73%-98%)	3 (10%, 2%-27%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	3 (10%, 2%-27%)	29 (97%, 83%-100%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	1 (3%, 0%-17%)
Joint pain	28 (93%, 78%-99%)	2 (7%, 1%-22%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	2 (7%, 1%-22%)	27 (90%, 73%-98%)	3 (10%, 2%-27%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	3 (10%, 2%-27%)
Muscle ache	27 (90%, 73%-98%)	3 (10%, 2%-27%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	3 (10%, 2%-27%)	27 (90%, 73%-98%)	3 (10%, 2%-27%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	3 (10%, 2%-27%)
Fatigue	19 (63%, 44%-80%)	8 (27%, 12%-46%)	3 (10%, 2%-27%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	11 (37%, 20%-56%)	22 (73%, 54%-88%)	5 (17%, 6%-35%)	3 (10%, 2%-27%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	8 (27%, 12%-46%)
Headache	21 (70%, 51%-85%)	8 (27%, 12%-46%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	9 (30%, 15%-49%)	26 (87%, 69%-96%)	3 (10%, 2%-27%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	4 (13%, 4%-31%)
Malaise	26 (87%, 69%-96%)	3 (10%, 2%-27%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	4 (13%, 4%-31%)	26 (87%, 69%-96%)	3 (10%, 2%-27%)	1 (3%, 0%-17%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	4 (13%, 4%-31%)
Nausea	28 (93%, 78%-99%)	2 (7%, 1%-22%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	2 (7%, 1%-22%)	27 (90%, 73%-98%)	3 (10%, 2%-27%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	0 (0%, 0%-12%)	3 (10%, 2%-27%)

*Figures in brackets reflect the proportion and 95% exact Binomial confidence interval of participants experiencing the corresponding symptom at the corresponding severity level, of those participants who provided data for that symptom.

Table S10 Solicited local and systemic adverse reactions in the 7 days after priming and boosting with low dose vaccine (LD/LD) in participants aged 70+ years as recorded in participant symptom e-diaries (n=46)

	Prime dose						Boost dose					
Symptom	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**	**None**	**Mild**	**Moderate**	**Severe**	**Hospitalisation**	**Any**
Pain	42 (91%, 79%-98%)	3 (7%, 1%-18%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	4 (9%, 2%-21%)	42 (93%, 82%-99%)	3 (7%, 1%-18%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	3 (7%, 1%-18%)
Redness	45 (98%, 88%-100%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)	43 (96%, 85%-99%)	2 (4%, 1%-15%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	2 (4%, 1%-15%)
Warmth	45 (98%, 88%-100%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)	44 (98%, 88%-100%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)
Itch	45 (98%, 88%-100%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)	45 (100%, 92%-100%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)
Swelling	45 (98%, 88%-100%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)	43 (96%, 85%-99%)	2 (4%, 1%-15%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	2 (4%, 1%-15%)
Induration	45 (98%, 88%-100%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)	43 (96%, 85%-99%)	2 (4%, 1%-15%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	2 (4%, 1%-15%)
Tenderness	35 (76%, 61%-87%)	11 (24%, 13%-39%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	11 (24%, 13%-39%)	35 (78%, 63%-89%)	9 (20%, 10%-35%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	10 (22%, 11%-37%)
Feverish	45 (98%, 88%-100%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)	42 (93%, 82%-99%)	2 (4%, 1%-15%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	3 (7%, 1%-18%)
Fever	44 (96%, 85%-99%)	2 (4%, 1%-15%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	2 (4%, 1%-15%)	45 (100%, 92%-100%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)
Chills	45 (98%, 88%-100%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)	44 (98%, 88%-100%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)
Joint pain	42 (91%, 79%-98%)	4 (9%, 2%-21%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	4 (9%, 2%-21%)	44 (98%, 88%-100%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)
Muscle ache	41 (89%, 76%-96%)	5 (11%, 4%-24%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	5 (11%, 4%-24%)	40 (89%, 76%-96%)	4 (9%, 2%-21%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	5 (11%, 4%-24%)
Fatigue	32 (70%, 54%-82%)	10 (22%, 11%-36%)	4 (9%, 2%-21%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	14 (30%, 18%-46%)	36 (80%, 65%-90%)	8 (18%, 8%-32%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	9 (20%, 10%-35%)
Headache	40 (87%, 74%-95%)	6 (13%, 5%-26%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	6 (13%, 5%-26%)	41 (91%, 79%-98%)	4 (9%, 2%-21%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	4 (9%, 2%-21%)
Malaise	40 (87%, 74%-95%)	6 (13%, 5%-26%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	6 (13%, 5%-26%)	43 (96%, 85%-99%)	2 (4%, 1%-15%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	2 (4%, 1%-15%)
Nausea	43 (93%, 82%-99%)	3 (7%, 1%-18%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	3 (7%, 1%-18%)	44 (98%, 88%-100%)	1 (2%, 0%-12%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	0 (0%, 0%-8%)	1 (2%, 0%-12%)

*Figures in brackets reflect the proportion and 95% exact Binomial confidence interval of participants experiencing the corresponding symptom at the corresponding severity level, of those participants who provided data for that symptom.

Table S11 Solicited local and systemic adverse reactions in the 7 days after priming and boosting in groups receiving either two low (LD/LD) or two standard doses (SD/SD) of ChAdOx1 nCoV-19

Symptom	Dose	Age group	Any	None	Adjusted p-value*
Pain	LD prime	18-55 years	23 (46.0%)	27 (54.0%)	0.003
		56-69 years	8 (26.7%)	22 (73.3%)	
		70+ years	4 (8.7%)	42 (91.3%)	
	SD prime	18-55 years	30 (61.2%)	19 (38.8%)	0.003
		56-69 years	13 (43.3%)	17 (56.7%)	
		70+ years	10 (20.4%)	39 (79.6%)	
	LD boost	18-55 years	8 (15.7%)	43 (84.3%)	>0.999
		56-69 years	5 (16.7%)	25 (83.3%)	
		70+ years	3 (6.7%)	42 (93.3%)	
	SD boost	18-55 years	24 (49.0%)	25 (51.0%)	0.002
		56-69 years	10 (34.5%)	19 (65.5%)	
		70+ years	5 (10.2%)	44 (89.8%)	
Redness	LD prime	18-55 years	0 (0.0%)	50 (100.0%)	>0.999
		56-69 years	0 (0.0%)	30 (100.0%)	
		70+ years	1 (2.2%)	45 (97.8%)	
	SD prime	18-55 years	0 (0.0%)	49 (100.0%)	>0.999
		56-69 years	0 (0.0%)	30 (100.0%)	
		70+ years	1 (2.0%)	48 (98.0%)	
	LD boost	18-55 years	1 (2.0%)	50 (98.0%)	>0.999
		56-69 years	0 (0.0%)	30 (100.0%)	
		70+ years	2 (4.4%)	43 (95.6%)	
	SD boost	18-55 years	1 (2.0%)	48 (98.0%)	>0.999
		56-69 years	0 (0.0%)	29 (100.0%)	
		70+ years	1 (2.0%)	48 (98.0%)	
Warmth	LD prime	18-55 years	9 (18.0%)	41 (82.0%)	0.343
		56-69 years	1 (3.3%)	29 (96.7%)	
		70+ years	1 (2.2%)	45 (97.8%)	

Symptom	Dose	Age group	Any	None	Adjusted p-value*
	SD prime	18-55 years	7 (14.3%)	42 (85.7%)	
		56-69 years	2 (6.7%)	28 (93.3%)	>0.999
		70+ years	7 (14.3%)	42 (85.7%)	
	LD boost	18-55 years	3 (5.9%)	48 (94.1%)	
		56-69 years	0 (0.0%)	30 (100.0%)	>0.999
		70+ years	1 (2.2%)	44 (97.8%)	
	SD boost	18-55 years	6 (12.2%)	43 (87.8%)	
		56-69 years	4 (13.8%)	25 (86.2%)	>0.999
		70+ years	2 (4.1%)	47 (95.9%)	
Itch	LD prime	18-55 years	2 (4.0%)	48 (96.0%)	
		56-69 years	2 (6.7%)	28 (93.3%)	>0.999
		70+ years	1 (2.2%)	45 (97.8%)	
	SD prime	18-55 years	2 (4.1%)	47 (95.9%)	
		56-69 years	2 (6.7%)	28 (93.3%)	>0.999
		70+ years	2 (4.1%)	47 (95.9%)	
	LD boost	18-55 years	1 (2.0%)	50 (98.0%)	
		56-69 years	0 (0.0%)	30 (100.0%)	>0.999
		70+ years	0 (0.0%)	45 (100.0%)	
	SD boost	18-55 years	6 (12.2%)	43 (87.8%)	
		56-69 years	1 (3.4%)	28 (96.6%)	>0.999
		70+ years	1 (2.0%)	48 (98.0%)	
Swelling	LD prime	18-55 years	0 (0.0%)	50 (100.0%)	
		56-69 years	0 (0.0%)	30 (100.0%)	>0.999
		70+ years	1 (2.2%)	45 (97.8%)	
	SD prime	18-55 years	0 (0.0%)	49 (100.0%)	
		56-69 years	0 (0.0%)	30 (100.0%)	>0.999
		70+ years	2 (4.1%)	47 (95.9%)	
	LD boost	18-55 years	0 (0.0%)	51 (100.0%)	
		56-69 years	0 (0.0%)	30 (100.0%)	>0.999
		70+ years	2 (4.4%)	43 (95.6%)	
	SD boost	18-55 years	0 (0.0%)	49 (100.0%)	>0.999

Symptom	Dose	Age group	Any	None	Adjusted p-value*
		56-69 years	0 (0.0%)	29 (100.0%)	
		70+ years	2 (4.1%)	47 (95.9%)	
Induration	LD prime	18-55 years	0 (0.0%)	50 (100.0%)	>0.999
		56-69 years	0 (0.0%)	30 (100.0%)	
		70+ years	1 (2.2%)	45 (97.8%)	
	SD prime	18-55 years	0 (0.0%)	49 (100.0%)	>0.999
		56-69 years	0 (0.0%)	30 (100.0%)	
		70+ years	1 (2.0%)	48 (98.0%)	
	LD boost	18-55 years	0 (0.0%)	51 (100.0%)	>0.999
		56-69 years	0 (0.0%)	30 (100.0%)	
		70+ years	2 (4.4%)	43 (95.6%)	
	SD boost	18-55 years	0 (0.0%)	49 (100.0%)	>0.999
		56-69 years	0 (0.0%)	29 (100.0%)	
		70+ years	1 (2.0%)	48 (98.0%)	
Tenderness	LD prime	18-55 years	36 (72.0%)	14 (28.0%)	<0.001
		56-69 years	12 (40.0%)	18 (60.0%)	
		70+ years	11 (23.9%)	35 (76.1%)	
	SD prime	18-55 years	37 (75.5%)	12 (24.5%)	0.547
		56-69 years	20 (66.7%)	10 (33.3%)	
		70+ years	24 (49.0%)	25 (51.0%)	
	LD boost	18-55 years	30 (58.8%)	21 (41.2%)	0.016
		56-69 years	11 (36.7%)	19 (63.3%)	
		70+ years	10 (22.2%)	35 (77.8%)	
	SD boost	18-55 years	30 (61.2%)	19 (38.8%)	>0.999
		56-69 years	17 (58.6%)	12 (41.4%)	
		70+ years	23 (46.9%)	26 (53.1%)	
Feverish	LD prime	18-55 years	8 (16.0%)	42 (84.0%)	>0.999
		56-69 years	4 (13.3%)	26 (86.7%)	
		70+ years	1 (2.2%)	45 (97.8%)	
	SD prime	18-55 years	21 (42.9%)	28 (57.1%)	0.008
		56-69 years	3 (10.0%)	27 (90.0%)	

Symptom	Dose	Age group	Any	None	Adjusted p-value*
		70+ years	5 (10.2%)	44 (89.8%)	
	LD boost	18-55 years	3 (5.9%)	48 (94.1%)	
		56-69 years	1 (3.3%)	29 (96.7%)	>0.999
		70+ years	3 (6.7%)	42 (93.3%)	
	SD boost	18-55 years	5 (10.2%)	44 (89.8%)	
		56-69 years	4 (13.8%)	25 (86.2%)	>0.999
		70+ years	4 (8.2%)	45 (91.8%)	
Fever	LD prime	18-55 years	0 (0.0%)	50 (100.0%)	
		56-69 years	2 (6.7%)	28 (93.3%)	>0.999
		70+ years	2 (4.3%)	44 (95.7%)	
	SD prime	18-55 years	12 (24.5%)	37 (75.5%)	
		56-69 years	0 (0.0%)	30 (100.0%)	<0.001
		70+ years	0 (0.0%)	49 (100.0%)	
	LD boost	18-55 years	0 (0.0%)	51 (100.0%)	
		56-69 years	1 (3.3%)	29 (96.7%)	>0.999
		70+ years	0 (0.0%)	45 (100.0%)	
	SD boost	18-55 years	0 (0.0%)	48 (100.0%)	
		56-69 years	0 (0.0%)	29 (100.0%)	-
		70+ years	0 (0.0%)	49 (100.0%)	
Chills	LD prime	18-55 years	6 (12.0%)	44 (88.0%)	
		56-69 years	3 (10.0%)	27 (90.0%)	>0.999
		70+ years	1 (2.2%)	45 (97.8%)	
	SD prime	18-55 years	17 (34.7%)	32 (65.3%)	
		56-69 years	3 (10.0%)	27 (90.0%)	0.004
		70+ years	2 (4.1%)	47 (95.9%)	
	LD boost	18-55 years	3 (5.9%)	48 (94.1%)	
		56-69 years	1 (3.3%)	29 (96.7%)	>0.999
		70+ years	1 (2.2%)	44 (97.8%)	
	SD boost	18-55 years	7 (14.3%)	42 (85.7%)	
		56-69 years	3 (10.3%)	26 (89.7%)	0.787
		70+ years	0 (0.0%)	49 (100.0%)	

Symptom	Dose	Age group	Any	None	Adjusted p-value*
Joint pain	LD prime	18-55 years	9 (18.0%)	41 (82.0%)	>0.999
		56-69 years	2 (6.7%)	28 (93.3%)	
		70+ years	4 (8.7%)	42 (91.3%)	
	SD prime	18-55 years	16 (32.7%)	33 (67.3%)	>0.999
		56-69 years	5 (16.7%)	25 (83.3%)	
		70+ years	7 (14.3%)	42 (85.7%)	
	LD boost	18-55 years	3 (5.9%)	48 (94.1%)	>0.999
		56-69 years	3 (10.0%)	27 (90.0%)	
		70+ years	1 (2.2%)	44 (97.8%)	
	SD boost	18-55 years	3 (6.1%)	46 (93.9%)	>0.999
		56-69 years	5 (17.2%)	24 (82.8%)	
		70+ years	4 (8.2%)	45 (91.8%)	
Muscle ache	LD prime	18-55 years	17 (34.0%)	33 (66.0%)	0.285
		56-69 years	3 (10.0%)	27 (90.0%)	
		70+ years	5 (10.9%)	41 (89.1%)	
	SD prime	18-55 years	26 (53.1%)	23 (46.9%)	0.029
		56-69 years	11 (36.7%)	19 (63.3%)	
		70+ years	9 (18.4%)	40 (81.6%)	
	LD boost	18-55 years	11 (21.6%)	40 (78.4%)	>0.999
		56-69 years	3 (10.0%)	27 (90.0%)	
		70+ years	5 (11.1%)	40 (88.9%)	
	SD boost	18-55 years	17 (34.7%)	32 (65.3%)	>0.999
		56-69 years	7 (24.1%)	22 (75.9%)	
		70+ years	9 (18.4%)	40 (81.6%)	
Fatigue	LD prime	18-55 years	27 (54.0%)	23 (46.0%)	>0.999
		56-69 years	11 (36.7%)	19 (63.3%)	
		70+ years	14 (30.4%)	32 (69.6%)	
	SD prime	18-55 years	37 (75.5%)	12 (24.5%)	0.046
		56-69 years	15 (50.0%)	15 (50.0%)	
		70+ years	20 (40.8%)	29 (59.2%)	
	LD boost	18-55 years	18 (35.3%)	33 (64.7%)	>0.999

Symptom	Dose	Age group	Any	None	Adjusted p-value*
		56-69 years	8 (26.7%)	22 (73.3%)	
		70+ years	9 (20.0%)	36 (80.0%)	
		18-55 years	27 (55.1%)	22 (44.9%)	
	SD boost	56-69 years	12 (41.4%)	17 (58.6%)	>0.999
		70+ years	16 (32.7%)	33 (67.3%)	
		18-55 years	21 (42.0%)	29 (58.0%)	
	LD prime	56-69 years	9 (30.0%)	21 (70.0%)	0.133
		70+ years	6 (13.0%)	40 (87.0%)	
		18-55 years	32 (65.3%)	17 (34.7%)	
	SD prime	56-69 years	15 (50.0%)	15 (50.0%)	>0.999
Headache		70+ years	20 (40.8%)	29 (59.2%)	
		18-55 years	13 (25.5%)	38 (74.5%)	
	LD boost	56-69 years	4 (13.3%)	26 (86.7%)	>0.999
		70+ years	4 (8.9%)	41 (91.1%)	
		18-55 years	15 (30.6%)	34 (69.4%)	
	SD boost	56-69 years	10 (34.5%)	19 (65.5%)	>0.999
		70+ years	10 (20.4%)	39 (79.6%)	
		18-55 years	12 (24.0%)	38 (76.0%)	
	LD prime	56-69 years	4 (13.3%)	26 (86.7%)	>0.999
		70+ years	6 (13.0%)	40 (87.0%)	
		18-55 years	20 (40.8%)	29 (59.2%)	
	SD prime	56-69 years	8 (26.7%)	22 (73.3%)	>0.999
Malaise		70+ years	12 (24.5%)	37 (75.5%)	
		18-55 years	5 (9.8%)	46 (90.2%)	
	LD boost	56-69 years	4 (13.3%)	26 (86.7%)	>0.999
		70+ years	2 (4.4%)	43 (95.6%)	
		18-55 years	14 (28.6%)	35 (71.4%)	
	SD boost	56-69 years	3 (10.3%)	26 (89.7%)	>0.999
		70+ years	6 (12.2%)	43 (87.8%)	
Nausea	LD prime	18-55 years	5 (10.0%)	45 (90.0%)	>0.999
		56-69 years	2 (6.7%)	28 (93.3%)	

Symptom	Dose	Age group	Any	None	Adjusted p-value*
		70+ years	3 (6.5%)	43 (93.5%)	
	SD prime	18-55 years	13 (26.5%)	36 (73.5%)	>0.999
		56-69 years	4 (13.3%)	26 (86.7%)	
		70+ years	4 (8.2%)	45 (91.8%)	
	LD boost	18-55 years	5 (9.8%)	46 (90.2%)	>0.999
		56-69 years	3 (10.0%)	27 (90.0%)	
		70+ years	1 (2.2%)	44 (97.8%)	
	SD boost	18-55 years	4 (8.2%)	45 (91.8%)	>0.999
		56-69 years	6 (20.7%)	23 (79.3%)	
		70+ years	3 (6.1%)	46 (93.9%)	

*p-values from Cochran-Armitage exact tests for trend. Bonferroni adjustments applied to account for multiple comparisons.

Table S12 Solicited local and systemic adverse reactions in the 7 days after priming and boosting participants randomised to 2 doses

Dose	Prime/Boost	Symptom Group	18-55 years	56-69 years	70+ years
ChAdOx1 LD/LD	Prime		*n=50*	*n=30*	*n=46*
		Local or systemic	45 (90%, 78%-97%)	22 (73%, 54%-88%)	28 (61%, 45%-75%)
		Local	42 (84%, 71%-93%)	14 (47%, 28%-66%)	13 (28%, 16%-43%)
		Systemic	36 (72%, 58%-84%)	16 (53%, 34%-72%)	23 (50%, 35%-65%)
	Boost		*n=50*	*n=30*	*n=45*
		Local or systemic	38 (76%, 62%-87%)	18 (60%, 41%-77%)	20 (44%, 30%-60%)
		Local	29 (58%, 43%-72%)	11 (37%, 20%-56%)	12 (27%, 15%-42%)
		Systemic	25 (50%, 36%-64%)	12 (40%, 23%-59%)	15 (33%, 20%-49%)
ChAdOx1 SD/SD	Prime		*n=49*	*n=30*	*n=49*
		Local or systemic	48 (98%, 89%-100%)	28 (93%, 78%-99%)	39 (80%, 66%-90%)
		Local	43 (88%, 75%-95%)	22 (73%, 54%-88%)	30 (61%, 46%-75%)
		Systemic	42 (86%, 73%-94%)	23 (77%, 58%-90%)	32 (65%, 50%-78%)
	Boost		*n=49*	*n=29*	*n=49*
		Local or systemic	42 (86%, 73%-94%)	28 (97%, 82%-100%)	35 (71%, 57%-83%)
		Local	37 (76%, 61%-87%)	21 (72%, 53%-87%)	27 (55%, 40%-69%)
		Systemic	32 (65%, 50%-78%)	21 (72%, 53%-87%)	21 (43%, 29%-58%)
2 doses MenACWY	Prime		*n=58*	*n=20*	*n=20*
		Local or systemic	43 (74%, 61%-85%)	11 (55%, 32%-77%)	8 (40%, 19%-64%)
		Local	33 (57%, 43%-70%)	5 (25%, 9%-49%)	7 (35%, 15%-59%)
		Systemic	35 (60%, 47%-73%)	9 (45%, 23%-68%)	6 (30%, 12%-54%)
	Boost		*n=58*	*n=19*	*n=20*
		Local or systemic	53 (91%, 81%-97%)	10 (53%, 29%-76%)	6 (30%, 12%-54%)
		Local	50 (86%, 75%-94%)	7 (37%, 16%-62%)	4 (20%, 6%-44%)
		Systemic	39 (67%, 54%-79%)	6 (32%, 13%-57%)	5 (25%, 9%-49%)

*Figures in brackets reflect the proportion and 95% exact Binomial confidence interval of participants experiencing the solicited symptom/symptom group, calculated using all participants providing diary information for that symptom/symptom group as denominator.

Table S13 Moderate or severe solicited local and systemic adverse reactions in the 7 days after priming and boosting in participants randomised to 2 doses

Dose	Prime/Boost	Symptom Group	18-55 years	56-69 years	70+ years
ChAdOx1 LD/LD	Prime		*n=50*	*n=30*	*n=46*
		Local or systemic	16 (32%, 20%-47%)	4 (13%, 4%-31%)	5 (11%, 4%-24%)
		Local	1 (2%, 0%-11%)	0 (0%, 0%-12%)	1 (2%, 0%-12%)
		Systemic	16 (32%, 20%-47%)	4 (13%, 4%-31%)	5 (11%, 4%-24%)
	Boost		*n=50*	*n=30*	*n=45*
		Local or systemic	11 (22%, 12%-36%)	3 (10%, 2%-27%)	4 (9%, 2%-21%)
		Local	1 (2%, 0%-11%)	0 (0%, 0%-12%)	1 (2%, 0%-12%)
		Systemic	11 (22%, 12%-36%)	3 (10%, 2%-27%)	3 (7%, 1%-18%)
ChAdOx1 SD/SD	Prime		*n=49*	*n=30*	*n=49*
		Local or systemic	26 (53%, 38%-67%)	6 (20%, 8%-39%)	9 (18%, 9%-32%)
		Local	8 (16%, 7%-30%)	1 (3%, 0%-17%)	3 (6%, 1%-17%)
		Systemic	25 (51%, 36%-66%)	6 (20%, 8%-39%)	6 (12%, 5%-25%)
	Boost		*n=49*	*n=29*	*n=49*
		Local or systemic	17 (35%, 22%-50%)	6 (21%, 8%-40%)	5 (10%, 3%-22%)
		Local	7 (14%, 6%-27%)	1 (3%, 0%-18%)	0 (0%, 0%-7%)
		Systemic	14 (29%, 17%-43%)	5 (17%, 6%-36%)	5 (10%, 3%-22%)
2 dose MenACWY	Prime		*n=58*	*n=20*	*n=20*
		Local or systemic	13 (22%, 13%-35%)	2 (10%, 1%-32%)	2 (10%, 1%-32%)
		Local	2 (3%, 0%-12%)	0 (0%, 0%-17%)	0 (0%, 0%-17%)
		Systemic	12 (21%, 11%-33%)	2 (10%, 1%-32%)	2 (10%, 1%-32%)
	Boost		*n=58*	*n=19*	*n=20*
		Local or systemic	15 (26%, 15%-39%)	0 (0%, 0%-18%)	0 (0%, 0%-17%)
		Local	8 (14%, 6%-25%)	0 (0%, 0%-18%)	0 (0%, 0%-17%)
		Systemic	10 (17%, 9%-29%)	0 (0%, 0%-18%)	0 (0%, 0%-17%)

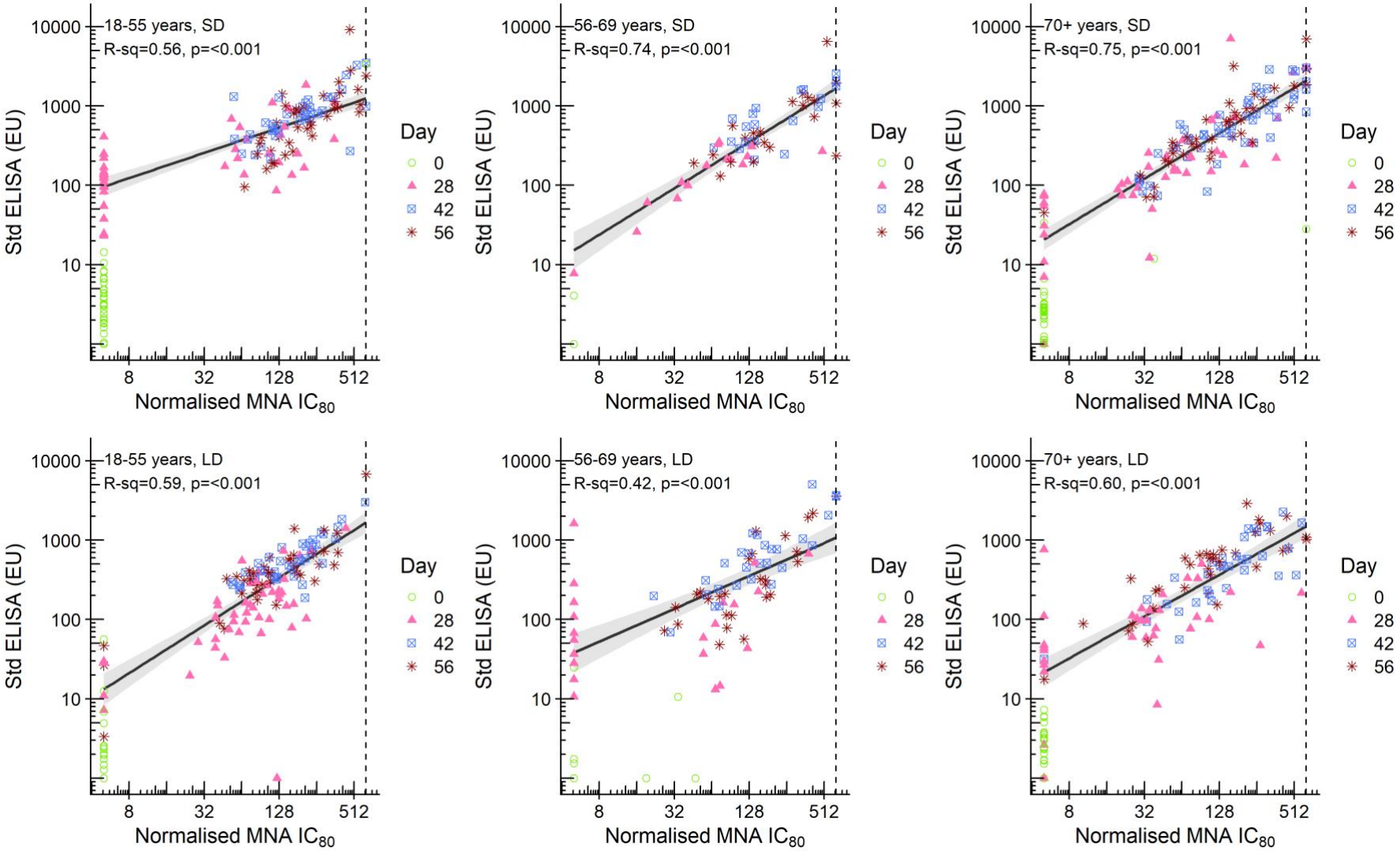
*Figures in brackets reflect the proportion and 95% exact Binomial confidence interval of participants experiencing a moderate/severe reaction of the solicited symptom/symptom group, calculated using all participants providing diary information for that symptom/symptom group as denominator.

Table S14 List of SAEs in participants included in this paper, across both trial arms as of 26th October 2020

Randomised group	Days since prime	Days since boost	Diagnosis/symptoms	Classification	Causality as assessed by site investigator	SUSAR
LD or MenACWY groups						
18-55 years	35	7	Appendicitis	Hospitalisation	No relationship	No
18-55 years	80	51	Allergic reaction wasp sting	An important medical event	Unlikely	No
56-69 years	29	n/a	Pneumonia	An important medical event	Unlikely	No
70+ years	53	17	Unstable angina	An important medical event	No relationship	No
70+ years	59	24	Sigmoid volvulus	Hospitalisation	No relationship	No
70+ years	42	n/a	Limb ischaemia	Hospitalisation	No relationship	No
70+ years	117	n/a	Acute diverticulitis	Hospitalisation	No relationship	No
70+ years	117	n/a	Vertebral fracture	Hospitalisation	No relationship	No
SD or MenACWY groups						
18-55 years	29	1	Ovarian cyst	Hospitalisation	Unlikely	No
70+ years	46	11	Hernia	Hospitalisation	No relationship	No
70+ years	63	n/a	Prostate cancer	An important medical event	No relationship	No
70+ years	66	33	Polymyalgia rheumatica	Hospitalisation	Unlikely	No
70+ years	75	43	Bilateral lower limb oedema	Hospitalisation	Unlikely	No

SD = standard dose, LD= low dose.

Figure S6 Correlation between post-baseline total anti –spike IgG measured by standardized ELISA and live virus SARS-CoV-2 microneutralisation assay (PHE – normalized MNA_{80}) by age and vaccine dose, in those randomised to receive two doses of vaccine



*Baseline values shown in plots were not included in the regression analysis

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Clinical Study Plan

1. STUDY DETAILS

Study title:	A phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19
Short title:	Investigating a Vaccine Against COVID-19
Protocol version:	13.0
Sponsor:	University of Oxford
Funder:	UK Research and Innovation
Chief Investigator:	Prof A. Pollard
REC reference:	20/SC/0179
IRAS	281904

2. PURPOSE

This Clinical Study Plan (CSP) outlines specific information relating to the COV002 study, supplementary to the study protocol or other existing Standard Operating Procedures (SOPs). Where current SOPs are to be used, these are referenced in the text and will be accessible to all members of staff.

3. STUDY OVERVIEW

This is a Phase 2/3, participant-blinded, randomised controlled trial in adults and healthy children aged 5-12 years in the UK, administering either a single dose or two-doses of ChAdOx1 nCoV-19 or licensed MenACWY vaccine via intramuscular injection with sequential age escalation/de-escalation. The study will assess efficacy, safety and immunogenicity of ChAdOx1 nCoV-19.

There will be 12 study groups with up to approximately 12,390 volunteers across all groups and sites. Groups 1, 3, 5, 7 & 11 will be recruited in Oxford only. Groups 2 and 8 will be recruited at Southampton only. Group 12 will be recruited at two London sites. Groups 4, 6, 9 & 10 will be recruited across all study sites.

Group	Site	Age years	Dose of ChAdOx-nCov19	No in ChAdOx group	No in MenACWY group
1	Oxford	56-69	a1) Single dose $5x10^{10}$vp (Abs 260) a3) Two-dose $5x10^{10}$vp (Abs 260) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost (at earliest available opportunity and a minimum of 4 weeks from prime) b1) Two-dose $5x10^{10}$vp (Abs 260) prime and 2.2 $x10^{10}$vp (qPCR) boost (4-6 weeks apart)	30 up to 30 (from 1a1) 30	10 up to 10 10
2	Soton	≥70	a1) Single dose $5x10^{10}$vp (Abs 260) a3) Two-dose $5x10^{10}$vp (Abs 260) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost (at earliest available opportunity and a minimum of 4 weeks from prime) b1) Two-dose $5x10^{10}$vp (Abs 260) prime and 2.2 $x10^{10}$vp (qPCR) boost (4-6 weeks apart)	50 up to 50 (from 2a1) 50	10 up to 10 10

3	Oxford	5-12	$2.5x10^{10}$vp (qPCR)	30	30
4	All sites	18-55	a1) Single dose $5x10^{10}$vp (Abs 260) b1) Two-dose $5x10^{10}$vp (Abs 260) prime and $2.2x10^{10}$vp (qPCR) boost, (4-6 weeks apart) c1) Two-dose $5x10^{10}$vp (Abs 260) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost OR $5x10^{10}$vp (qPCR) boost, (at least 4 weeks apart)	up to 1775 up to 50 (from 4a1) up to 1725 (from 4a1)	up to 1775 up to 50 up to 1725
5	Oxford	18-55	a1) $5x10^{10}$vp (Abs 260) a3) Two-dose $5x10^{10}$vp (Abs 260) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost (at earliest available opportunity and a minimum of 4 weeks from prime) b1) $5x10^{10}$vp (qPCR) c1) $5x10^{10}$vp (qPCR) d1) Two dose 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp Abs 260, corrected for PS80), (4-6 weeks apart)	50 up to 50 (from 5a1) 25 25 50	50 up to 50 25 25 10
6	All sites	18-55	a1) $5x10^{10}$vp (qPCR) b1) Two-dose $5x10^{10}$vp (qPCR) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp Abs 260, corrected for PS80) boost OR $5x10^{10}$vp (qPCR) boost (at earliest available opportunity and a minimum of 4 weeks from prime)	up to 3000 up to 3000 (from 6a1)	up to 3000 up to 3000
7	Oxford	56-69	a1) Single dose $5x10^{10}$vp (qPCR) b1) Two-dose $5x10^{10}$vp (qPCR) (4-6 weeks apart)	30 30	10 10
8	Soton	≥70	a1) Single dose $5x10^{10}$vp (qPCR) b1) Two-dose $5x10^{10}$vp (qPCR) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost* OR $5x10^{10}$vp (qPCR) boost (4-6 weeks apart)	50 50	10 10
9	All sites	56-69	a1) Two dose 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80), (4-6 weeks apart)	500	500
10	All sites	≥70	a1) Two dose 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80), (4-6 weeks apart)	500	500
11	Oxford	18-55	Adults who previously received a ChAdOx1 vectored vaccine a1) Two dose 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80), (4-6 weeks apart)	up to 60	n/a
12	Imperial GSTT	18-55	HIV positive adults a1) Two dose ChAdOx1 nCoV-19 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80), (4-6 weeks apart)	up to 60	n/a

4. SCOPE

This CSP applies to the named study for screening, enrolment, vaccination and routine follow-up study visits conducted in Oxford. This CSP does not cover the management of participants with possible or confirmed COVID-19 infection. This CSP will not cover group 3 and group 12.

5. DEFINITIONS/ ABBREVIATIONS

CCVTM	Centre for Clinical Vaccinology and Tropical Medicine
CSP	Clinical Study Plan
CTRG	Clinical Trials and Research Governance
DHSC	Department of Health and Social Care
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
HCP	Health Care Professional
GMO	Genetically modified organism
JWW	John Warin Ward, Churchill Hospital
OLS	Office of Life Sciences
OPD	Outpatients Department
OUH	Oxford University Hospitals
OVC	Oxford Vaccine Centre (Collaborating clinical trials unit of the Jenner Institute)
RA	Risk Assessment
TOPS	The Over Volunteering Prevention System
WOCP	Women of childbearing potential

6. RESPONSIBILITIES

CTRG	Monitors study to ensure compliance with the protocol.
DSMB	Monitors study to ensure safety of study participants.
Lead Clinical Research Fellow	Writes/reviews CSP and ensures all staff working on the study are trained.
Lead Nurse	Writes/reviews CSP and ensures all staff working on the study are trained. Responsible for the day to day running of study.
Other study personnel	Ensure that they are familiar with the current version of the CSP and follow the procedures described therein.
Principal Investigator	Reviews and approves the CSP.
University of Oxford	Sponsors the study.

7. Inclusion and Exclusion Criteria

A screening visit will be conducted for all participants in order to assess eligibility and inform the decision to include a volunteer in the study.

Adult participants will be assessed for presence of severe or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness, which would exclude them from study participation. Conditions that would be considered severe and exclude a participant from the study includes, but is not limited to, the list of comorbidities as given in Table 1. Any other comorbidities deemed severe or uncontrolled as determined by the clinical judgement of the Investigator would also exclude the participant from the study. Comorbidities assessed as mild or moderate and well controlled by the Investigator are permissible by protocol. In circumstances where there is uncertainty regarding the nature or severity of the medical co-morbidity, the participant may be excluded, at the discretion of the investigator. This may apply in the following circumstances:

- Where a new medical diagnosis has been recently established
- Where a new symptom, disorder or finding is currently under investigation
- Where there has been a recent change or deterioration in a symptom, disorder or finding

Females of childbearing potential are required to practice continuous effective contraception and have a negative pregnancy test on the day(s) of screening and vaccination. Females or women of childbearing potential (WOCP) will be defined as any pre-menopausal adult participant. Post-menopausal females will not be required to practice continuous effective contraception and will not undergo urine pregnancy testing. For the purposes of the COV002 study, a post-menopausal female will be defined as:

- Any female aged >55 years
- Any female aged 45-55 years (inclusive) with the last menstrual period >12 months ago with no alternative medical cause and not currently using hormonal contraception

Public Health England (PHE) have defined a group of 'clinically extremely vulnerable' individuals based on medical co-morbidities, who are at greater risk of severe illness from COVID-19 disease. To abide with public health measures, participants will be asked if they or a household member fall into this group. At the peak of the pandemic, these individuals should have been contacted and advised to "shield". Currently, government advice states that shielding has been paused for clinically extremely vulnerable groups, however local or national guidance of this may change in the future. PHE guidance should be referenced for the most up-to-date definitions of clinically extremely vulnerable groups and shielding recommendations for these individuals. (https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19)

Any potential participant who either meets, or has a household member that meets, the criteria of being extremely vulnerable to COVID-19 and has been advised to shield by the government will usually be excluded from the study, under the exclusion criterion, "Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data". However, where the participant's usual activities represent a greater exposure risk than participation in the study (e.g. frontline healthcare professionals), this would not prevent study participation. Clinical judgement will be applied to such cases in consultation with senior clinicians. During periods when government guidance does not advise shielding of the extremely vulnerable, this exclusion criteria will not be applicable.

Participants will need to attend the trial site if they develop symptoms of COVID infection. Individuals who would rely solely on public transport to attend a symptomatic visit may put members of the public at risk and so should not be enrolled to the study.

System	Comorbidity
Chronic respiratory disease	Chronic obstructive pulmonary disease (COPD) requiring long-term oxygen therapy Interstitial lung fibrosis Asthma with previous severe or life-threatening attack or requiring critical care admission Asthma requiring specialist therapies, e.g. theophyllines or on high dose steroid inhaler (see **Appendix B2 BTS categorisation of steroid inhaler doses**) COPD with day-to-day symptoms affecting quality of life or ≥1 hospital admission due to COPD exacerbation or ≥2 exacerbations requiring steroids +/- antibiotics in past year
Chronic heart disease	Unstable angina or recent myocardial infarction (NSTEMI or STEMI) Congenital heart disease requiring lifelong follow-up Congestive heart failure meeting criteria ≥ New York Heart Association Class III or Class C Symptomatic bradycardia Known cardiac condition with risk of sudden cardiac death, e.g. long QT syndrome, Brugada syndrome Cardiac condition requiring implantable cardioverter defibrillator (ICD), cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P)
Chronic kidney disease	Chronic kidney disease requiring dialysis
Chronic gastrointestinal disease	Severe inflammatory bowel disease requiring immunosuppressive therapies or biologics
Chronic liver disease	Chronic hepatitis Liver disease with presence of ascites, encephalopathy or renal involvement Cirrhosis
Chronic neurological disease	Recent (in last 6 months) stroke or transient ischaemic attack (TIA) Progressive neurological disorders e.g. motor neurone disease, myasthenia gravis, multiple sclerosis, Parkinson's disease Neurological conditions where respiratory function may be compromised e.g. cerebral palsy, quadraplegia or hemiplegia Seizure within last 2 years (controlled epilepsy if seizure-free for >2 years is permissible)
Diabetes	Uncontrolled diabetes, defined as most recent HbA1c >58where available
Other endocrinological disorders	Untreated thyroid disease Adrenal insufficiency on steroid replacement
Immunosuppression	HIV (except for group 12) Genetic disorders affecting immune system (IRAK-4, NEMO, complement disorder) History of organ or bone marrow transplant with ongoing immunosuppressive therapy Chemotherapy for active cancer
Asplenia or dysfunction of the spleen	Splenectomy Splenic dysfunction e.g. homozygous sickle cell disease

System	Comorbidity
History of cancer	Current diagnosis, treatment or ongoing follow-up of any cancer (except basal cell carcinoma or cervical carcinoma in situ)
Autoimmune/rheumatological disorder	Any systemic autoimmune or rheumatological disorder e.g. rheumatoid arthritis, systemic lupus erythematosus (SLE), systemic sclerosis, ITP. Coeliac disease is acceptable. History of Guillain-Barre syndrome Vasculitides
Chronic haematological disease	Myeloproliferative diseases and plasma cell disorders
Vascular disease	Recent history of malignant hypertension

Table 1 Medical comorbidities classed as severe for eligibility assessment for COV002 study

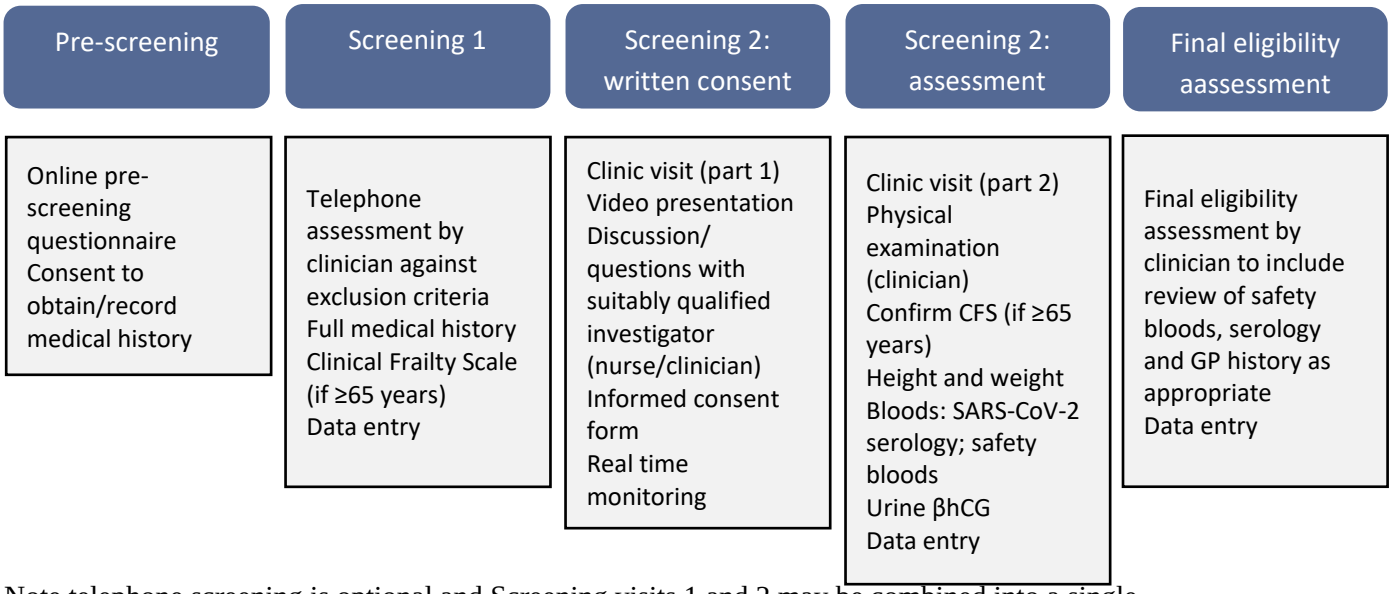
Participants will also be assessed for any history of a serious psychiatric condition likely to affect participation in the study. Psychiatric conditions, or a psychiatric history, as listed in **Error! Reference source not found.** would exclude participants from the study. Any other history of a serious psychiatric condition likely to affect study participation, as assessed by the Investigator, would also deem the participant ineligible. A history of admission to an inpatient psychiatric facility may exclude the volunteer if within the last 10 years and due to psychosis or severe depression with suicidal ideation/attempt, but if > 10 years ago and due to a psychiatric condition that is now well controlled it may be permissible to enrol the volunteer at the discretion of the Investigator.

Psychiatric disorders	Current or recent (in past year) severe depression Recent (in past year) suicidal ideation or suicide attempt Bipolar and related disorders Psychotic disorders including schizophrenia Personality disorders Current or recent alcohol or drug dependency Current or recent eating disorder Dementia or cognitive impairment Recent history of involvement of secondary or tertiary psychiatric care

Table 2 Psychiatric history and comorbidities deemed severe and likely to affect participation in the COV002 study

Members of staff (e.g. from OVG and the Jenner Groups) working directly on the COV002 trial will also not be allowed to take part in the study and would be excluded under the exclusion criterion, "Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data".

8. Screening Flow



Note telephone screening is optional and Screening visits 1 and 2 may be combined into a single physical visit.

9. Pre-screening questionnaire, response handling and screening bookings

Recruitment will be processed through an online screening system. Staff assisting in recruitment will receive specific training. Screening will be conducted according to SOP Participant Enrolment into Studies and as detailed below.

The following "high exposure" groups in the 18-55yrs cohort will be preferentially targeted:

- Hospital workers (including clinical staff, cleaners, porters, but excluding office workers)
- Social Care workers and care home workers (excluding office only staff)
- Primary care workers (including reception, but excluding office only staff)
- Other healthcare workers (including paramedics)

Volunteers are directed to the pre-screening questionnaire from adverts posted on email distribution lists, websites, posters, social media and other approved recruitment methods. On completion of the pre-screening questionnaire, if the volunteer is not eligible, an onscreen message will inform them of this fact. An invitation for telephone of physical screening visit will be issued for applications deemed potentially eligible.

All booked volunteers will be put on the Participant Management database with their booked screening dates and times. A screening number is generated by the online screening system and is solely for the use of participant response management. The screening number will not be used for any other purposes.

Participants invited to a physical screening visit will be sent a confirmation email containing essential information about their appointment with directions and a request for participants to bring an official form of photo ID, bank details, GP contact details and their National Insurance Number details or Passport. The email will also contain instructions for participants to minimise the amount of belongings they bring into the clinic, and will be advised to bring their own bottle of water. They will

be asked to NOT attend and cancel their screening appointment if they develop a fever, new onset cough or shortness of breath, or loss of smell or sense of taste, prior to the screening visit.

All volunteers will be sent reminder SMS for next day's appointments using the university SMS service and global templates that have been set up specifically for this study. These messages will include information about their appointment and instructions to NOT attend their visit should they develop potential symptoms of COVID-19 (fever, new onset cough or shortness of breath, or loss of smell or sense of taste).

10. Participant ID

Participants will be allocated sequential ID numbers at screening, which will be used throughout the study with a screening/enrolment log maintained on a secure server. This ID number will be retained throughout the study; no additional ID's will be issued. All samples and data entries will relate to this identification code. Participant ID will consist of:

Study theme (COV), study code (-02), site ID (01 (Oxford)) and individual ID XXXXX i.e. *COV-020100001*

11. Data entry of blood results

A data extract of blood results from the OUH blood result database (LIMs) is generated daily and passed to the data entry team for inputting using a two-pass verification ("double data entry") to ensure data integrity.

The daily data extract may also be used for the following purposes:

- Identify any missing blood results that may be added retrospectively to the laboratory request to avoid re-bleeding the volunteer
- Quality control (QC) and assurance (QA) processes by the internal monitoring/QA team

12. Screening 1 visit

If a participant is deemed eligible on the basis of response to the pre-screening questionnaire and consent has been obtained to collect and record information about medical history, a telephone screening will be conducted by a clinically qualified staff member. Volunteers will be questioned about their medical history in accordance with the inclusion/exclusion criteria (**see** Error! Reference source not found.**) and the 'Screening Part One' eCRF will be completed.**

History of recreational drug use will be assessed using clinical discretion, however, where recreational drug use is recent or current, participants will be asked to discontinue use for the duration of the study to be considered eligible for enrolment.

Eligibility of the participant will be assessed following the Screening 1 visit and advice of a senior clinician may be sought, where appropriate.

If the participant is deemed eligible following the Screening 1 visit, a Screening 2 visit will be arranged. The Investigator/assessing clinician needs to indicate at the end of the screening 1 CRF if a targeted examination is required, or if there are any aspects of the history that should be explored further in person at the Screening 2 visit.

If telephone screening is not carried out, during a physical screening visit both Screening Part 1 and Screening Part 2 eCRFs should be completed to cover both medical and social history and observations and examination as required.

13. Screening 2 visit

13.1. Informed consent procedures

For those participants aged <55ys (in Groups 4, 5, 6 or 11) this will be a combined single visit where a full history will be elicited in addition to taking consent, performing observations, taking bloods, urinary pregnancy test (where applicable) +/- an examination. For Groups 1, 6, 7, 9, 10 (>55yrs), the history (and so part eligibility assessment) will already have been elicited at the telephone Screening 1 visit, but all other named procedures will take place at the Screening 2 visit.

The Participant Information Sheet (PIS) will be made available to all participants prior to consent being obtained. To supplement the written information, participants will also either view a pre-recorded video presentation of the information within the PIS or will have a one-to-one discussion with a suitably qualified healthcare professional. Where used, the video presentation may be screened to small cohorts of participants, individually or it may be made available for participants to access it remotely. All participants will also have the opportunity for individual discussion with an appropriately trained and delegated researcher, and be able to ask any questions, prior to signing the Informed Consent Form (ICF). A medically qualified member of staff will be available at all times, should participants wish to discuss the study with a clinician before signing the ICF. Where this discussion takes place in an open setting such as the bays in John Warin ward, every attempt will be made to maintain privacy. **Please refer to Consent script and FAQ sheet.**

All female participants of childbearing potential will be required to consent to practicing continuous effective contraception for the duration of the trial. This will be re-emphasized when re-consenting them for a booster vaccination.

The research staff must complete the version and date of the participant information sheet before the participant signs.

Study Procedures *Please initial each line where you agree with the statement, tick No or N/A where not applicable or you don't agree*

1. I confirm that I have read, and understand, the Participant Information Sheet ages ___ to __ years pertaining to **COV002 Version**_____, **Dated**_____. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. **1**.....

Consent forms will be monitored in real time to ensure accurate completion of study paperwork. This will be particularly necessary during larger clinics. The monitor will review the consent form and request corrections in real time if needed be.

13.2. Collection of personal details

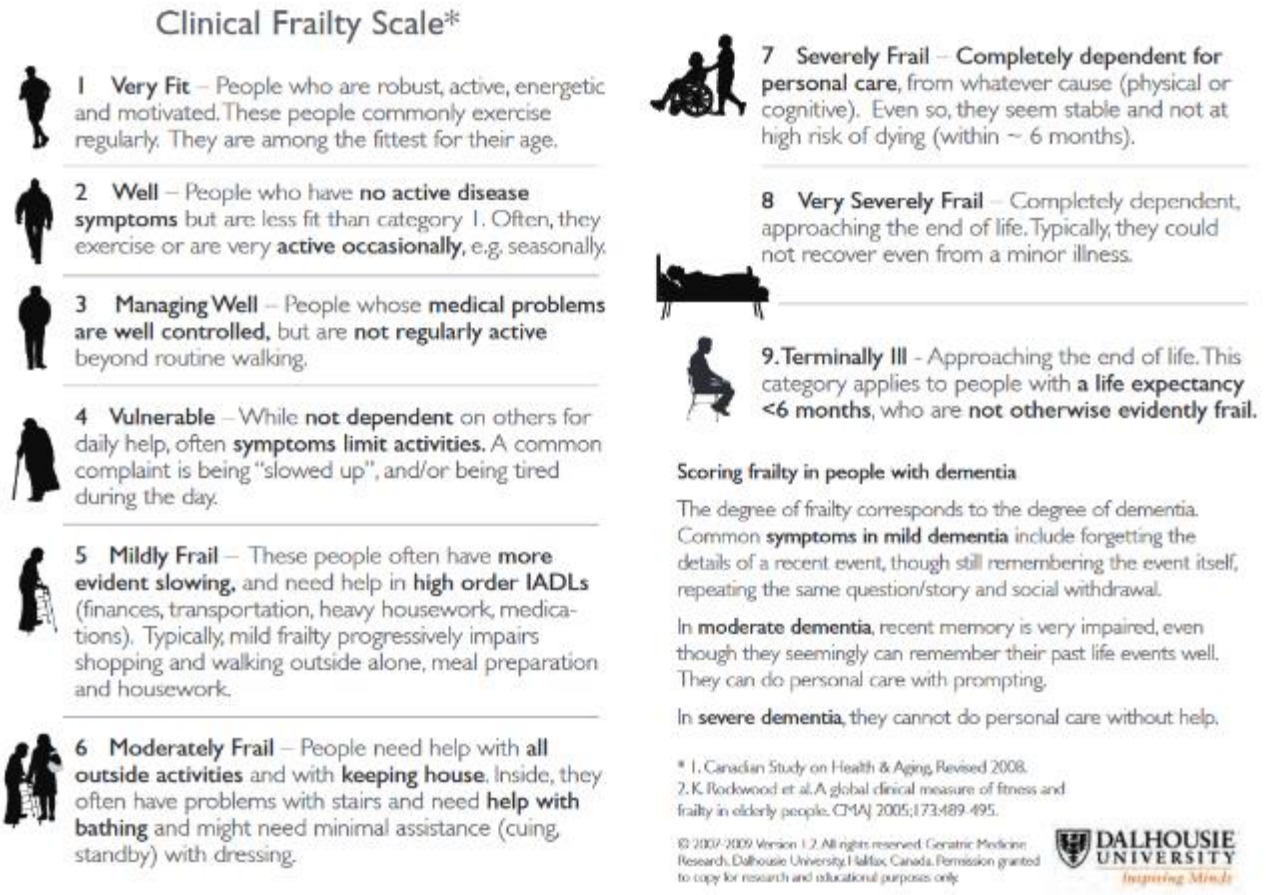
Personal details of volunteers, including bank details for compensation payments will be collected using the following generic documents:
To facilitate the flow of visits with large numbers of volunteers, participants may be asked to complete the forms ahead of signing the ICF. Any participants who decide they do not want to take part in the study will have their above forms destroyed and no personal data will be kept for volunteers who do not consent to be in the study.

13.3. Clinical assessments

If written consent is obtained, a targeted physical examination will be conducted, height and weight will be measured and blood tests will be taken. Urine pregnancy testing will also be performed for female participants of childbearing potential. Blood tests will include SARS-CoV-2 serology

screening test (all groups except in groups 5d, 9, 10 and 11) and safety bloods (in Groups 1, 5 & 7). Where not already obtained by phone, a medical history will also be taken.

For participants aged 65 years and older, the visit will also involve additional history for an initial assessment of frailty using the Clinical Frailty Scale (CFS, see below). Participants assessed as CFS 4 (Vulnerable) and above will be deemed ineligible for the study.



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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To avoid unnecessary additional venepuncture, if the appropriate safety blood test results for screening are available for the same volunteer from a screening visit for another study, these results may be used for assessing eligibility (provided the results date is within the 6 months preceding enrolment in COV002). SARS-CoV-2 serology testing should be conducted a maximum of 14 days prior to enrolment date, and ideally within 7 days of enrolment.

Observations will include temperature, heart rate, blood pressure and respiratory rate. Group 1 and 7 participants aged >55 years will routinely also undergo heart and lung auscultation, skin, abdominal, cervical lymph node examination. For participants in other groups, targeted examination may be performed at the discretion of the investigator. Vital signs that meet the grading scale (**Error! Reference source not found.**) will be highlighted to a medically qualified doctor. The examination, detection of abnormal findings and other medical notes/comments will be detailed in the Screening 2 CRF.

Height (to the nearest cm) and weight (to the nearest 0.1kg) will also be measured and BMI will be calculated automatically.

13.4. Sample collection – screening

Training requirements to be completed in order to be delegated are:	
Blood collection	Pre-existing competency/competency sign off for previously trained individuals
	Read *Screening Bloods training* document
Urinalysis	Read *Clinitek for urine and pregnancy test* document

Screening bloods will consist of:

Safety bloods Groups 1, 2, 5, 7 & 8	**Bottle**
2ml K3 EDTA tube for FBC	
3ml PSTII tube for biochemistry (U&E, LFTs)	
5ml SSTII tube for serology (HIV Ab/Ag, HCV Ab and HBsAg)	

All participants at screening (except groups 5d, 9, 10, 11)	**Bottle**
5ml SSTII tube for SARS-CoV-2 serology	

All samples should be collected in accordance with SOP (most recent version).

All safety blood specimens will be sent to the OUH laboratory using standard NHS request forms. Samples should be placed in the basket on CCVTM reception and will be transported by runners or collected by the hospital porters service during weekdays. For samples left after 4pm on weekdays, where porters are required, they should be phoned to collect them. Whenever possible, runners will take the blood samples to the Churchill hospital pathology labs. On weekends, samples will be transported from CCVTM to the OUH laboratories at pre-arranged pick up times.

SARS-CoV-2 serology will be conducted at screening (except in groups 5d, 9, 10 and 11). Samples collected for SARS-CoV-2 serology will be sent to the Oxford Vaccine Group laboratories for initial processing, before testing by the Jenner immunology laboratories. The COV002 Sample Collection Form should be used and samples should be placed in a BioJar for transportation from CCVTM clinical areas, in accordance with SOP. As Sample Collection Forms are carbon copy, participant IDs must be written in pen, and ID labels should not be used. Runners will take the blood samples to the Oxford Vaccine Group laboratories at regular intervals.

13.5. Sample labelling

In each participant screening CRF pack there is a sheet of labels for adding to sample forms and samples. When adding to sample tubes, fix the label lengthways.

13.6. Urine pregnancy testing

Urine pregnancy testing will be performed for female participants of childbearing potential using either the Clinitek analyser (SOP most recent version) or a regular non-instrument analysed pregnancy test. Print-outs of results (from the Clinitek analyser) will be attached to notes for review. Where a non-instrument analysed test has been performed the result will be recorded on paper as "pregnancy test negative or positive", dated and signed.

In the event of any borderline or positive test result, the result should be signed as “ineligible”. The participant should be informed of the result by a qualified medical professional and need for a repeat test due to the possibility of a false positive should be explained. A repeat urine pregnancy test with a fresh specimen of urine should be performed. If a second pregnancy test is borderline or positive, the participant result should be discussed with the participant by a qualified medical professional, reiterating the possibility of a false positive, and the participant should be advised to seek further testing and advice from the GP. Urine pregnancy testing results will be entered on the Screening 2 CRF.

13.7. Assessment of eligibility at Screening 2 visit

The eligibility of the volunteer will be reviewed throughout the Screening 2 visit. Ineligibility of a participant may become apparent either prior to written consent procedures or after consent has been obtained (e.g., abnormal finding on examination or measurement of observations). In all cases of exclusion at the screening visit, since consent for recording medical information has already been obtained at the pre-screening questionnaire, the reason for exclusion will be recorded using the appropriate sections of the inclusion/exclusion criteria within the Screening 1 or Eligibility CRFs and using the "Investigator comments" section in the Eligibility CRF. The paper exclusion paper document will also be completed. The administrative team will update the Access database using the paper exclusion document, as appropriate. Decisions to exclude the volunteer from enrolling in the trial will be at the discretion of the Investigator.

Hypertension:

If a participant has a blood pressure (BP) >160/90 at screening the below algorithm can be followed to aid in assessment of eligibility:

a. If known hypertensive on chronic antihypertensive medications with no recent history of malignant hypertension:
    i. Any BP <180 systolic and <95 diastolic is acceptable and there is no need for a second reading to confirm the measurements
    ii. If the BP is =>180 systolic or =>95 diastolic, the participant should be excluded
b. If NOT previously known hypertensive/ not on medications:
    i. BP =<160 systolic and <=90 diastolic is acceptable
    ii. If >160/90, repeat up to 3 times in clinic to exclude white coat hypertension
    iii. If persistently >160/90 exclude the participant and refer back to their GP (UNLESS in group 1/5/7 and there is a GP letter confirming no recent history of hypertension)

14. Assessment of SARS-CoV-2 serology results

SARS-CoV-2 serological testing results will be reported by the Jenner immunology laboratory team or Target Discovery Institute (TDI) testing team via email to the study inbox. All results received by email will be printed, reviewed and signed by a clinician then filed in the CRF. Results from the Jenner Immunology laboratory will be reported as either "likely seronegative", 'indeterminate' or "likely seropositive". The equivalent results from the TDI testing team will be reported as 'not-detected, 'equivocal' or 'detected' Any result designated "indeterminate/equivocal" or "likely seropositive/detected" will deem the participant ineligible and should be signed as such. Only "likely seronegative/not detected" results should be signed as "eligible".

15. Assessment of haematology, biochemistry and blood-borne viral serology test results

Blood results will be accessed via the OUH Case Notes system.

Results entered using the incorrect details by the OUH labs should be corrected in order to ensure appropriate data feed of results. If any results are phoned through as urgent due to results being out of the normal range, this call will go to the on call telephone to a study clinician.

Each day a named clinician will be tasked with reviewing and assessing all outstanding blood results. If bloods are abnormal, it should be documented whether any action is required and/or whether result

excludes the participant. This may be signed in person on the case notes printout or remotely by emailing a PDF of the case notes extract with confirmation of eligibility (see details for this process in **Error! Reference source not found.**).

Groups 1, 5 and 7 will undergo baseline haematology, biochemistry and blood-borne viral (HIV Ab/Ag, HCV Ab and HBsAg) screening blood tests to inform eligibility assessment. Further testing may be requested at the clinician's discretion. Any result other than a negative blood-borne viral screen will deem the participant ineligible. If a result is either positive or inconclusive, the volunteer will be informed of the result and appropriate medical care arranged with the permission of the volunteer.

Laboratory findings on haematology and biochemistry screening blood tests will be assessed by clinically qualified staff and guided by site-specific laboratory adverse event grading scales (**Error! Reference source not found.**). Any blood test result classed as grade 3 and above will deem the participant ineligible, with the exception of creatinine where this is in-keeping with previous results in known, stable chronic kidney disease. Laboratory results outside the normal range classed as grade 2 or below will be considered in the context of the medical history and recorded previous blood test results (e.g. as recorded on GP medical summary). Abnormal results which are in-keeping with known mild-moderate, stable chronic disease or likely transient and not clinically significant will be permissible, at the discretion of the Investigator. The advice of a senior clinician may be sought for clinical assessment of any blood test abnormality.

Any abnormal test result deemed clinically significant and not in-keeping with known chronic conditions and/or previous blood test results (e.g. as recorded on GP medical summary) may be repeated to ensure it is not a single occurrence. If an abnormal finding is deemed to be new and clinically significant, the volunteer will be informed, excluded from the study and appropriate medical care arranged with the permission of the volunteer.

Not all elements from full blood count reports are gradable (e.g. MCV, MCH, MCHC) and these are analysed within the broad clinical context. Isolated abnormalities to non-gradable variables on FBC do not require any further clinical action and are irrelevant for safety reporting procedures. These are treated as not clinically significant, provided the gradable variables are within normal or clinically acceptable ranges. Non gradable variables are therefore not recorded.

Given the large numbers of participants expected to express an interest in the study, priority should be given to volunteers who do not require a repeat blood test in order to confirm eligibility, however, repeat tests may be arranged at the discretion of the investigator. A repeat blood test may also be arranged for safety reasons, at the clinician's discretion, regardless of whether the participant may be enrolled.

16. GP letters and medical records

For all study Groups, GPs will be notified that the subject has volunteered for the study. For participants assessed as potentially eligible following screening for Groups 1 and 7 only, a GP letter will be sent requesting information about the medical history of the participant by a member of the admin team. The below template email will be sent to the named GP using the OVG NHS email account ensuring the subject heading includes the participant ID.

> *Dear Dr XXXX*
>
> *Please find enclosed an urgent request for a copy of the named individuals medical records (an EMIS brief summary would be ideal) with patient's consent on page 2. They have attended a screening appointment to assess eligibility to participate in a COVID-19 vaccine trial. Further information and a copy of their consent is included.*

*If you have any queries, please do not hesitate to contact one of the clinical trial team members on **XXXXXXXXX.***

GP summaries will come into the OVG NHS inbox. This will be monitored by the admin team who will print a copy of the GP summary when received, who will link to the participant ID and put a participant label on the print out. Once printed the team will record receipt of GP summary on Access and file email in the NHS inbox into the "GP summaries received" folder. Once GP letter and all results have been received for a participant, the CRF pack will be moved to "screened and ready for eligibility review" file.

17. Final eligibility assessment

The screening results query on the Access database will be used to generate list of participants who have attended screening visits and any outstanding result. This should be checked daily by the lead nurse/admin supporting the eligibility assessment pathway. A paper checklist will also be completed by a named research nurse or admin support as evidence that the below are complete before final eligibility assessment:

- SARS-CoV-2 result reviewed (where applicable)
- Safety blood results reviewed (where applicable)
- GP summary received (where applicable)
- Urine pregnancy result reviewed (where applicable)

Eligibility to participate in the trial will be reviewed by an appropriately delegated medically qualified doctor. Medical history, all results and the GP medical summary, where applicable, will be reviewed to make final eligibility assessment. For urine pregnancy tests, this will involve review of the original result to avoid assessment being made on the basis of results which have been incorrectly entered into the database and may not have yet been reviewed during the monitoring process.

The clinician's review of the medical summary, and any other results which have not already been reviewed, will be documented by a clinician's signature and date. The clinician will mark the GP summary as "eligible" or "ineligible" according to clinical judgement. If any new information relevant to eligibility assessment is evident from the GP letter, the clinician will enter this new relevant information into the screening eCRF. 'Relevant information' is information which in the clinician's judgement contributes either to a participant's ineligibility, or would be required for the management of the safety of the participant while on trial. Medical and scientific judgement will be applied in identifying non-relevant and relevant information.

The eligibility assessment against the trial inclusion and exclusion criteria will be made on the Eligibility eCRF. If the participant is excluded, the reason for exclusion should be clearly documented in "Investigator comments" in the Eligibility eCRF. There shall be one dedicated eligibility coordinator each day to oversee and deal with any queries. Any eligibility queries can be promptly discussed with a senior clinician, who will also be available daily. For Groups 1 and 7 no participant should be excluded at final eligibility check unless they have been discussed with a senior clinician. Any participant found to be ineligible will be informed by a trial clinician (by telephone or email). Following eligibility assessment, the assessing clinician will update the access database and complete the paper exclusion document, documenting here if participant has been informed.

CRF's of participants assessed as eligible will be filed in the "eligible to book", or "excluded" section of the study cupboard, as appropriate. A named individual (as per admin rota) will invite the participant to the vaccination visit and provide them with their study schedule of visits based on the group allocation.

18. Clinically significant incidental findings identified at screening or screening investigations

A clinically significant incidental finding may be identified either during the screening visit (i.e. on physical examination) or on the basis of investigations conducted as part of the screening procedure. Where the incidental finding is identified at the screening visit (Screening 2), the participant will be informed of the finding and potential clinical significance. Specific consent to inform the GP will be sought from the participant at the screening. Clinical findings and consent from the participant to inform the GP will be recorded within the "Investigator comments" of the Screening 2 CRF. It is the responsibility of the screening clinician to record the relevant details, discuss the findings with the participant and to ensure appropriate medical care arranged with the permission of the volunteer.

Where the incidental finding relates to results of investigations after the screening visit, communication of the result to the participant and arrangement of appropriate medical care within a clinically appropriate timeframe will be the responsibility of the clinician reviewing the result. The SOP (most recent version) provides guidance on what action should be taken when this occurs.

Where the incidental finding results in the exclusion of the participant, the relevant sections of the Eligibility CRF should be completed. In order to track incidental findings and action required, at the earliest opportunity, the clinician will also update the Access database to record what further action is needed, and will update again once this further action has been completed. A copy of any correspondence relating to arrangement of appropriate medical care (e.g. referral letter to GP), should be printed and filed in the participant CRF.

19. Group allocation

Enrolment and group allocation will be based on participant age and site of enrolment. Enrolment into groups 1 and 7 (adults 56-69 years old) will occur in Oxford and groups 2 and 8 (>70 years old) will occur in Southampton. Enrolment into group 4 and 6 will occur across all sites for adults aged 18-55 years first. Participants aged 56 and above will only be recruited into groups 9 or 10 following safety review of groups 1, 2, 7 & 8. Recruitment to Group 11 will be targeted at those volunteers who have previously received an alternative ChAdOx1 vectored vaccine.

20. Study enrolment

Volunteers will be considered enrolled in to the trial at the point of their first vaccination.

Before enrolment, the ongoing eligibility of the volunteer will be reviewed including checking for any new symptoms arising since the screening visit. Temperature will be taken and a urine pregnancy test will be performed on female participants of child bearing potential prior to vaccination. Pre-vaccination blood tests will be taken as per schedule of attendances.

If a volunteer has an acute respiratory illness (moderate or severe illness) and or a fever (oral temperature >37.8°C), the volunteer will be withdrawn from the study. If the participant is well, the 'Pre-vaccination' eCRF will be completed, including informed consent check. A clinician will confirm that the participant is fit to proceed to vaccination by completing COV002 Vaccine Authorisation. Randomisation of participant will then occur.

21. Randomisation

Randomisation will occur on a 3:1:3:1 ratio in groups 1 & 7 and 5:1:5:1 ratio in groups 2 & 8. Participants will be randomised on a 1:1 ratio in groups 4, 5, 6, 9 and 10. All participants in Group 11 will receive 2 doses of ChadOX01-nCOV19.

Randomisation will take place at the vaccination visit. Only study staff delegated to randomisation and preparing vaccines for administration will have access to this eCRF. Select electronic

randomisation method, date/time, appropriate study site then press the Randomise button to confirm that you wish to randomise the participant. Once confirmed, it will assign each participant to the vaccine that they are going to receive (either ChadOX01-nCOV19 or MenACWY).

22. Processes for Unblinding of Participants

The Lead Statistician has responsibility for creating and maintaining the master randomisation list. Randomisation of participants will be done as described in section **Error! Reference source not found.**. Participants will be blinded to the arm they have been allocated to, whether investigational vaccine or MenACWY. All study research nurses involved in vaccine administration will have access to the unblinded vaccination CRF..

If a member of the study team feels that the clinical condition of a participant requires unblinding, this must be discussed with the CI or a senior clinician. Once the decision to unblind has been confirmed, this can be done by:

- accessing the unblinded vaccination eCRF for the participant or
- opening the sealed envelope containing the participant's individual vaccine record in their paper CRF

All decisions and processes regarding unblinding will be documented on the Investigator comments CRF.

This system will be tested after the first 25 participants.

23. Storage and Preparation of ChAdOX1 nCOV19 and MenACWY vaccines

Storage and preparation of the IMPs will be as documented in COV002 Vaccine Storage and Preparation SOP and the Transport of Vaccines on Dry ice – COVID-19 trials SOP (most recent versions). The Vaccine Preparation page of the relevant Vaccine Record Form and vaccine accountability logs should be completed by the vaccine preparation team.

24. Vaccination

Vaccine administration will be recorded under the 'Vaccination' eCRF and on the COV002 Vaccination Administration page of the COV002 Vaccine Record form. Vaccinations will be administered intramuscularly according to site specific SOPs. After vaccination, the injection site will be covered with a sterile dressing. Participants will wait in the clinical area for at least 15 minutes to observe them for any immediate adverse reactions. The sterile dressing will then be removed and the injection site inspected. The '**Postvaccination 15mins**' eCRF should be completed to document the post-vaccination review.

25. GMO Vaccine Management

Waste, spills, needle stick injuries, splashes and recording of incidents involving a GMO vaccine is outlined in the SOP GMO Vaccine Management (most recent version).

26. Prophylactic paracetamol post vaccination

Participants enrolled into groups 4, 6, 9 and 10 will be advised to take prophylactic paracetamol 1g every 4-6 hours for 24 hours after vaccination to reduce possible reactogenicity from vaccination. This will not be a requirement for study participation, and participants will have the option to not follow the advice.

27. Participant e-diaries and post-vaccination take home packs

Participants in groups 1, 5, 7 & 11 will be set up with access to an e-diary for recording of post-vaccination solicited AEs for 7 days and unsolicited AEs for 28 days post vaccination. Only a subset of participants in groups 4, 6, 9, and 10 will be required to complete an e-diary for solicited and unsolicited AEs for 7 days post vaccination. The participant email is their username and their participant ID number is the password for the e-diary. Each volunteer will be provided with the following during the vaccination visit to take home:

- Medic alert card with participant ID and contact details for on-call team
- Oral digital thermometer
- Tape measure
- Back up paper diary if unable to generate access to e-diary
- self-swabbing packs and FAQs sheet

28. Booster vaccinations

Booster vaccinations are part of the planned vaccination schedule or will be offered to volunteers in all groups except groups 5b, 5c, 7a & 8a. Booster vaccinations should not be given if there are safety/medical contra-indications to boosting such as pregnancy. Participants who test positive for COVID-19 by PCR after their first vaccination should only receive a booster vaccination after a minimum of 2 weeks from the date of their 1st positive PCR test if asymptomatic; or at least 4 weeks if they were symptomatic at the time of their COVID-19 PCR test (in this case they need to be clinically well before receiving a booster vaccination). In participants who have recently received or are due a licensed influenza or pneumococcal vaccination, (trial) booster vaccination should be given at least 7 days after or before any influenza or pneumococcal vaccinations.

In those groups where booster vaccinations are optional - if participants decline a booster vaccination, they continue follow-up visits as per their original schedule of attendances. If participants undergo booster vaccination, subsequent follow-up visits are scheduled in relation to the date of their booster vaccination and these follow-up visits are termed ‘post boost’ or ‘PB’ visits (refer to schedule of attendances in protocol). Booster vaccinations will follow the original randomisation allocation from their 1st vaccination. Those participants initially receiving the control vaccine will be boosted with control vaccine. Participants who received ChAdOx1 n-CoV-19 will receive a second dose of ChAdOx1 n-CoV-19.

When participants from those groups, such as groups 4 & 6, in which booster vaccinations are optional attend for booster vaccinations, complete the relevant ‘Booster Option’ eCRF eg ‘**Group 4 & 6 Booster Option**’. Then complete ‘**PB Pre-vaccination**’ eCRF. Look up the participant’s original randomisation allocation from their 1st vaccination in the ‘Randomisation’ eCRF and prepare and administer the allocated vaccine. Complete ‘**Vaccination 2**’ and ‘**Postvaccination 15mins 2**’ eCRF. For subsequent post booster vaccination study visits, the relevant ‘PB review‘ eCRFs should be completed eg ‘**PB 28 Review**’ for the 28 days post booster vaccination visit.

In those groups in which booster vaccinations are scheduled at 4 weeks post prime, such as in groups 9, 10 & 11, participants will undergo booster vaccinations at their D28 visits. At the D28 visit, the ‘**D28 Review and Pre-vaccination 2**’ eCRF should be completed. The relevant booster vaccination eCRFs are ‘**Vaccination 2**’ and ‘**Postvaccination 15mins 2**’ eCRFs. For subsequent post booster study visits, the relevant ‘PB review’ eCRFs should be used eg ‘PB 28 Review’ for the 28 days post booster vaccination visit.

29. Routine Study Visit Procedures

Visit procedures and blood draws for each routine visit are specified for each group as per the schedule of attendances table. Participants in groups 1, 5 , 7 & 11 will be assessed for local and systemic adverse events, interim history, physical examination as required, review of diary cards until day 28 and blood tests for safety and immunology at the time points as detailed in the schedule of attendances. Participants in group 4, 6, 9 & 10 will only have blood tests taken for immunology at their routine clinic visits (no safety bloods).

At the start of each routine visit, check the identification of the participant and ongoing consent. Take the temperature and ascertain if the participant has been unwell and if they have had any symptoms consistent with COVID-19 infection. If the participant has had any of the following symptoms, they require testing for COVID as per the Symptomatic Participant Pathway (see Section 38 onwards): fever >37.8C, new persistent cough, shortness of breath, anosmia (loss of smell) and ageusia (loss of taste).

If the participant is unwell with non-Covid symptoms, following medical history and examination by a clinician and safety bloods and immunology bloods if possible, the ongoing clinical management of the participant should be discussed with the oncall consultant.

Otherwise during a routine visits staff should:

- Ascertain any solicited and unsolicited adverse events and record and grade
- Check participant's e-Diary (applicable to only a subset of group 4, 6, 9 or 10)
- Take blood tests as per visit schedule
- Remind volunteer of next appointment and counsel regarding on call trial phone

If a participant is due to attend for a routine visit but they are self-isolating as per current PHE guidelines (e.g. due to symptomatic household contacts or due to being symptomatic themselves), then this visit may be performed as a telephone and/or video consultation instead.

32.1. Sample collection – pre-vaccination and routine visits

All samples should be collected in accordance with SOPs and the most recent version of the COV002 laboratory manual. Bloods samples should be labelled with the pre-printed labels found in each participant's CRF pack. Affix the label lengthways on the blood tubes. All safety/HLA specimens will be sent to the OUH laboratory using standard NHS request forms. Exploratory immunology specimens will be sent to OVG labs. For transportation of samples to OUH and OVG labs, completion of request cards and blood forms see SOP for Transport of Samples in the Community.

32.2. Weekly surveillance PCR for Covid-19

Subject to availability of resources and assay validation, participants will be requested to submit a weekly sample for COVID-19 PCR. This may be either a self-collected nasopharyngeal swab or saliva sample. Participants will be given a link to a NHS video which shows how to collect the appropriate specimen prior to their vaccination visit (https://www.youtube.com/watch?v=8lo6g-TYZ-c). The process is then as follows:

1. At the vaccination visit, participants will be provided with information on how to take a self-swab (using self-swab kit instructions).
2. Participants will be given 4 packs of swabs to take home – each of these will contain a swab, an instruction leaflet, appropriate packaging/postage and sample labels.
3. At weekly intervals, starting at day 7 post vaccination, participants will perform a self-swab, register their details on the Department of Health and Social Care (DHSC) website and return

these via post to a central Office of Life Sciences (OLS) lab (Milton Keynes Lighthouse initially).

4. A reminder text/email will be sent to the participant every week to ask them to collect the sample.
5. The participant's results will be texted/emailed directly to them by OLS. The participant will be asked to inform us of any positive result upon their receipt.
6. Further packs will be handed to the participants at subsequent clinic visits as required.
7. If a swab from an asymptomatic volunteer is positive, they will be advised to self-isolate as per the latest PHE advice from the date of the first positive swab. If they are a HCW, they need to seek local occupational health guidance which will take precedence. Participants will be advised to contact the vaccine study administration team within working hours if they have a vaccine follow-up visit planned when they are due to be self-isolating. They do not need otherwise need to contact the study team unless they become symptomatic.
8. PCR results from the OLS labs will be communicated to Oxford. This data will be sorted by participant location and will be disseminated to sites.

See Symptomatic Pathway CSP (most recent version) for further details on processes relating to results of swabs, stool sample collection on PCR +ve individuals, processes for volunteers informing trial staff of swab results taken outside the trial and detailed guidance on self-isolation in different circumstances.

33. Participant safety - Participant e-diaries

E-diaries will be set up and kept for 28 days from prime vaccinations and again for booster vaccinations where applicable for groups 1, 5, 7 & 11. A subset of participants in groups 4, 6, 9, and 10 will be required to keep an e-diary for 7 days only. Participants should be asked to complete their e-diaries by 10pm at night to facilitate review by study staff the next day**.** Any diary AEs of Grade 3 or higher will automatically trigger an email to the Lead Study Doctor and the delegated clinical safety team. This dedicated clinical safety team will minimise the risk of inadvertent investigator unblinding. The clinical safety team will be responsible for reviewing participants' e-diary responses and following up any actions from arising from these.

34. Participant safety - Blood results

Each day a team of named clinicians will be tasked with accessing CaseNotes to review safety blood results of the participants who had a study visit on the previous day. The same procedures as for looking up safety blood tests from screening should be followed (see section **Error! Reference source not found.** and**Error! Reference source not found.**). If any results are phoned through as urgent due to results being out of the normal range, this call will go to the on call telephone held by a study clinician. Any laboratory AEs of Grade 3 or higher will automatically trigger an email to the Lead Study Doctor and a delegated cohort of the Clinical Study Team. For grading of laboratory abnormalities see **Error! Reference source not found.**.

All **Grade 1- 2** Laboratory Adverse Events

- Reviewed by clinical doctor to determine clinical significance and whether further action (e.g. repeat blood sampling) is required.

All **Grade 3-4** Laboratory Adverse Events:

- Discussion with senior study clinician +/- CI and prompt action including possible medical referral.
- **Grade 3**: Consider whether needs to be reported as a Serious Adverse Event (SAE).
- **Grade 4**: Report as Serious Adverse Event (SAE).

All clinically significant discussions and actions taken must be documented in the participant eCRF. All SAEs must be entered as new line listing on the 'Adverse Event' eCRF.

35. Household questionnaire

All participants except healthcare workers, will be asked to complete a weekly questionnaire to monitor their exposure to COVID-19 in the community. Completion of this will be monitored at intervals by the study team and reminder texts or emails sent as required.

36. Unscheduled Visits

In the event of an unexpected or serious adverse event, a participant may need to have unscheduled clinic visits. These visits would have the same format as subsequent visits and safety bloods may be sent at these visits, at the discretion of the investigator. Unscheduled reviews may also take the form of a telephone and/or video consultation according to investigator discretion. All communication regarding an unscheduled visit (including phone calls and emails preceding the visit) should be clearly documented in the eCRF under 'Investigator Comments' and 'Extra Blood Results'. Participants should be encouraged to contact their GP with all medical concerns as they usually would, if it cannot be dealt with appropriately by the study team.

37. Reporting of Adverse Events and Serious Adverse Events

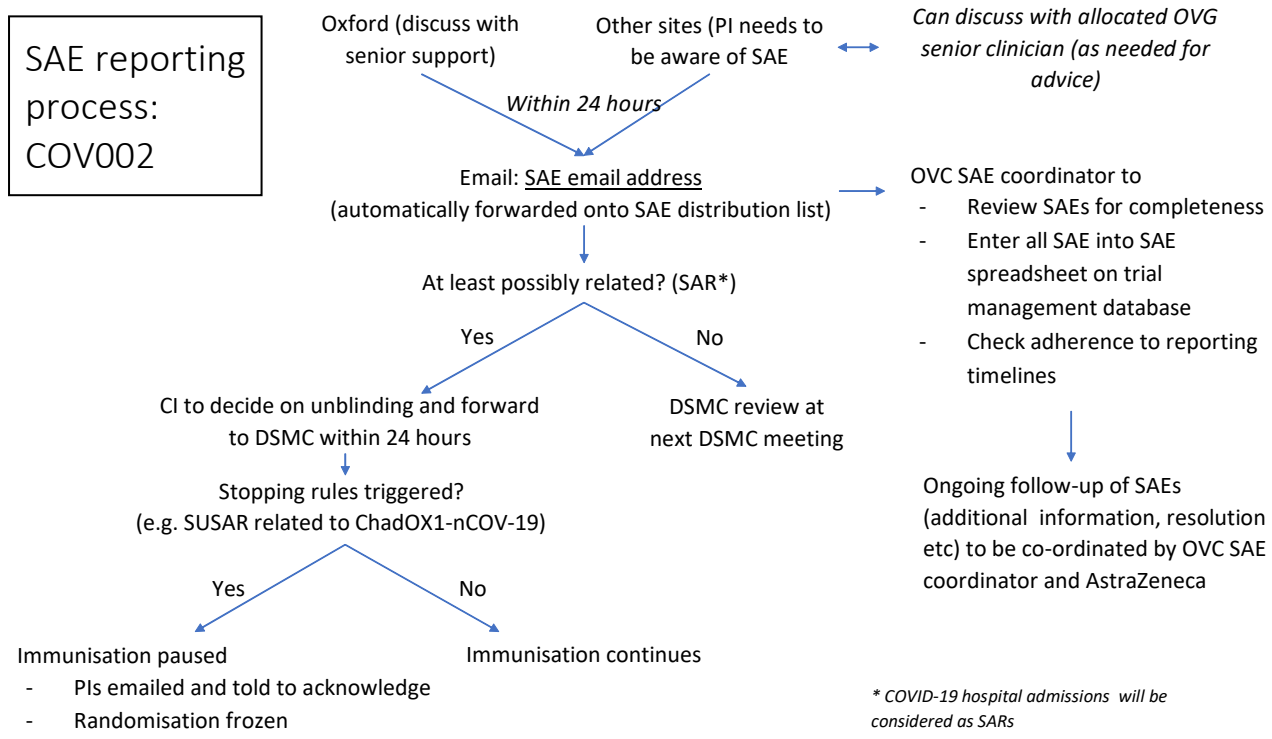
For definitions of Adverse Events (AE), Adverse events of special interest (AESI), Serious Adverse Events (SAE), Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reactions (SUSAR) refer to the protocol.

AEs should be recorded in the 'AE' eCRF:

- Enter only one diagnosis (if known) or medical term per log line (single AE eCRF form). For example, a diagnosis of influenza should be entered, not the individual symptoms (cough, fever, sore throat). For additional AEs, a new AE eCRF form should be used.
- If a diagnosis is not known and symptoms are entered, then only 1 symptom should be entered per log line (eg abdominal pain)
- Use standard medical terminology
- Provide a clear, concise description of a single event. Include qualifying text to enhance the medical meaning (right vs. left; increased vs. decreased; etiology/cause of event).
- Provide specific information rather than a general term when possible. For example, otitis should specify in the AE term the location as otitis media. For thrush, the location should be specified in the AE term as oral thrush.
- Viral illness: indicate the location of the viral illness (viral lower respiratory tract infection, viral gastroenteritis, etc.).
- For any bacterial infections, please provide infectious organism, if known. For example, pneumococcal pneumonia.
- Do not use abbreviations or acronyms
- Only enter events that are deemed clinically significant on the AE page. Physical exam findings and laboratory results should only be entered if they are clinically significant.

All SAEs must be entered as new line listing on the 'AE' eCRF. Of note all grade 4 laboratory AEs should be reported as SAEs and under the category of outcome of an important medical event. The exception to this is eosinophilia of ≥ 1.5 x10^9/L, which is a grade 2 laboratory AE but should be reported as an SAE because it is an AESI. No IMP related SAEs are expected in this study and all SARs should therefore be reported as SUSARs.

For reporting procedures, refer to SOP Safety Reporting for CTIMPs (most recent version). SAEs are required to be reported to the Chief Investigator at Oxford within 24 hours of becoming aware of the event and SAE reporting forms should be sent to the SAE email address. If this is deemed to be at least possibly related to the IMP it will be classified as a SUSAR (as there are no expected SARs to the IMP). The CI will then decide on whether to unblind and will forward to the DSMC within 24 hours of becoming aware. If stopping rules are triggered, immunisations will be halted pending further assessment by the DSMC. The flow-chart below gives further details on the process:



38. Pregnancy

If a volunteer becomes pregnant at any point in the study they will not receive any further doses of the IMP but will remain in the study for safety follow-up and attend routine study visits (which can be conducted as phone reviews). Pregnant participants should enter the symptomatic pathway if they develop symptoms of COVID-19 (refer to COV001/COV002 symptomatic pathway CSP). There should be a very low threshold for discussion of any symptomatic, pregnant participants with the on call senior clinician. Pregnant participants will not have any further venepunctures, other than for safety reasons/ clinical need (eg safety blood tests will be done at an S0 visit) but no bloods will be taken for immunology at any study visit.

Pregnant participants will be followed up until pregnancy outcome and/or until 3 months post-partum. No participant should be withdrawn because of pregnancy, unless this is specifically requested by the participant.

In the event that a participant becomes pregnant, complete the '**Pregnancy Notification**' eCRF.

39. Infection Control

Procedures for infection control will be as per SOP (COVID-19 PPE and Infection Control). Participants will be attending study visits in small groups and may be asked to wait in their transport if they arrive early to minimise the number of people in waiting rooms. Waiting areas, consent presentation areas and post-vaccination observation areas will have seating arranged to ensure

appropriate social distancing. Wherever possible and where rotation of staff is necessary to retain rapid flow, participants will remain in situ and the staff will rotate. Appropriate disinfection procedures of participant chairs, high touch surfaces and medical equipment will take place after consultation. Hand basins and alcohol rub will be widely available. Where participants require use of pens for study visits, a new pen will be supplied to each participant to minimise risk of cross infection. Following completion of any study visit, participants will be required to exit the building to avoid overcrowding in waiting areas.

40. Staff Safety

Any member of staff exposed to infection by needle-stick injury should contact the Occupational Health Department for advice. If urgent advice is needed out-of-hours, please attend the A&E department at the John Radcliffe Hospital for risk assessment and further management. Any member of staff who develops clinical symptoms consistent with COVID infection will be offered screening as described in Symptomatic Staff SOP (most recent version).

41. Study Staff Training

All study staff will complete training in the iPassport system to document their readiness for delegation. The appropriate tasks will be sent to staff by the project manager or senior research nurse. Training must be done prior to delegation and commencement of work on study. Training requirements will be dictated by the training matrix and include reading and face to face sessions.

42. References

Trial Protocol: COV002 version 13.0

43. Appendices

Appendix A: Template letter to GP regarding abnormal results

Date:

Dear Dr

Re: DOB:

Participant number:

The above named person has expressed an interest in taking part in a clinical trial and has identified you as their GP. They have attended a screening appointment to assess eligibility to enter a phase I/II study to determine efficacy, safety and immunogenicity of the candidate COVID-19 vaccine ChAdOx1 nCoV-19 in healthy adult volunteers.

During screening participants undergo physical examination, blood and urine examination.

As a result of screening the following abnormality was found:

……

We would be very grateful if you could

……

This person has been excluded from the trial.

If you have any queries, please do not hesitate to contact one of the clinical trial team members on [redacted]

Yours sincerely,

Clinical Research Fellow

Oxford Vaccine Centre

Appendix B1: Screening 1 telephone screening script

This script is intended as a guide for Screening 1 visits when conducted by telephone. Throughout the visit, appropriate language tailored to the individual participant should be used to aid understanding. The responses from the completed pre-screening questionnaire should be available and used as a reference for the call, and to aid data entry.

1. Hello, my name is [name and role] from the COVID-19 vaccine trial team. I am calling to speak to [name of participant], can I confirm that is you?

Confirm name and date of birth against pre-screen questionnaire responses and thank participant.

2. In today's call, I will be asking some questions relating to your personal details and medical history, in order to assess your eligibility to take part in the study. The information will be recorded in the study database. You will also have the opportunity to ask any questions you have about the study. Would this be ok with you?

If no, do not proceed, if yes record confirmed verbal consent in Screening 1 CRF and thank participant.

3. Firstly, have you had a chance to read the Participant Information Sheet? Do you have any questions you would like to ask about the study?

Answer any questions raised at this stage. Refer to FAQs as necessary.

4. We can also now confirm that participants in the study would be taking part in weekly swab testing as part of the home testing pathway conducted by the DHSC. The aim is to detect if participants have COVID-19 each week. This would involve taking a swab of the throat and front of the nose on a weekly basis, and sending this back to a central lab in the post. Initially, this will be for a minimum of eight weeks but may be extended for a longer period. Would this be something that you would be happy to do? Do you have any questions on this?

   Answer any questions and refer to FAQs as necessary. Explain that further information and opportunity for questions will be given at the clinic screening visit. If the participant is not able or not willing to take weekly self-swab study procedures, the participant would be excluded - explain the rationale, answer any questions and end call, ensuring that the Screening 1 CRF is saved as complete.

5. I would now like to ask you a few initial screening questions.

Complete demographics section and exclusion criteria sections of Screening CRF.

N.B. For exclusion criterion concerning any confirmed or suspected immunosuppressive or immunodeficient state, this should be asked as a series of questions as follows:

   I. Do you have any problems with your immune system?
   II. Do you have any problems with your spleen?
   III. Have you had any repeated, severe infections?
   IV. Have you taken any medication that suppresses your immune system in the last 6 months?
   V. Have you had any steroid treatment in last 6 months (topical steroids or short-term oral steroids for ≤14 days are allowed)? **Note that anyone on high dose inhaled steroids should be excluded – see Appendix B2 for reference.**

   If any exclusion criteria met, explain that participant would not be eligible to take part in the study and the rationale. If no exclusion criteria met, proceed with visit.

6. I would now like to ask you some more detailed questions about your medical history.

If any medical comorbidity is identified under any question, the interviewer should check with the participant if they have any other relevant condition before moving on to the next question.

a) Have you ever had any problems with your heart, blood pressure or any vascular disease?
b) Have you ever been diagnosed with any respiratory disorders or had any problems with your breathing?
c) Do you have diabetes?
d) Do you have any kidney problems?
e) Have you ever had a stroke or a mini stroke?
f) Have you ever had any problems affecting the stomach or digestive system?
g) Have you ever had any problems with your liver or gallbladder?
h) Have you ever been diagnosed with an endocrine (or hormonal) disorder?
i) Have you ever had any medical problems affecting your brain or nervous system?
j) Have you ever had cancer?
k) Do you see your GP regularly for anything not already mentioned?
l) Do you currently see a specialist for any medical condition?
m) Have you ever seen a specialist for any condition or been investigated for any reason?
n) Any other medical diagnoses other than anything already discussed?
o) Have you ever had any operations?
p) Have you ever had any problems with your mental health or ever seen a psychiatrist or psychiatric team?
q) Since February 2020, have you experienced any new, persistent cough, fever, new shortness of breath or change to your sense of smell or taste, or any other cold or flu-like illness?
r) Have you had any contact with anyone who was confirmed to have COVID-19?

Complete remainder of CRF including previous clinical trial participation, medications, allergies, smoking and alcohol history plus social history for participants aged 65 and older and contraception history for pre-menstrual females.

7. On the basis of today's call:
   a) You may be eligible to take part in the study and we would like to invite you to a screening visit at the clinic. This will involve watching a presentation with information about the study, signing a consent form, temperature check, blood tests, physical examination (and for WOCP only urine pregnancy test). The appointment will take approximately 1 hour. Would you be available to attend on [date and time of appointment]?

(If eligible, book in a Screening part 2 visit with volunteer over the phone using COVID Sharepoint calendar and inform participant they will receive a confirmation email with details of where to attend.)

   b) Unfortunately, you would be ineligible to take part in the study.

If ineligible, explain the rationale to the participant and answer any questions. Complete the relevant sections of the Eligibility CRF and save as complete.

8. That completes today's visit. If you haven't done so already, please do make sure to read the Participant Information Sheet carefully before attending your screening vist. Do you have any further questions?

Answer any further questions, refer to FAQs as necessary, thank participant and end call. Ensure Screening 1 CRF is saved as complete.

Appendix B2: BTS Categorisation of Inhaled Corticosteroid Doses

ICS	Dose		
	Low dose	Medium dose	High dose#
Pressurised metered dose inhalers (pMDI)			
Beclometasone dipropionate			
Non-proprietary	100 micrograms two puffs twice a day	200 micrograms two puffs twice a day	200 micrograms four puffs twice a day
Clenil Modulite pMDI	100 micrograms two puffs twice a day	200 micrograms two puffs twice a day	250 micrograms two puffs twice a day 250 micrograms four puffs twice a day
Kelhale pMDI (extrafine)	50 micrograms two puffs twice a day	100 micrograms two puffs twice a day	100 micrograms four puffs twice a day
Qvar pMDI (extrafine) Qvar Autohaler (extrafine) Qvar Easi-Breathe (extrafine)	50 micrograms two puffs twice a day	100 micrograms two puffs twice a day	100 micrograms four puffs twice a day
Soprobec pMDI	100 micrograms two puffs twice a day	200 micrograms two puffs twice a day	250 micrograms two puffs twice a day 250 micrograms four puffs twice a day
Ciclesonide			
Alvesco pMDI	80 micrograms two puffs once a day	160 micrograms two puffs once a day	160 micrograms two puffs twice a day
Fluticasone propionate			
Flixotide Evohaler	50 micrograms two puffs twice a day	125 micrograms two puffs twice a day	250 micrograms two puffs twice a day
Dry powder inhalers (DPI)			
Beclometasone			
Non-proprietary Easyhaler	200 micrograms one puff twice a day	200 micrograms two puffs twice a day	n/a
Budesonide			
Non-proprietary Easyhaler	100 micrograms two puffs twice a day	200 micrograms two puffs twice a day	400 micrograms two puffs twice a day
Budelin Novolizer	n/a	200 micrograms two puffs twice a day	200 micrograms four puffs twice a day
Pulmicort Turbohaler	100 micrograms two puffs twice a day 200 micrograms one puff twice a day	200 micrograms two puffs twice a day 400 micrograms one puff twice a day	400 micrograms two puffs twice a day
Fluticasone propionate			
Flixotide Accuhaler	100 micrograms one puff twice a day	250 micrograms one puff twice a day	500 micrograms one puff twice a day
Mometasone			
Asmanex Twisthaler	200 micrograms one puff twice a day	400 micrograms one puff twice a day	n/a

ICS	Dose		
	Low dose	Medium dose	High dose#
Combination inhalers			
Beclometasone dipropionate (extrafine) with formoterol			
Fostair (pMDI)	100/6 one puff twice a day	100/6 two puffs twice a day	200/6 two puffs twice a day
Fostair (NEXThaler)	100/6 one puff twice a day	100/6 two puffs twice a day	200/6 two puffs twice a day
Budesonide with formoterol			
DuoResp Spiromax	160/4.5 one puff twice a day	160/4.5 two puffs twice a day 320/9 one puff twice a day	320/9 two puffs twice a day
Symbicort Turbohaler	100/6 two puffs twice a day 200/6 one puff twice a day	200/6 two puffs twice a day 400/12 one puff twice a day	400/12 two puffs twice a day
Fobumix Easyhaler	80/4.5 two puffs twice a day 160/4.5 one puff twice a day	160/4.5 two puffs twice a day 320/9 one puff twice a day	320/9 two puffs twice a day
Fluticasone propionate with formoterol			
Flutiform MDI	50/5 two puffs twice a day	125/5 two puffs twice a day	250/10 two puffs twice a day
Flutiform K-haler	50/5 two puffs twice a day	125/5 two puffs twice a day	n/a
Fluticasone propionate with salmeterol			
Aerivio Spiromax	n/a	n/a	500/50 one puff twice a day
AirFluSal Forspiro	n/a	n/a	500/50 one puff twice a day
AirFluSal pMDI	n/a	125/25 two puffs twice a day	250/25 two puffs twice a day
Aloflute pMDI	n/a	125/25 two puffs twice a day	250/25 two puffs twice a day
Combisal pMDI	50/25 two puffs twice a day	125/25 two puffs twice a day	250/25 two puffs twice a day
Fusacomb Easyhaler	n/a	250/50 one puff twice a day	500/50 one puff twice a day
Sereflo pMDI	n/a	125/25 two puffs twice a day	250/25 two puffs twice a day
Seretide Accuhaler	100/50 one puff twice a day	250/50 one puff twice a day	500/50 one puff twice a day
Seretide Evohaler	50/25 two puffs twice a day	125/25 two puffs twice a day	250/25 two puffs twice a day
Sirdupla pMDI	n/a	125/25 two puffs twice a day	250/25 two puffs twice a day
Stalpex Orbicel	n/a	n/a	500/50 one puff twice a day
Fluticasone furoate with vilanterol			
Relvar Ellipta	n/a	92/22 one puff once a day	184/22 one puff once a day

* Different products and doses are licensed for different age groups and some are not licensed for use in children. Prior to prescribing, the relevant summary of product characteristics (SPC) should be checked (www.medicines.org.uk/emc).

High doses (shaded boxes) should only be used after referring the patient to specialist care.

Ref: BTS/SIGN Asthma Guideline Table 13: Categorisation of inhaled corticosteroids by dose:

https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/

Appendix C: Blood results review pathway

In-office working

1. Member of the clinical or administrative team uses the screening blood results tracker query on Access database and the COV001 calendar (additional bloods) to generate the list of participants with any outstanding blood results (biochemistry, haematology and/or microbiology).
2. Member of the clinical team (or medical student) prints all outstanding results (biochemistry, haematology and serology) via Casenotes (may be performed by a member of the clinical team or a medical student).
3. All bloods are reviewed by a trial clinician:
    i. Clinician collects printed results
    ii. Clinician signs all blood results reviewed, actions any abnormal results and updates Access database.
    iii. Clinician checks that all outstanding results have been reviewed using Access database and COV001 calendar.
    iv. Signed blood results are placed in the tray for filing and admin team will file in screening packs

Home working

(Note: any action required should also be completed by the reviewing clinician working remotely, where this is not possible, this should be verbally handed over to a clinician working in office)

1. Clinician runs screening bloods results query on access to generate the list of participants with outstanding results (biochemistry, haematology and/or microbiology).
2. Results are reviewed via Casenotes and actioned as required.
3. In lieu of signature, clinician sends email to study inbox with subject heading: Blood results – [Participant ID]
4. A PDF of the results from Casenotes should be attached to each email.
5. The following template is used for the text of each email:
    a. FBC/Biochemistry/Serology (deleted as appropriate) reviewed and acceptable

    OR

    b. FBC/Biochemistry/Serology (deleted as appropriate) not acceptable
    c. Abnormal results – yes/no, if yes detail action required
    d. Where relevant, the email should also state if the participant has been excluded, giving the reason
6. Admin team member will print the email and PDF, file in CRF pack and update Access database.

Repeat bloods

Repeat or additional blood tests may be performed at the discretion of the investigator. Where required, participants may be booked in at 9am on any day of the week via the COV002 calendar – all bookings should state the full participant number and the test needed, e.g. COV-0201XXXX repeat FBC. Appointments for repeat blood tests will also be recorded on the Access database. Wherever possible, the numbers of participant booked in for repeat bloods on any given day will be kept to a maximum of 3 participants, however, this will be flexible depending on clinical urgency to repeat a blood test. Results from repeat bloods will be reviewed by a clinician on the same day. Completion of visits will be tracked via the Access database in order to facilitate participant compensation payments.

Appendix D: Severity Grading of AEs

GRADE 0	None
GRADE 1	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
GRADE 2	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
GRADE 4	Potentially Life-threatening: requires assessment in A&E or hospitalisation

This table is taken from the protocol and is added to this for reference only.

Appendix E: Severity grading criteria for physical observations

Vital Signs	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**	**Grade 4 Potentially Life threatening**
Fever (oral)	38.0°C - 38.4°C	38.5°C – 38.9°C	39.0°C - 40°C	> 40°C
Tachycardia (bpm)*	101 – 115	116 – 130	>130	A&E visit or hospitalisation for arrhythmia
Bradycardia (bpm)**	50 – 54	45 – 49	<45	A&E visit or hospitalisation for arrhythmia
Systolic hypertension (mmHg)	141 – 150	151 – 155	≥155	A&E visit or hospitalization for malignant hypertension
Diastolic hypertension (mmHg)	91 – 95	96 – 100	>100	A&E visit or hospitalization for malignant hypertension
Systolic hypotension (mmHg)***	85 – 89	80 – 84	<80	A&E visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21-25	>25	Intubation

Table 3 Severity grading criteria for physical observations (applies to adults only).

**Taken after ≥10 minutes at rest **When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterising bradycardia among some healthy subject populations, for example, conditioned athletes. ***Only if symptomatic (e.g. dizzy/ light-headed)*

Hypoxia as measured by saturations will be graded according to following criteria

	Grade 1 (mild)	**Grade 2 (moderate)**	**Grade 3 (severe)**	**Grade 4 (life threatening)**
Hypoxia (oxygen saturations)	95-96%	93-94%	92% or lower	imminent respiratory arrest

Appendix F - Severity grading criteria for laboratory abnormalities

Haematology			**Lab Range**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin Absolute	**Male**	g/l	130 – 170	115-125	100-114	85-99	<85
Haemoglobin Absolute	**Female**		120 – 150	105-113	90-104	80-89	<80
Haemoglobin Change from Baseline (Decrease)			n/a	10-15	16-20	21-50	>50
White Blood Cells	**Elevated**	x109/l	11	11.5-15.00	15.01-20	20.01-25	>25
White Blood Cells	**Low**		4.0	2.5-3.5	1.5-2.49	1.0-1.49	<1.0
Platelets	**Low**		150-400	125-140	100-124	25-99	<25
Neutrophils	**Low**		2.0-7.0	1.5-1.99	1.0-1.49	0.5-0.99	<0.50
Lymphocytes	**Low**		1.0-4.0	0.75-0.99	0.5-0.74	0.25-0.49	<0.25
Eosinophils	**Elevated**	x109/l	0.02 - 0.5	0.65-1.5	1.51-5.00	>5.00	Hypereosinophilia
Biochemistry							
Sodium	**Elevated**	mmol/l	145	146-147	148-149	150-155	>155
Sodium	**Low**		135	132-134	130-131	125-129	<125
Potassium	**Elevated**	mmol/l	5	5.1-5.2	5.3-5.4	5.5-6.5	>6.5
Potassium	**Low**		3.5	3.2-3.3	3.1	2.5-3.0	<2.5
Urea	**Elevated**	mmol/l	2.5 - 7.4	8.2-9.3	9.4-11.0	>11.0	Requires dialysis
Creatinine	**Elevated**	µmol/l	49 – 104	1.1-1.5xULN 114-156	>1.5-2.0xULN 157-312	>2.0xULN >312	Requires dialysis
Bilirubin	**Normal LFTs**	µmol/l	0-21	1.1-1.5xULN 23-32	>1.5-2xULN 33-42	>2-3xULN 43-63	>3xULN >64
Bilirubin	**Abnormal LFTs**	µmol/l	0 – 21	1.1-1.25xULN 23-26	>1.25-1.5xULN 27-32	>1.5-1.75xULN 33-37	>1.75xULN >37
ALT		IU/l	10 – 45	1.1-2.5xULN 49-112	>2.-5xULN 113-225	>5-10xULN 226-450	>10xUPN >450
Alk Phosphatase	**Elevated**	IU/l	30 -130	1.1-2xULN 143-260	>2.-3xULN 261-390	>3-10xULN 391-1300	>10xULN >1300
Albumin		g/l	32-50	28-31	25-27	<25	-
CRP	**Elevated**		<10	>10-30	31-100	101-200	>200

Table 4 Severity grading criteria for clinically significant laboratory abnormalities (adapted from FDA guidelines using OUH NHS Trust laboratory reference ranges

Appendix G – SAE form completion guidance

Oxford Sponsored COVID trials SAE form completion guidance

Report Number

- Leave this blank, the SAE number will be added on receipt.

Study details

- Enter site name and PI Name.

Participant details

- Enter subject ID
- Select gender
- Enter age at time of event in years.

Report details

- Select box to indicate whether this is an initial SAE report or an update report. If completing an update report, indicate number of report (e.g. 1st update report would be number 01).
- Indicate what date the site became aware of this SAE. Note, if this is an AE that has progressed to an SAE, the date entered here must be the date the site became aware the AE had progressed to serious.

SAE Classification

- Select SAE classification that most appropriately describes the event. If the SAE applies to multiple categories, the most severe of the options should be ticked (e.g. life threatening supersedes hospitalisation). For other medical events ensure the description of events (see below) includes why the event is deemed serious e.g. laboratory event (see protocol for further information).

Diagnostic Term

- Enter diagnosis
- Only enter one main event per form
- Do not enter symptoms here.

SAE start and end dates and Outcomes

- Enter start date of SAE. This may be different to the date site became aware of the SAE. If an AE is classified as a SAE due to a hospital admission, even if the participant's symptoms started before admission, it is the admission date that would be the start date.
- For SAEs that are ongoing or with an unknown End date tick the relevant box.
- Outcomes and End Dates: As a general principle, SAEs must be followed up and reported to resolution. For SAEs with an outcome of "resolved/ recovered" or "resolved with sequelae"

enter End date of the SAE; N.B. if the outcome is marked “resolved with sequelae” this closes the SAE report. Therefore, if these sequelae need to be followed or it is likely that further clinically-relevant information is going to become available, it is best to leave the outcome as “ongoing” to allow recording of further updates within the SAE form, before the SAE is finally closed. This is to avoid multiple separate SAE reports being made in relation to the same participant (e.g., in the context of a chronic condition such as malignancy, where multiple hospital admissions are likely to occur). By contrast, for a hospital admission where no further follow-up of the condition is required once the participant is discharged from hospital (i.e., the outcome is resolved/recovered) then the End data can be the date of hospital discharge.

Study vaccine administration details

- Enter date of study vaccine administration and injection site details for prime and if applicable boost. If participant is in a one dose group or in two dose group but has not yet received their booster vaccine, please score out the second study vaccine administration and injection site details line with a single line, date and initial.

Causality assessment

- An appropriately delegated clinician at site must make an initial assessment of the relationship of the event to the administration(s) of the vaccine. An interpretation of the causal relationship of the intervention(s) to the SAE in question must be made, based on the type of event; the relationship of the event to the time of vaccine administration(s); and the known biology of the vaccine therapy (Table 1). Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination should be considered and investigated.

- If a participant has received 2 doses of vaccine the clinician must consider both doses in reaching a causality decision.

- Select appropriate box to indicate assessment of causality.

0	**No Relationship**	No temporal relationship to study product ***and*** Alternate aetiology (clinical state, environmental or other interventions); ***and*** Does not follow known pattern of response to study product
1	**Unlikely**	Unlikely temporal relationship to study product ***and*** Alternate aetiology likely (clinical state, environmental or other interventions) ***and*** Does not follow known typical or plausible pattern of response to study product.
2	**Possible**	Reasonable temporal relationship to study product; ***or*** Event not readily produced by clinical state, environmental or other interventions; ***or*** Similar pattern of response to that seen with other vaccines
3	**Probable**	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions ***or*** Known pattern of response seen with other vaccines
4	**Definite**	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions; ***and*** Known pattern of response seen with other vaccines

Table 1 - Guidelines for assessing the relationship of vaccine administration to an AE.

Description of events

- Provide a description of events including symptoms, investigations/diagnostic tests, diagnosis, follow-up plan, as well as pre-existing conditions and concomitant medications of relevance to the event. This can be similar in format to that of a discharge summary. If admitted to hospital include admission and discharge dates.

- Ensure details (name, role and signature) of the clinician completing the SAE form and date the form was completed are entered at the bottom of page 1.

SAE updates

- An update form should be provided if further clinical information becomes available and when the SAE has resolved or if there is any change to the SAE classification, the diagnostic term, the SAE end date, SAE outcome or SAE causality assessment. A new form is to be submitted for each update. A narrative describing and summarizing the events since the initial SAE report is needed in the description of events section. If you have been given the coordinating centre's reference number please include it in the subject line of follow up emails. If you have not yet received it please include the volunteer's ID number.

Submission of forms

- If a delegated clinician is not available another member of the study team may submit a draft initial report without causality in order to meet the requirement for reporting to the sponsor

within 24 hours. They should not sign as the bottom of the form as this must be a delegated clinician. They should clearly print their name, role, signature and date in the narrative section. A clinician must carefully review the information and submit an updated form with causality assessment as soon as possible.

- **Send forms to SAE email address within 24 hours of the site becoming aware of the event. Original report should be retained at site and filed in ISF along with all communication related to the SAE.**

- Please call XXXX for all enquiries relating to serious adverse events.

- Ensure the SAE is entered on the AE eCRF even if entered elsewhere.

AESI and Grade 4 Lab AEs

- Adverse Events of Special Interest are listed in the study protocol. These should be reported as SAEs with the exception of 'Thrombocytopenia' which should only be reported as an SAE if it's at grade 3 or above (<100 $x10^9$/L). Pseudo thrombocytopenia (e.g. EDTA induced clumping) should not be recorded as SAEs

- Grade 4 lab AEs will be recorded as SAEs. Medical conditions leading to the Grade 4 abnormality should be recorded as the event term, rather than the lab abnormality itself. The description of the event on the SAE form should state that reason for reporting the event as an SAE is the grade 4 lab abnormality where the event itself wouldn't have necessarily met the SAE reporting criteria (e.g. grade 4 raised ALT due to acute EBV infection). Thrombocytopenia should be reported as SAE when grade 3 or above (as described above) and eosinophilia will be reported as SAE when grade 2 or above (as per protocol).

- Solicited AEs will only be reported as SAEs when serious (i.e. if they meet the SAE criteria listed in the study protocol).

- All AESI (including serious solicited AEs) and Grade 4 Lab AEs will be assessed for causality as described above.

Corrections

- Strike through any errors, add the correction, add your initials and current date. Do not obscure the original, it should remain readable unless it is an identifier being redacted.

SAE form completion guidance for Sponsor review

Report Number

- Add the report number to page 1 and page 2 if known at the time of completion.

Subject ID:

- Copy from page 1.

Date received

- Date SAE report intial/update received by Sponsor.

Sponsor actions on receipt of form:

a. Check form for errors and omissions e.g. delay in sending, fields not completed (e.g. check "End date" and "Ongoing" aren't both completed). Check causality assessment has been completed by the site and check form has been signed and dated by a clinician.

b. Acknowledge report to sender with requests for corrections as above if needed. Give them the report number for future communications.

The above actions and communication with the sender should be carried out by the designated on-call senior clinician for SAE reporting. It may be that further internal discussions amongst senior members of the Oxford team (recipients of SAE email address) are warranted regarding e.g., causality or requirement for further information. However, these should be discussed and agreed internally and then communicated back to the sender by the designated senior on-call clinician for SAEs. This is to avoid any confusion/ duplication/ conflicting communication to the site.

Causality assessment

- An appropriately delegated clinician at the Sponsor site site must make an assessment of the relationship of the event to the administration of the vaccine. An interpretation of the causal relationship of the intervention to the SAE in question must be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of the vaccine therapy (Table 1). Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination should be considered and investigated.

- If the site investigator and sponsor disagree with the assessment of causality, the most conservative assessment must be reported, with both assessments being documented. The sponsor cannot downgrade or pressurise the investigator to alter their decision.

- If participant has received 2 doses of vaccine the clinician must consider both doses in reaching a causality decision.

- Select the appropriate box to indicate assessment of causality.

Expectedness

- Leave this blank for SAEs which are not related or unlikely to be related.

- If causality is deemed possible, probable or definite select unexpected.

Actions

- Select the first box for SAEs which are not related or unlikely to be related.

- Select the third box if causality is deemed possible, probable or definite.

SAE correspondence

- Any email correspondence between the Sponsor and the Investigator relating to the SAE (including clinical summaries or reports) should be filed with the SAE form in the paper TMF and on the network drive. (If further email discussions occur between the site investigator and

the Sponsor (Oxford clinician), outside of the SAE email recipient list, then these must be filed by the Oxford clinician directly as the SAE administrator will not be aware).

SAE reporting by Sponsor

- All SAEs deemed at least possibly related to the IMP by either the Investigator or the Sponsor will be considered to be SUSARs and must be reported to the CI and then the DSMC Chair within 24 hours as described in the study protocol and OVC005: Safety Reporting for CTIMPs.

- Need for unblinding of the participant must be discussed with the CI and the DSMC. If stopping rules are triggered, all further immunisations will be halted pending further assessment by the DSMC.

- All SAEs deemed to be SUSARs will also be reported in an expedited manner to the MHRA and REC as described in the study protocol and OVC005: Safety Reporting for CTIMPs.

- Principal Investigators will be informed by the Sponsor of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

Corrections

- Strike through any errors, add the correction, add your initials and current date. Do not obscure the original it should remain readable unless it is an identifier being redacted.

Clinical Study Protocol

Trial Title: A phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19

Short title Investigating a Vaccine Against COVID-19

Study Reference: (COV002)

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and other regulatory bodies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Prof Andrew Pollard.

Statement of Compliance
The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice, Medicines for Human Use (Clinical Trial) Regulations 2004 (as amended) and all other applicable regulatory requirements.

Investigator Agreement and Notification of Conflict of Interest
Details can be found in Appendix 1

1 SYNOPSIS

Title	A phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19
Trial Identifier	COV002
Trial Registration	EudraCT number: 2020-001228-32 REC Reference: 20/SC/0179 IRAS: 281904
Clinical Phase	2/3
Design	A single-blind, randomised safety and efficacy study, with immunogenicity sub studies in older and younger age groups
Population	Main efficacy trial: Healthy adults aged ≥18 years. Sequential age escalation/de-escalation immunogenicity sub studies: 1. Healthy adults aged between 56 – <70 years 2. Healthy adults aged 70 years or older 3. Healthy children aged 5 to 12 years, inclusive 4. Healthy adults aged 18 – 55 years. 5. HIV positive adults aged 18 – 55 years.
Planned Sample Size	Total number to enrol: up to 12,390 participants. **Sequential age escalation/de-escalation groups:** **Group 1: Adults aged between 56 – 69 years** a1) Single dose ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260)*, N=30, OR a2) Single dose MenACWY N=10, OR a3) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost*, N=up to 30 participants recruited from group 1a1 will be invited to receive a booster dose at the earliest available opportunity (minimum 4 weeks from prime), OR a4) Two-dose MenACWY, N=up to 10 participants recruited from group 1a2 will be invited to receive a booster dose at the earliest available opportunity (minimum 4 weeks from prime). b1) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260) prime and 2.2 $x10^{10}$vp (qPCR) boost * (4-6 weeks apart), N=30, OR b2) Two-dose MenACWY(4-6 weeks apart) , N=10

Group 2: Adults aged 70 years and above

a1) Single dose ChAdOx1-nCoV-19 $5x10^{10}$vp (Abs 260)*, N=50, OR

a2) Single dose MenACWY N=10, OR

a3) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost*, N=up to 50 participants recruited from group 2a1 will be invited to receive a booster dose at the earliest available opportunity (minimum 4 weeks from prime), OR

a4) Two-dose MenACWY, N=up to 10 participants recruited from group 2a2 will be invited to receive a booster dose at the earliest available opportunity (minimum 4 weeks from prime).

b1) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260) prime and 2.2 $x10^{10}$vp (qPCR) boost * (4-6 weeks apart), N=50, OR

b2) Two-dose MenACWY (4-6 weeks apart), N=10

Group 3: Children aged 5 – 12 years, inclusive

ChAdOx1 nCoV-19 $2.5x10^{10}$vp (qPCR)*, N=30 ,OR

Control vaccine: MenACWY, N=30

Group 4: Adults aged 18-55 (n=up to 3550)

a1) Single dose ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260)*, N= up to 1775, OR

a2) MenACWY, N= up to 1775 OR

b1) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260) prime and $2.2x10^{10}$vp (qPCR) boost*, (4-6 weeks apart), N= up to 50, OR

b2) Two-dose MenACWY, (4-6 weeks apart), N=up to 50

NB: A subset of up to 100 participants in group 4a will be invited to receive a booster dose in 4b, keeping the overall sample size in group 4 the same.

c1) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost* OR ChAdOx1 nCoV-19 $5x10^{10}$vp (qPCR) boost, (at least 4 weeks apart), N= up to 1725, OR

c2) Two-dose MenACWY, (at least 4 weeks apart), N=up to 1725

NB: Participants in group 4a, excluding those already in 4b, will be invited to receive a booster dose in 4c, keeping the overall sample size in group 4 the same.

Group 5: Adults aged 18-55 years

a1) ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260)*, N= 50 OR

a2) MenACWY, N= 50, OR

a3) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (Abs 260) prime and 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80) boost*, N=up to 50 participants recruited from group 5a1 will be invited to receive a booster dose at the earliest available opportunity (minimum 4 weeks from prime),

a4) Two-dose MenACWY, N=up to 50 participants recruited from group 5a2 will be invited to receive a booster dose at the earliest available opportunity (minimum 4 weeks from prime).

b1) ChAdOx1 nCoV-19 $5x10^{10}$vp (qPCR)*, N= 25 OR

b2) MenACWY, N= 25

(B cell immunology only)

c1) ChAdOx1 nCoV-19 $5x10^{10}$vp (qPCR)*, N= 25 OR

c2) MenACWY, N= 25

(B and T-cell immunology)

d1) Two dose ChAdOx1 nCoV-19 0.5mL (3.5 – 6.5 × 10^{10} vp Abs 260, corrected for PS80)*, (4-6 weeks apart) N=50, OR

d2) Two dose MenACWY, N= 10

(B cell immunology and T-cell in a subset)

Group 6: Adults aged 18-55 years (n= up to 6000)

a1) ChAdOx1 nCoV-19 $5x10^{10}$vp (qPCR), N= up to 3000

a2) MenACWY, N= up to 3000

b1) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (qPCR) prime and 0.5mL (3.5 – 6.5 × 10^{10} vp Abs 260, corrected for PS80) boost* OR ChAdOx1 nCoV-19 $5x10^{10}$vp (qPCR) boost, (at least 4 weeks apart), N= up to 3000, OR

b2) Two-dose MenACWY, (at least 4 apart), N=up to 3000

NB: Participants in group 6a, will be invited to receive a booster dose in 6b, keeping the overall sample size in group 6 the same.

Group 7: Adults aged between 56 – 69 years (n=80):
a1) Single dose ChAdOx1-nCoV-19 $5x10^{10}$vp (qPCR)*, N=30, OR

a2) Single dose MenACWY N=10, OR

b1) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (qPCR)* (4-6 weeks apart), N=30, OR

b2) Two-dose MenACWY(4-6 weeks apart) , N=10

Group 8: Adults aged 70 years and above (n=120):
a1) Single dose ChAdOx1-nCoV-19 $5x10^{10}$vp (qPCR)*, N=50, OR

a2) Single dose MenACWY N=10, OR

b1) Two-dose ChAdOx1 nCoV-19 $5x10^{10}$vp (qPCR) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost* OR ChAdOx1 nCoV-19 $5x10^{10}$vp (qPCR) boost (4-6 weeks apart), N=50, OR

b2) Two-dose MenACWY (4-6 weeks apart), N=10

Group 9: Adults aged 56-69 (n=1000, +/- 10%)
a1) Two dose ChAdOx1 nCoV-19 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) N=500, OR

a2) Two dose MenACWY (4-6 weeks apart), N= 500

Group 10: Adults aged 70 years and above (n=1000, +/- 10%)
a1) Two dose ChAdOx1 nCoV-19 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) N=500, OR

a2) Two dose MenACWY (4-6 weeks apart), N= 500

Group 11: Adults aged 18-55 who previously received a ChAdOx1 vectored vaccine (n=up to 60)

a1) Two dose ChAdOx1 nCoV-19 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) N=up to 60

Group 12: HIV positive adults aged 18-55 (n=up to 60)
a1) Two dose ChAdOx1 nCoV-19 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) N= up to 60

* See section 8.5 for further information on dosing

Visit Schedule : See schedule of attendances tables in section 7.3.3

Planned Trial Duration	12 months post last vaccination per participant

	Objective	**Outcome Measure**
Primary	To assess efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19 in adults aged 18 years and older.	Virologically confirmed (PCR* positive) symptomatic cases of COVID-19

Co-Primary	To assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in adults and children.	Occurrence of serious adverse events (SAEs) throughout the study duration.
Secondary	To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19	a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination; b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following vaccination; c) occurrence of unsolicited adverse events (AEs) for 28 days following vaccination ; d) change from baseline for safety laboratory measures (except groups 4, 6, 9 and 10); e) Occurrence of disease enhancement episodes
	To assess efficacy of the candidate ChAdOx1 nCoV-19 against severe and non-severe COVID-19	a) Hospital admissions associated with COVID-19 b) Intensive care unit (ICU) admissions associated with COVID-19 c) Deaths associated with COVID-19 d) Seroconversion against non-Spike SARS-CoV-2 antigens e) Severe COVID-19 disease (defined according to clinical severity scales)
	To assess humoral immunogenicity of ChAdOx1 nCoV-19	a) Antibodies against SARS-CoV-2 spike protein (seroconversion rates) at Day 28 post-vaccination. b) Proportion of seroconversion to antibodies against SARS-CoV-2 spike protein at Day 28 post-vaccination.

	To assess cellular immunity of ChAdOx1 nCoV-19 in older adults and in children (groups 1, 2, 3, 7 and 8 only)	a) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein;
	To assess the safety and immunogenicity of a booster dose of ChAdOx1 nCoV-19 in older adults aged 56 years or older (two-dose schedules for groups 1, 2, 7 and 8 only)	a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following booster vaccination; b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following booster vaccination; c) occurrence of unsolicited adverse events (AEs) for 28 days following booster vaccination; d) change from baseline and change from pre-booster for safety laboratory measures and; e) Occurrence of disease enhancement episodes f) Antibodies against SARS-CoV-2 spike protein at Day 56 post-vaccination. g) Proportion of seroconversion to antibodies against SARS-CoV-2 spike protein at Day 56 post-vaccination
Tertiary	Exploratory Immunology	a) virus neutralising antibody (NAb) assays against live and/or pseudotype SARS-CoV-2 virus b) Cell analysis by flow cytometry assays c) Functional antibody assays d) Anti-vector immunity induced by 1 or 2 doses of ChAdOx1 nCoV-19
	Measure exposure to COVID-19	Reported by weekly survey to collect information about cases amongst

		household contacts and friends, contact with the general public, infection control procedures
	Exploratory efficacy against infection • To assess efficacy of the candidate ChAdOx1 nCoV-19 against SARS-CoV-2 infection	a) PCR* positive SARS-CoV-2 infection b) Differences in viral loads between those with severe, mild, and asymptomatic PCR+* SARS-CoV-2 infections
	Compare safety, reactogenicity and immunogenicity between different manufacturing batches of ChAdOx1 nCoV-19 used in COV001 and COV002	a) Differences in safety, reactogenicity and immunogenicity profiles between Group 1 in COV001 and Group 5 in COV002 (proportion of Grade 3 solicited AEs, occurrence of fevers, seroconversion rates at D28, neutralising antibody titres and differences in T-cell responses at D14).
	Compare safety, reactogenicity and immunogenicity between different methods for measuring doses (Abs260, Abs 260 corrected for PS80 and qPCR) of ChAdOx1 nCoV-19	a) Differences in safety, reactogenicity and immunogenicity profiles between Groups 1, 2, and 5A compared with Groups, 7, 8, and 5B, C and D respectively (proportion of Grade 3 solicited AEs, occurrence of fevers, seroconversion rates at D28, neutralising antibody titres and differences in T-cell responses at D14).
	To assess vaccine induced mucosal immunity	Nasal mucosa IgA levels at D0 and D28 in a subset of individuals
	To compare viral shedding on stool samples of SARS-CoV-2 PCR* positive individuals	Differences in viral shedding on stool at 7 days and beyond post SARS-CoV-2 positivity.
	To compare immunogenicity of ChAdOx1 nCoV-19 in participants receiving 1 or 2 doses in groups 1, 2, 7 and 8	a) Differences in antibody titres (ELISA and Neutralising antibodies) in participants who received 1 or 2 doses of ChAdOx1 nCoV-19 (groups 1, 2, 7 and 8) b) Longevity of immune responses in participants who received 1 or 2 doses of ChAdOx1 nCoV-19

	To describe the impact of previous vaccination with other ChAdOx1 vectored vaccines on safety and immune responses to ChAdOx1 nCoV-19	Differences reactogenicity profile, antibody titres and T-cell responses between groups 5d and 11 and their relationship with anti-vector neutralising antibody titres.
	To assess the cell-mediated and humoral immunogenicity profile of ChAdOx1 nCoV-19 vaccine in HIV infected adults	Cell-mediated and humoral responses against SARS-Cov-2 These will be measured by the following: a) Proportion of seroconversion to antibodies (Ab) against SARS-CoV-2 spike protein measured by ELISA. b) Interferon-gamma enzyme linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein c) Intracellular Cytokine analyses of CD4 and CD8-specific SARS-CoV-2 spike protein responses d) Further exploratory immunology
	To assess whether increasing age and or CD4 nadir are associated with a lack of immune response in HIV infected adults	a) relationship between nadir CD4 count and vaccine immune responses b) relationship between age at enrolment and vaccine immune response c) Immune responses to ChAdOx1 nCoV-19 (assessed as described above)
	To assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in HIV infected adults	a) Occurrence of serious adverse events (SAEs) throughout the study duration b) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination c) occurrence of solicited systemic signs and symptoms for 7 days following each vaccination d) occurrence of unsolicited AEs for 28 days following each vaccination
	To assess Impact of vaccination on HIV reservoirs	Change in Total HIV DNA copies per million CD4 T cells

Investigational products	a) ChAdOx1 nCoV-19, a replication-deficient simian adenoviral vector expressing the spike (S) protein of SARS-CoV-2 b) MenACWY, Meningococcal Group A, C, W-135 and Y conjugate vaccine

*or other nucleic acid amplification test (NAAT)

Formulation	ChAdOx1 nCoV-19: Aqueous solution for injection MenACWY: powder and solvent for solution for injection
Route of Administration	Intramuscular (IM)
Dose per Administration	ChAdOx1 nCoV-19*: - 2.2 x 10^{10} vp (qPCR) - 2.5 x 10^{10} vp (qPCR) - 5 x 10^{10} VP (Abs 260) - 5 x 10^{10} VP (qPCR) - 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80)* Men ACWY: 0.5 mL

* See section 8.5 for further information on dosing

2 ABBREVIATIONS

Abs 260	Absorbance 260 nm
AdHu	Human adenovirus
AdHu5	Human adenovirus serotype 5
AE	Adverse event
AID	Autoimmune Disease
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine, Oxford
CBF	Clinical BioManufacturing Facility
CEF	Chick embryo fibroblast
ChAdOx	Chimpanzee adenovirus 1
CI	Confidence interval
COP	Code of Practice
CRF	Case Report Form or Clinical Research Facility
CTRG	Clinical Trials & Research Governance Office, Oxford University
CTL	Cytotoxic T Lymphocyte
DSUR	Development Safety Update Report
ELISPOT	Enzyme-linked immunospot
GCP	Good Clinical Practice
GMO	Genetically modified organism
GMT	Geometric Mean Titre
GP	General Practitioner
HCG	Human Chorionic Gonadotrophin
HEK	Human embryonic kidney
HIV	Human Immunodeficiency virus
HLA	Human leukocyte antigen
HRA	Health Research Authority
IB	Investigator Brochure
ICH	*International Council for Harmonisation*
ICMJE	*International Committee of Medical Journal Editors*
ICS	*Intracellular Cytokine Staining*
ID	Intradermal
IFNγ	Interferon gamma
IM	Intramuscular
IMP	Investigational Medicinal Product
IMP-D	Investigational Medicinal Product Dossier
IV	Intravenous
NAAT	Nucleic acid amplification assay
MenACWY	Quadrivalent capsular group A, C, W and Y meningococcal protein-polysaccharide conjugate vaccine
MHRA	Medicines and Healthcare Products Regulatory Agency
MVA	Modified vaccinia virus Ankara
NHS	National Health Service
NIH	National Institutes of Health
NIHR	National Institute for Health Research
PBMC	*Peripheral blood mononuclear cell*
PCR	Polymerase chain reaction
PI	Principal Investigator
PS80	Polysorbate 80
QP	Qualified Person

qPCR	Quantitative polymerase chain reaction
REC	Research Ethics Committee
SAE	Serious adverse event
SC	Subcutaneous
SmPc	Summary of Product characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
µg	microgram
Vp	viral particle
VV	viral vector
WHO	World Health Organisation

3 BACKGROUND AND RATIONALE

3.1 Background

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China and were later confirmed to be infected with a novel coronavirus, known as 2019-nCoV [1]. The virus was subsequently renamed to SARS-CoV-2 because it is similar to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), a lineage B betacoronavirus. SARS-CoV-2 shares more than 79% of its sequence with SARS-CoV, and 50% with the coronavirus responsible for Middle East respiratory syndrome (MERS-CoV), a member of the lineage C betacoronavirus[2]. COVID-19 is the infectious disease caused by SARS-CoV-2. By January 2020 there was increasing evidence of human to human transmission as the number of cases rapidly began to increase in China. Despite unprecedented containment measures adopted by the Chinese government, SARS-CoV-2 rapidly spread across the world. The WHO declared the COVID-19 outbreak a public health emergency of international concern on 30th January 2020. As of 26th May 2020, over 5, 584,091 cases have been reported with more than 349,894 deaths and 188 countries affected.

Coronaviruses (CoVs) are spherical, enveloped, large positive-sense single-stranded RNA genomes. One-fourth of their genome is responsible for coding structural proteins, such as the spike (S) glycoprotein, envelope (E), membrane (M) and nucleocapsid (N) proteins. E, M, and N are mainly responsible for virion assembly whilst the S protein is involved in receptor binding, mediating virus entry into host cells during CoVs infection via different receptors.[3] SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus* and it recognises the angiotensin-converting enzyme 2 (ACE2) as the entry receptor [4]. It is the seventh CoV known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV.

The spike protein is a type I, trimeric, transmembrane glycoprotein located at the surface of the viral envelope of CoVs, which can be divided into two functional subunits: the N-terminal S1 and the C-terminal S2. S1 and S2 are responsible for cellular receptor binding via the receptor binding domain (RBD) and fusion of virus and cell membranes respectively, thereby mediating the entry of SARS-CoV-2 into target cells.[3] The roles of S in receptor binding and membrane fusion make it an ideal target for vaccine and antiviral development, as it is the main target for neutralising antibodies.

ChAdOx1 nCoV-19 vaccine consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigen of the SARS CoV-2 (nCoV-19), with a leading tissue plasminogen activator (tPA) signal sequence. ChAdOx1 nCoV-19 expresses a codon-optimised coding sequence for the Spike protein from genome sequence accession GenBank: MN908947. The tPA leader sequence has been shown to be beneficial in enhancing immunogenicity of another ChAdOx1 vectored CoV vaccine (ChAdOx1 MERS) [5].

3.2 Preclinical studies

Refer to the Investigator Brochure for most recent pre-clinical data update

3.2.1 Immunogenicity (Jenner Institute, unpublished)

Mice (balb/c and CD-1) were immunised with ChAdOx1 expressing SARS-CoV-2 Spike protein or green fluorescent protein (GFP). Spleens were harvested for assessment of IFY ELISpot responses and serum samples were taken for assessments of S1 and S2 antibody responses

on ELISA at 9 or 10 days post vaccination. The results of this study show that a single dose of ChAdOx1 nCoV was immunogenic in mice.

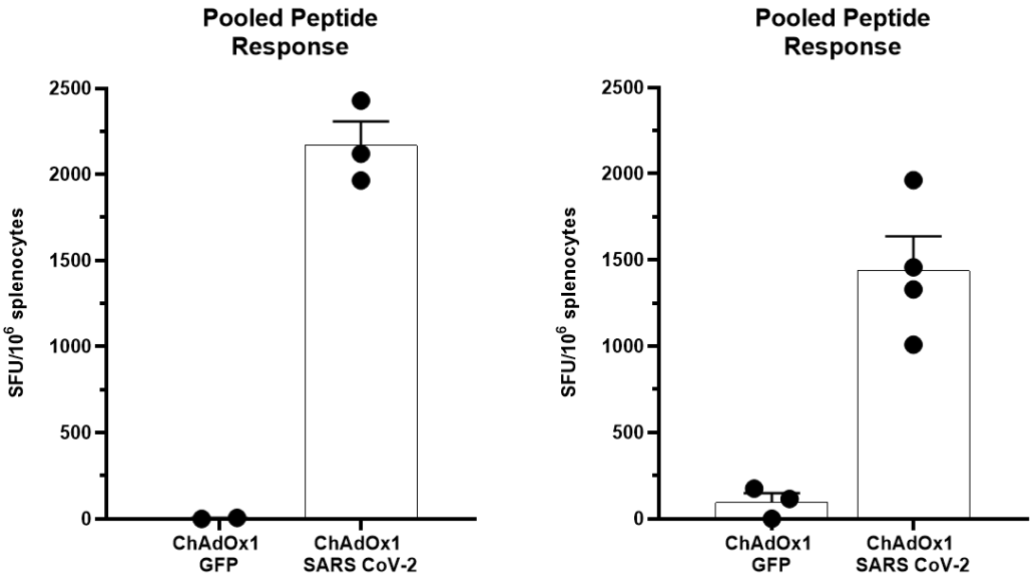

Figure 1. Summed splenic IFN-γ ELISpot responses of BALB/c (left panel) and CD-1 (right panel) mice, in response to peptides spanning the spike protein from SARS-CoV-2, nine or ten days post vaccination, with 1.7×10^{10} vp ChAdOx1 nCoV-19 or 8×10^{9} vp ChAdOx1 GFP. Mean with SEM are depicted

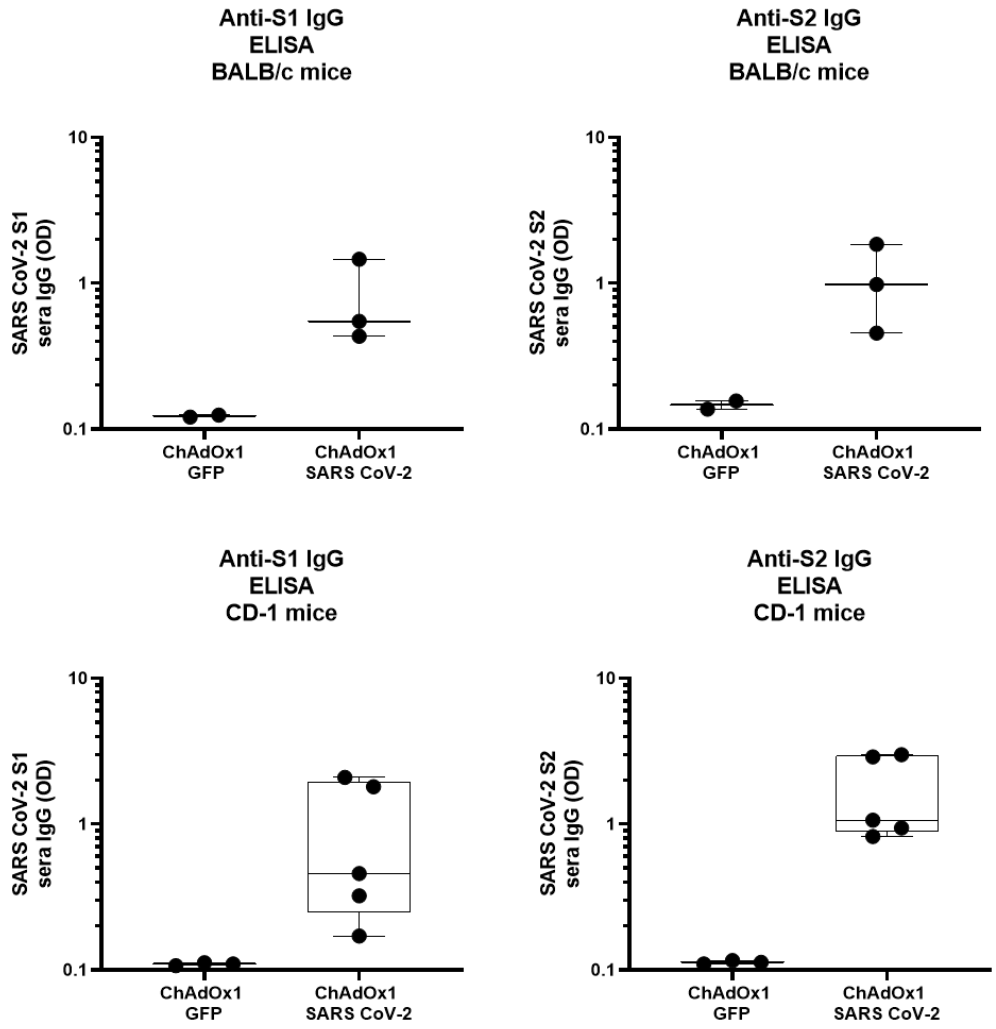

Figure 2. Box and whisker plot of the optical densities following ELISA analysis of BALB/C mouse sera (Top panel) incubated with purified protein spanning the S1 domain (left) or purified protein spanning the S2 domain (right) of the SARS-CoV-2 spike nine or ten days post vaccination, with 1.7×10^{10} vp ChAdOx1 nCoV-19 or 8×10^{9} vp ChAdOx1 GFP. Box and whisker plots of the optical densities following ELISA analysis of CD-1 mouse sera (Bottom panel) incubated with purified protein spanning the S1 domain (left) or purified protein spanning the S2 domain (right) of the SARS-CoV-2 spike.

Two mouse strains (BALB/c, N=5 and outbred CD1, N=8) were vaccinated intramuscularly (IM) with ChAdOx1 nCoV-19 or ChAdOx1 GFP, a control vaccine expressing green fluorescent protein. Humoral and cellular immunity were studied 9-14 days later. Total IgG titers were detected against spike protein subunits S1 and S2 in all vaccinated mice (Figure 3a). Profiling of the IgG subclasses showed a predominantly Th1 response post vaccination (Figure 4a). Virus-specific neutralising antibodies were detected in all mice vaccinated with ChAdOx1 nCoV-19, whereas no neutralisation was detected in serum from mice vaccinated with ChAdOx1 GFP (Figure 5b). Splenic T-cell responses measured by IFN-γ ELISpot and intracellular cytokine staining (ICS) were detected against peptides spanning the full length of the spike construct (Figure 3c). Again, a strong Th1-type response was detected post vaccination as supported by high levels of IFN-γ and TNF-α, and low levels of IL-4 and IL-10 (Figure 3d & Figure 4b-c).

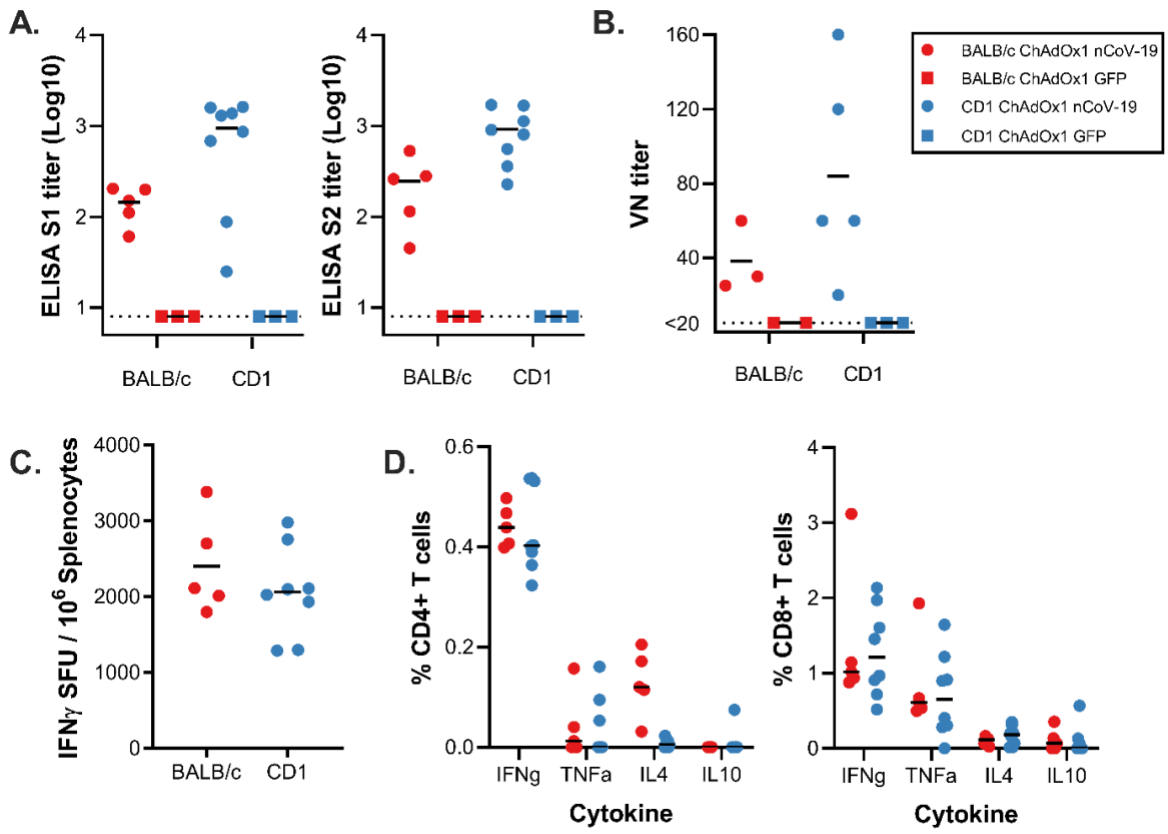

Figure 3: Humoral and cellular immune responses to ChAdOx1 58 nCoV-19 vaccination in mice. A). End point titer of serum IgG detected against S1 or S2 protein. Control mice were below the limit of detection. B). Virus neutralizing titer in serum. C). Summed IFN-γ ELISpot responses in splenocytes toward peptides spanning the spike protein. Control mice had low (<100 SFU) or no detectable response. D). Summed frequency of spike-specific cytokine positive CD4+ or CD8+ T cells. BALB/c = red; CD1 = blue; vaccinated = circle; control = square; dotted line = limit of detection; line = mean; SFU = spot-forming units.

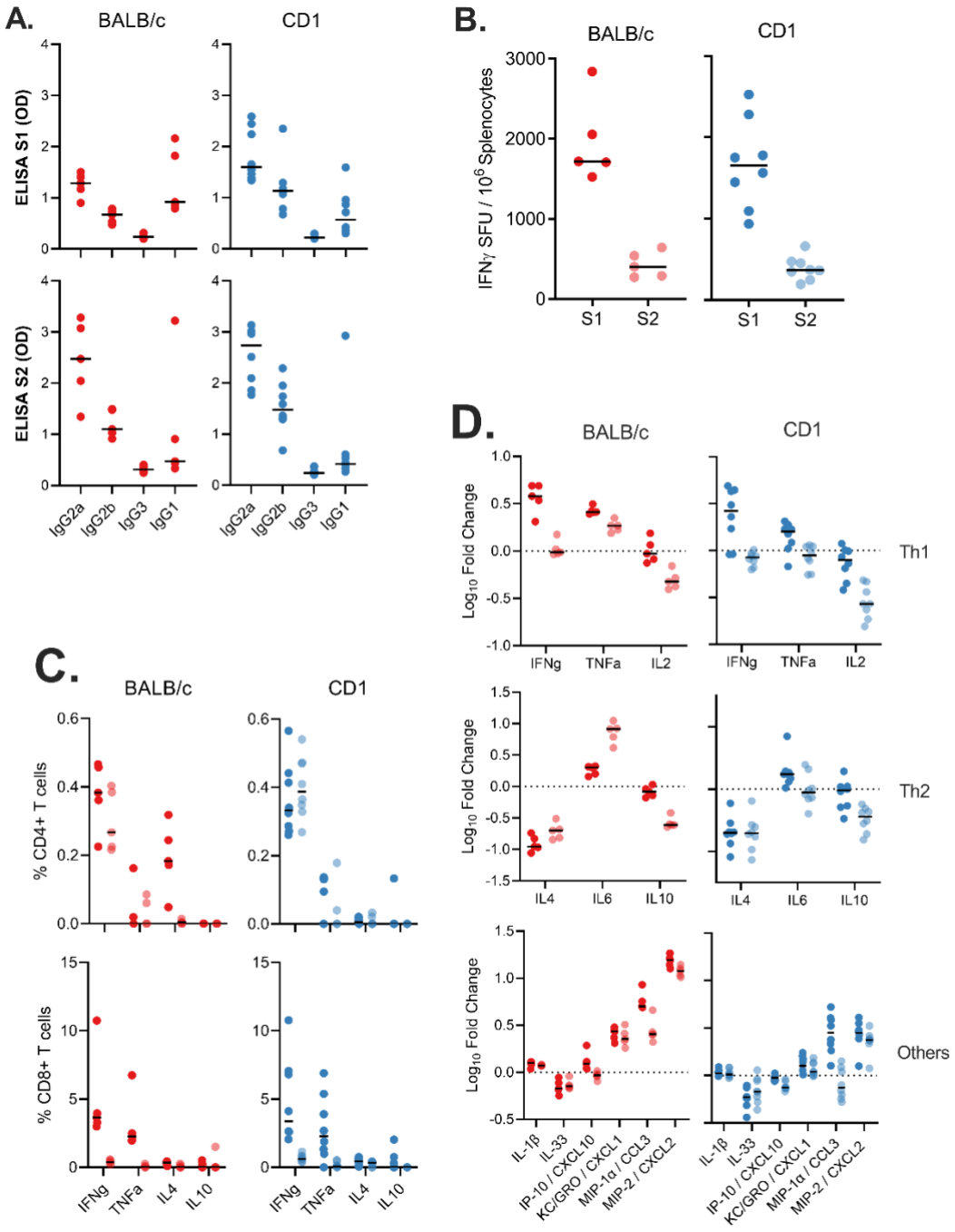

Figure 4. Antigen specific responses following ChAdOx1 nCov19 vaccination. A). IgG subclass antibodies detected against S1 or S2 protein in sera of BALB/c or CD1 mice. B).Frequency of cytokine positive CD4+ or CD8+ T cells following stimulation of splenocytes with S1 pool (dark) or S2 pool (transparent) peptides in BALB/c (red) and CD1 (blue) mice. C) Percentage of CD4+ or CD8+ T cells in BALB/c or CD1. D) Log10 fold change in cytokine levels in supernatant from S1 (dark) and S2 (transparent) stimulated splenocytes when compared to corresponding unstimulated 407 splenocyte sample for BALB/c and CD1 mice.

3.2.2 Non-human primate efficacy and immunogenicity – NIH (pre-print)

Details of this experiment are available at: https://www.biorxiv.org/content/10.1101/2020.05.13.093195v1 doi: https://doi.org/10.1101/2020.05.13.093195. In this study, two groups of rhesus macaques were utilized. Animals were adults, vaccinated group contained six animals, control group contained three animals. Group 1 was vaccinated with ChAdOx1 nCoV-19 at a dose of 2.5 x 10^{10} vp/animal at 28 days before challenge. Group 2 (control) was vaccinated with ChAdOx1 GFP at a dose of 2.5 x 10^{10} vp/animal at 28 days before challenge. The dose is half that which is planned for humans.

Animals were challenged with 2.6 x 10^{6} TCID¬50/animal of SARS-CoV-2 using 4 routes: intranasal (0.5ml per nostril), intratracheal (4ml), oral (1ml), and ocular (0.25ml per eye) of a 4x10^{5} TCID50/ml virus dilution in sterile DMEM.

Animals were examined on 1, 3, 5, and 7 days post challenge and will be euthanized at 7 days post challenge.

Humoral response

Antibodies in serum against SARS-CoV-2 spike protein were measured by ELISA. An increase in ELISA titer (Figure 5B) and neutralizing antibodies (Figure 5C) was found when comparing serum obtained before initial vaccination (-28), and at day of challenge (0).

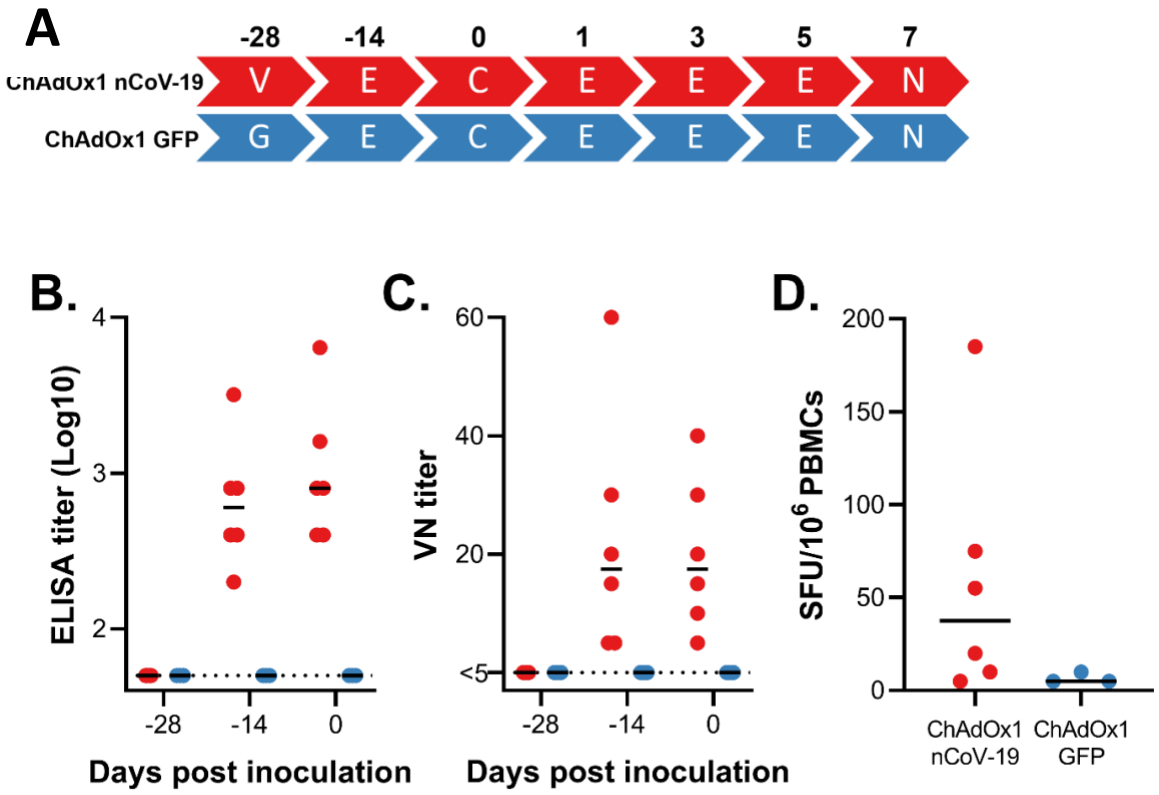

Figure 5. Humoral and cellular response to ChAdOx1 nCoV-19 vaccination in rhesus macaques. A. Study schedule for NHPs. V = vaccination with ChAdOx1 nCoV-19; G = vaccination with ChAdOx1 GFP; E = exam; N = necropsy. B. End point titre of serum IgG

detected against S protein via ELISA at -28, -14 and 0 DPI. C. Two-fold serial-diluted serum samples were tested for neutralizing antibodies against SARS CoV-2 in VeroE6 cells at -28, -14 and 0 DPI. D. Summed S protein specific IFN-γ ELISpot responses. Vaccinated animals = red; control animals = blue; dotted line = limit of detection.

Cytokine response

Cytokines in serum were analysed after challenge to monitor immune responses. We observed an upregulation in IFN-γ at 1 DPI in ChAdOx1 nCoV-19 vaccinated animals, but not in control animals. No significant differences were observed between ChAdOx1 nCoV-19 and control animals for TNF-α, IL-2, IL-4, IL-6, and IL-10 (Figure 6).

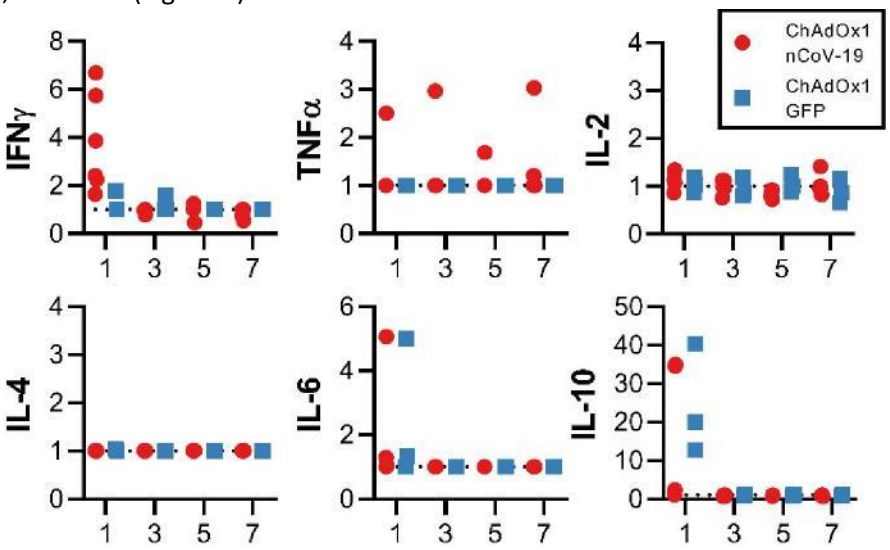

Figure 6. Serum cytokines in rhesus macaques challenged with SARS-CoV-2. Fold increase in cytokines in serum compared to 0 DPI values.

Shedding of virus

Viral gRNA load was high in lung tissue of control animals and viral sgRNA was detected in 2 out of 3 control animals (Figure 7d). In contrast, the viral gRNA load was significantly lower in lung tissue obtained from vaccinated animals as determined via Mann-Whitney's rank test and below limits of detection in two vaccinated animals. Viral sgRNA was detected in lung tissue obtained from 1 out of 6 vaccinated animals ($p<0.0001$, Figure 11d). Viral gRNA could be detected in other tissues but was low in both groups (Figure 8).

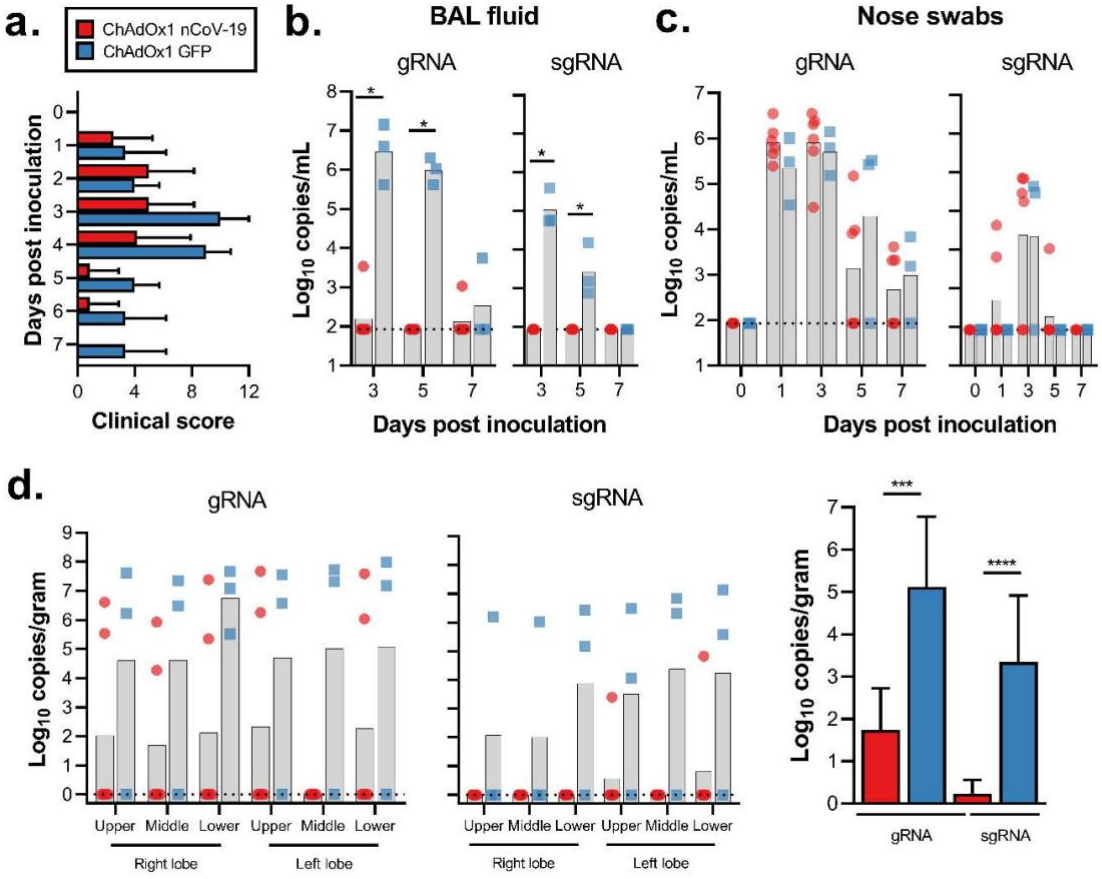

*Figure 7. Clinical signs and viral load in rhesus macaques inoculated with SARS-CoV-2 after vaccination with ChAdOx1 nCoV-19. a. Mean clinical score with standard deviation in NHPs. Any scoring associated with food was removed from final score. b. Viral load in BAL fluid obtained from rhesus macaques, bar at geometric mean. *=p-value<0.0166. c. Viral load in nose swabs obtained from rhesus macaques, bar at geometric mean. d. Viral load in tissues at 7 DPI. Pictured are individual values with geometric mean bars (left panels) and geometric mean of all lung lobes per group (right panel). ***=p-value<0.001; ****=p-value<0.0001. Vaccinated animals = red circles; control animals = blue squares; dotted line = limit of detection.*

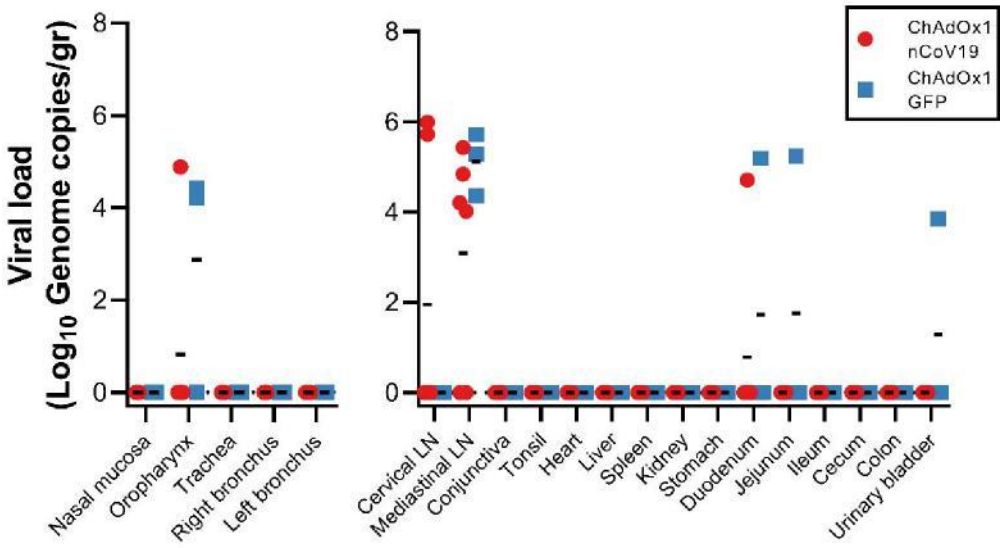

Figure 8. Viral load in rhesus macaques challenged with SARS-CoV-2. Viral genomic RNA in respiratory tissues excluding lung tissue (left panel) and other tissues (right panel). A two-tailed Mann-Whitney's rank test was performed to investigate statistical significance. Bonferroni correction was applied, and thus statistical significance was reached at p>0.0125.

Pulmonary pathology

At 7 days post inoculation, all animals were euthanized, and tissues were collected. None of the vaccinated monkeys developed pulmonary pathology after inoculation with SARS-CoV-2. All lungs were histologically normal and no evidence of viral pneumonia nor immune-enhanced inflammatory disease was observed. In addition, no SARS-CoV-2 antigen was detected by immunohistochemistry in the lungs of any of the vaccinated animals. Two out of 3 control animals developed some degree of viral interstitial pneumonia. Lesions were widely separated and characterized by thickening of alveolar septae by small amounts of edema fluid and few macrophages and lymphocytes. Alveoli contained small numbers of pulmonary macrophages and, rarely, edema. Type II pneumocyte hyperplasia was observed. Multifocally, perivascular infiltrates of small numbers of lymphocytes forming perivascular cuffs were observed. Immunohistochemistry demonstrated viral antigen in type I and II pneumocytes, as well as in alveolar macrophages (Figure 9.

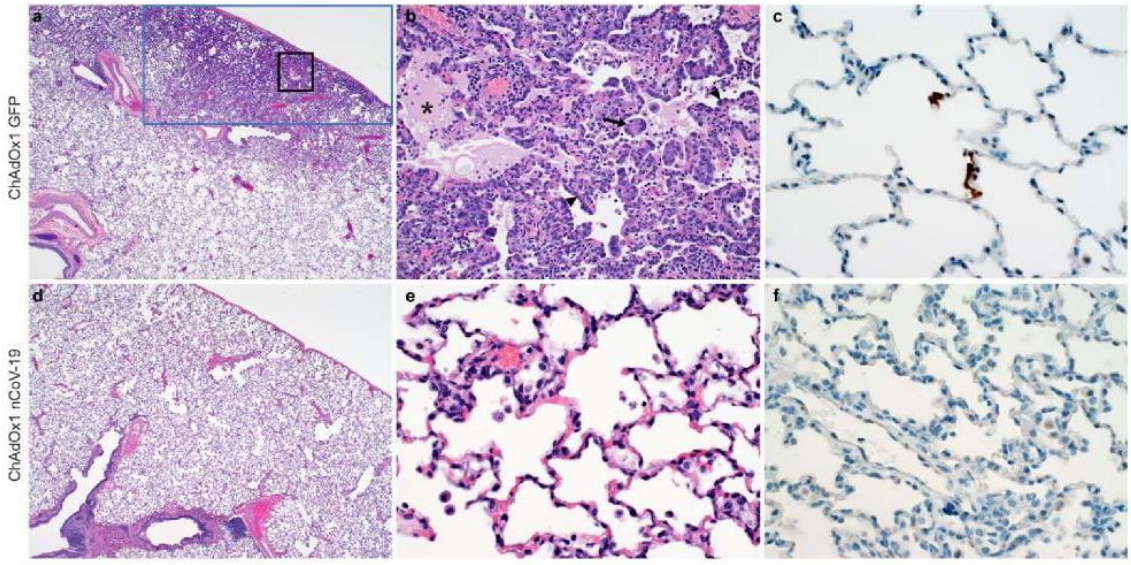

Figure 9 Histological changes in lungs of rhesus macaques on 7 dpi. a) Focal interstitial pneumonia in lungs of a control animal (blue box). The area in the black box is magnified in panel b. b) Interstitial pneumonia with edema (asterisk), type II pneumocyte hyperplasia (arrowhead) and syncytial cells (arrow) in control animals. c) SARS-CoV-2 antigen (visible as red-brown staining) was detected by immunohistochemistry in type I and type II pneumocytes in the lungs of control animals. d) No histological changes were observed in the lungs of ChadOx1 nCoV-19-vaccinated animals. e) Higher magnification of lung tissue in panel d. No evidence of pneumonia or immune-enhanced inflammation is observed. f) No SARS-CoV-2 antigen was detected by immunohistochemistry in the lungs of vaccinated animals. Magnification: panels a, d 40x; panels b, c, e, f 400x.

Further pre-clinical efficacy studies of ChAdOx1 nCoV-19 in ferrets and non-human primates are in progress. Results will be included in the Investigator's Brochure when available

3.2.3 Antibody Dependant Enhancement and Immunopathology

Safety concerns around the use of full length coronavirus Spike glycoproteins and other viral antigens (nucleoprotein) as a vaccine antigen have been raised following historical and limited reports of immunopathology and antibody dependant enhancement (ADE) reported *in vitro* and post SARS-CoV challenge in mice, ferrets and non-human primates immunised with whole SARS-CoV inactivated or full-length S protein based vaccines, including a study using Modified Vaccinia Ankara as a vector.[6-8] To date, there has been one report of lung immunopathology following MERS-CoV challenge in mice immunised with an inactivated MERS-CoV candidate vaccine.[9] However, in preclinical studies of ChAdOx1 immunisation and MERS-CoV challenge, no ADE was observed in hDPP4 transgenic mice, dromedary camels or non-human primates (van Doremalen et al, manuscript submitted).[10,11]

The risks of inducing lung immunopathology in the event of COVID-19 disease following ChAdOx1 nCoV-19 vaccination are unknown. The NHP study conducted by NIH described above showed no evidence of immune-enhanced inflammation in ChAdOx1 nCoV-19 vaccinated animals who underwent SARS-CoV-2 challenge 4 weeks post immunisation, at 7 days post challenge. Results from a separate challenge study conducted on a purified inactivated SARS-CoV-2 vaccine also corroborate

with NIH findings where no ADE has been detected in vaccinated animals [12]. However, the negative findings on ADE and lung immunopathology from both reports should be interpreted with caution, as challenged animals were sacrificed and examined shortly after challenge (7 days post inoculation). Further challenge studies on ChAdOx1 nCoV-19 vaccinated ferrets and NHPs with observation periods greater than 7 days after challenge are underway. These pre-clinical studies will report on presence or absence of lung pathology. Results will be reviewed as soon as they emerge and will inform discussions on risk/benefit to participants receiving the IMP. All pathology data arising from challenge studies of other SARS-CoV-2 vaccine candidates will also be taken into account.

3.3 Previous clinical experience

ChAdOx1 vectored vaccines expressing different inserts have previously been used in over 320 healthy volunteers taking part in clinical trials conducted by or in partnership with the University of Oxford in the UK and overseas (table 1 and 2). Most importantly, a ChAdOx1 vectored vaccine expressing the full-length Spike protein from another Betacoronavirus, MERS-CoV, has been given to 31 participants to date as part of MERS001 and MERS002 trials. ChAdOx1 MERS was given at doses ranging from $5x10^9$ vp to $5x10^{10}$ vp (table 2) with no serious adverse reactions reported. Further safety and immunogenicity results on ChAdOx1 MERS can be found on the Investigator's Brochure for ChAdOx1 nCoV-19 for reference.

Clinical trials of ChAdOx1 vectored vaccines encoding antigens for Influenza (fusion protein NP+M1), Tuberculosis (85A), Prostate Cancer (5T4), Malaria (LS2), Chikungunya (structural polyprotein), Zika (prM and E), MERS-CoV (full-length Spike protein) and Meningitis B are listed below.

None of the below mentioned clinical trials reported serious adverse events associated with the administration of ChAdOx1, which was shown to have a good safety profile.

Table 5. Clinical experience with ChAdOx1 viral vector vaccines.

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)	Publication / Registration Number
UK	FLU004	ChAdOx1 NP+M1	18-50	IM	$5x10^8$ vp	3	Antrobus et al, 2014. Molecular Therapy. DOI: 10.1038/mt.2013.284 [13]
					$5x10^9$ vp	3	
					$2.5x10^{10}$ vp	3	
					$5x10^{10}$ vp	6	
UK	FLU005	ChAdOx1 NP+M1 MVA NP+M1 (week 8)	18-50	IM	$2.5x10^{10}$ vp	12	Coughlan et al, 2018. EBioMedicine DOI: 10.1016/j.ebiom.2018.02.011 DOI: 10.1016/j.ebiom.2018.05.001 [14]
		ChAdOx1 NP+M1 MVA NP+M1 (week 52)	18-50	IM	$2.5x10^{10}$ vp	12	
		MVA NP+M1 ChAdOx1 NP+M1 (week 8)	18-50	IM	$2.5x10^{10}$ vp	12	
		MVA NP+M1 ChAdOx1 NP+M1 (week 52)	18-50	IM	$2.5x10^{10}$ vp	9	
		ChAdOx1 NP+M1	>50	IM	$2.5x10^{10}$ vp	12	
		ChAdOx1 NP+M1 MVA NP+M1 (week 8)	>50	IM	$2.5x10^{10}$ vp	12	
UK	TB034	ChAdOx1 85A	18-50	IM	$5x10^9$ vp	6	Wilkie et al, 2020 Vaccine DOI: 10.1016/j.vaccine.2019.10.102 [15]
					$2.5x10^{10}$ vp	12	
		ChAdOx1 85A	18-50	IM	$2.5x10^{10}$ vp	12	

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)	Publication / Registration Number
		MVA85A (week 8) ChAdOx1 85A (x2, 4weeks apart) MVA85A (at 4 months)	18-50	IM	$2.5x10^{10}$ vp	12	
Switzerland	TB039 (ongoing)	ChAdOx1 85A	18-55	Aerosol	$1x10^{9}$ vp	3	Clinicaltrials.gov: NCT04121494
				Aerosol	$5x10^{9}$ vp	3	
				Aerosol	$1x10^{10}$ vp	11	
				Aerosol/IM	$1x10^{10}$ vp	15	
Uganda	TB042 (ongoing)	ChAdOx1 85A	18-49	IM	$5x10^{9}$ vp	6	Clinicaltrials.gov: NCT03681860
					$2.5\ x10^{10}$	6	
UK	VANCE01	ChAdOx1.5T4 MVA.5T4	18 – 75	IM	$2.5x10^{10}$ vp	34	Clinicaltrials.gov: NCT02390063
UK	ADVANCE (ongoing)	ChAdOx1.5T4 MVA.5T4	≥18	IM	$2.5x10^{10}$ vp	23 (as of Feb 20)	Clinicaltrials.gov: NCT03815942
UK	VAC067	ChAdOx1 LS2	18-45	IM	$5x10^{9}$ vp	3	Clinicaltrials.gov: NCT03203421
					$2.5x10^{10}$ vp	10	

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)	Publication / Registration Number
UK	VAMBOX	ChAdOx1 MenB.1	18-50	IM	$2.5x10^{10}$ vp	3	ISRCTN46336916
					$5x10^{10}$ vp	26	
					$5x10^{9}$ vp	6	Clinicaltrials.gov:
					$2.5x10^{10}$ vp	9	NCT03590392
UK	CHIK001	ChAdOx1 Chik	18-50	IM	$5x10^{10}$ vp	9	DOI: https://doi.org/10.4269/ajtmh.abstract2019 Abstract #59, page 19.
UK	ZIKA001 (ongoing)	ChAdOx1 Zika	18-50	IM	$5x10^{9}$ vp	6	Clinicaltrials.gov:
					$2.5x10^{10}$ vp	3 (as of Feb 20)	NCT04015648
					$5x10^{10}$ vp	-	

Table 6. Clinical experience with ChAdOx1 MERS

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)	Publication / Registration Number
UK	MERS001 (ongoing)	ChAdOx1 MERS	18-50	IM	$5x10^9$ vp	6	Clinicaltrials.gov: NCT03399578
					$2.5x10^{10}$ vp	9	
					$5x10^{10}$ vp	9	Folegatti et.al. 2020, Lancet Infect.Dis DOI: https://doi.org/10.1016/S1473-3099(20)30160-2 [16]
					$2.5x10^{10}$ vp (homologous prime-boost)	3	
Saudi Arabia	MERS002 (ongoing)	ChAdOx1 MERS	18-50	IM	$5x10^9$ vp	4	Clinicaltrials.gov: NCT04170829
					$2.5x10^{10}$ vp	3	
					$5x10^{10}$ vp	-	

3.4 Rationale

The COVID-19 epidemic has caused major disruption to healthcare systems with significant socioeconomic impacts. Containment measures have failed to stop the spread of virus, which has reached pandemic levels. There are currently no specific treatments available against COVID-19 and accelerated vaccine development is urgently needed.

Live attenuated viruses have historically been among the most immunogenic platforms available, as they have the capacity to present multiple antigens across the viral life cycle in their native conformations. However, manufacturing live-attenuated viruses requires complex containment and biosafety measures. Furthermore, live-attenuated viruses carry the risks of inadequate attenuation causing disseminated disease, particularly in immunocompromised hosts. Given that severe disease and fatal COVID-19 disproportionally affect older adults with co-morbidities, making a live-attenuated virus vaccine is a less viable option. Replication competent viral vectors could pose a similar threat for disseminated disease in the immuno-suppressed. Replication deficient vectors, however, avoid that risk while maintaining the advantages of native antigen presentation, elicitation of T cell immunity and the ability to express multiple antigens [17]. Subunit vaccines usually require the use of adjuvants and whilst DNA and RNA vaccines can offer manufacturing advantages, they are often poorly immunogenic requiring multiple doses, which is highly undesirable in the context of a pandemic.

Chimpanzee adenovirus vaccine vectors have been safely administered to thousands of people using a wide range of infectious disease targets. ChAdOx1 vectored vaccines have been given to over 320 volunteers with no safety concerns and have been shown to be highly immunogenic at single dose administration. Of relevance, a single dose of a ChAdOx1 vectored vaccine expressing full-length spike protein from another betacoronavirus (MERS-CoV) has shown to induce neutralising antibodies in recent clinical trials.

The use of an active comparator (MenACWY) will minimise the chances of accidental participant unblinding, decreasing bias in reactogenicity or safety reporting and/or health seeking behaviours once symptomatic for COVID-19.

The use of prophylactic paracetamol reduces the incidence and severity of fever and other adverse events following immunisation (AEFI). It has been previously recommended following Meningococcal B vaccine administration without negatively impacting its immunogenicity profile (reference: Bexsero SmPC). Given the potential higher reactogenicity profile of ChAdOx1 nCoV-19 at $5x10^{10}$vp doses, a prophylactic paracetamol dose has been introduced in order to minimise severity of commonly observed local and systemic AEFI.

A batch comparison group (Group 5) has been included to assess potential differences in safety, reactogenicity and immunogenicity profiles across different ChAdOx1 nCoV-19 vaccine manufacturers.

Group 6 has been added to provide a comparison between efficacy at $5x10^{10}$vp dose on Abs260 and $5x10^{10}$ vp qPCR methods from different vaccine manufacturers.

Groups 7 and 8 have been added to provide safety, reactogenicity and immunogenicity data in older age groups receiving a $5x10^{10}$vp dose on qPCR, and replicate the study design in groups 1 and 2.

Group 4b has been added to provide immunogenicity data on homologous prime-boost at $5x10^{10}$vp (Abs260) prime and $2.2x10^{10}$vp (qPCR) boost, where up to 100 volunteers aged 18-55 initially recruited into group 4a will receive a booster dose of the vaccine 4-6 weeks apart.

Groups 4c and 6b have been added following interim immunogenicity results on homologous prime-boost groups showing improved neutralising antibody titres after 2 doses when compared to 1 dose regimen.

Groups 9 and 10 have been added as part of main safety and efficacy assessments in older age groups (56 – 69 years and 70 years and over) and removed from groups 4 and 6, as no vaccinations have been given to these age groups at the time of these group additions.

Group 11 has been added as an open-label and not randomised group to investigate the impact of previous ChAdOx1 vectored vaccines in immune responses elicited by ChAdOx1 nCoV-19.

Group 12 has been added as an open-label and not randomised group to investigate the safety and immunogenicity of ChAdOx1 nCoV-19 in people living with HIV.

3.4.1 Rationale for including older age groups

Deaths from COVID-19 infections are more common in adults aged 70 or older, and in those with pre-existing co-morbidities such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension and cancer. SARS-CoV-2 infects children as well as adults and the elderly. However, COVID-19 infections in children are less severe and rarely result in death. It is the oldest age group that is most at risk of death following natural infection, and in whom the vaccine would most likely be used first if deployed in a future public health campaign.

This study will recruit volunteers aged 56 to 70 years and those aged over 70 years. Simultaneously we will proceed to enrol a further up to 10,000 participants aged 18+ for a wide assessment of efficacy, with those over 55 years included in this larger cohort only as safety data become available from Group 1 and 2 cohorts.

3.4.2 Rationale for including younger age groups

ChAdOx1 vectored vaccines have not been administered to children before. However, ChAd63 – a closely related simian adenovirus vector- has been given to over 450 children and infants from 10 weeks old at doses ranging from 1 to 5 x 10^{10} vp, as part of malaria vaccine trials in Burkina Faso and West Africa [18,19]. Other adenoviral vectored vaccine (human adenovirus vector) expressing the RSV pre-fusion antigen (Ad26.RSV.pref) and the Ebola glycoprotein (Ad26.ZEBOV) has been previously administered to over 650 toddlers, children and adolescents at doses up to 5x10^{10}vp. None of these trials reported safety concerns with the use of adenoviral vectored vaccines in children. It is expected that ChAdOx1 nCoV-19 will have will have similar safety profile in paediatric groups.

Reports of COVID-19 amongst children are increasing and the majority of cases are considered to be milder or even asymptomatic [20-22]. Despite significantly lower case-fatality rates, severe presentations have been reported and at least 11 deaths recorded in England in paediatric groups (as of 30th April 2020, NHS England). Preliminary evidence suggests that children are just as likely to become infected with SARS-CoV-2 as adults but the importance of children in virus transmission remains uncertain [23]. Nonetheless, the WHO preferred target product profile for COVID-19 vaccines has all ages as target population, recognizing that herd immunity (and transmission blocking) will depend on broad immunization, likely including children (WHO, COVID-19 Vaccine TPP). In influenza, which has a similar age-dependent severity profile, universal vaccination of primary-school age children is an important strategy in UK immunisation policy to control disease through herd immunity.

We will, therefore, seek to enrol children aged 5-12 years old in order to obtain safety and immunogenicity data of ChAdOx1 nCoV-19 in paediatric groups. Given that a) immune responses in children aged 12-18 are unlikely to differ from those in adults; b) the comparator chosen in this study is routinely administered to children aged 13-15 in the UK; and c) the complexities around consent procedures and contraception requirements, we have taken a pragmatic approach to limit the upper age to 12 years old. The lower age limit has been chosen based on safety concerns of febrile induced seizures following immunisation in

younger children up to 5 years of age and potential for highest impact in curbing disease transmission in the community by prioritising school aged children.

[18,19]Since the benefit for children is lower than for adults in the population, we will accrue safety data from the phase I-III adult studies before embarking on the paediatric trial.

Recent reports of increased incidence in Kawasaki-like disease in children during the pandemic have raised concerns over the potential role for SARS-CoV-2 infection or its immune mediated response as a potential triggers [24]. The role of vaccine induced immune response against the SARS-CoV-2 in Kawasaki-like disease and other hyperinflammation syndromes is currently unknown. Kawasaki-like disease will be monitored and recorded as an adverse event of special interest.

3.4.3 Phase I/II study - COV001

The phase I/II study of efficacy, safety and immunogenicity of the ChAdOx1 nCoV19 vaccine (COV001, EudraCT 2020-001072-15) is the first evaluation of the vaccine in healthy adults aged 18-55 years in the UK started in April 2020. Over 1000 participants were enrolled and received either the investigational vaccine or a licensed MenACWY vaccine.

The two clinical studies are aligned in terms of study procedures and endpoints to allow data to be compared and combined across the two studies. The safety data from animal studies and from COV001 will be reviewed prior to vaccinating the first participant in COV002, and at each time point prior to expansion into additional age groups. See section 5 for further details.

3.4.4 Rationale for including HIV Infected persons

People living with HIV may have less functional immunity and have more associated co-morbidities than the general population. Indeed the chronic immune activation and inflammation observed in HIV-infected patients has been associated with poor antibody (Ab) responses to vaccines against influenza and HAV/HBV [25,26]. Evaluating immunological outcomes to the ChAdOx1 nCoV-19 vaccine allows us to assess whether responses are the same as in a matched HIV negative cohort, facilitating global policy on vaccine implementation in areas of high HIV prevalence

4 OBJECTIVES AND ENDPOINTS

	Objective	Outcome Measure	Timepoint of evaluation
Primary	To assess efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19 in adults aged 18 years and older.	Virologically confirmed (PCR* positive) symptomatic cases of COVID-19	Throughout the study
Co-Primary	To assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in adults and children.	Occurrence of serious adverse events (SAEs) throughout the study duration.	Throughout the study
Secondary	To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19	a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination; b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following vaccination; c) occurrence of unsolicited adverse events (AEs) for 28 days following vaccination ; d) change from baseline for safety laboratory measures and (except groups 4, 6, 9 and 10); e) Occurrence of disease enhancement episodes	a) Day 0-7 Self-reported symptoms recorded using electronic diaries b) Day 0-7 Self-reported symptoms recorded using electronic diaries c) Day 0-28 Self-reported symptoms recorded using electronic diaries d) See schedule of attendances e) Throughout the study

	To assess efficacy of the candidate ChAdOx1 nCoV-19 against severe and non-severe COVID-19	a) Hospital admissions associated with COVID-19 b) Intensive care unit (ICU) admissions associated with COVID-19 c) Deaths associated with COVID-19 d) Seroconversion against non-Spike SARS-CoV-2 antigens e) Severe COVID-19 disease (defined according to clinical severity scales)	Throughout the study See schedule of attendances Throughout the study
	To assess humoral immunogenicity of ChAdOx1 nCoV-19	a) Antibodies against SARS-CoV-2 spike protein at Day 28 post-vaccination. b) Proportion of seroconversion to antibodies against SARS-CoV-2 spike protein measured by ELISA at Day 28 post-vaccination.	Blood samples drawn at Day 0 and Day 28 post-vaccination
	To assess cellular immunity of ChAdOx1 nCoV-19 in older adults and in children (groups 1, 2, 3, 7 and 8 only)	a) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein;	See schedule of attendances
	To assess the safety and immunogenicity of a booster dose of ChAdOx1 nCoV-19 in older adults aged 56 years or older (two-dose schedules for groups 1, 2, 7 and 8 only)	a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following booster vaccination; b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following booster vaccination;	a) Day 28-35 Self-reported symptoms recorded using electronic diaries b) Day 28-35 Self-reported symptoms recorded using electronic diaries

		c) occurrence of unsolicited adverse events (AEs) for 28 days following booster vaccination; d) change from pre-booster for safety laboratory measures and; e) Occurrence of disease enhancement episodes f) Antibodies against SARS-CoV-2 spike protein at Day 56 post-vaccination. g) Proportion of seroconversion to antibodies against SARS-CoV-2 spike protein from baseline at Day 56 post-vaccination.	c) Day 28-56 Self-reported symptoms recorded using electronic diaries d) See schedule of attendances e) Throughout the study f) Blood samples drawn at day 0, 28 and at day 56. g) Blood samples drawn at day 0, 28 and at day 56.
Tertiary	Exploratory Immunology	a) virus neutralising antibody (NAb) assays against live and/or pseudotype SARS-CoV-2 virus b) Cell analysis by flow cytometry assays c) Functional antibody assays d) Anti-vector immunity induced by 1 or 2 doses of ChAdOx1 nCoV-19	See schedule of attendances
	Exploratory efficacy against infection • To assess efficacy of the candidate ChAdOx1 nCoV-19 against SARS-CoV-2 infection	a) PCR* positive SARS-CoV-2 asymptomatic infection b) Differences in viral loads between those with severe, mild, and asymptomatic PCR+* SARS-CoV-2 infections.	Throughout the study
	Measure exposure to COVID-19	Reported by weekly survey to collect information about cases amongst household	Weekly throughout the study

		contacts and friends, contact with the general public, infection control procedures	
	Compare safety, reactogenicity and immunogenicity between different manufacturing batches of ChAdOx1 nCoV-19 used in COV001 and COV002	Differences in safety, reactogenicity and immunogenicity profiles between Group 1 in COV001 and Group 5 in COV002 (proportion of Grade 3 solicited AEs, occurrence of fevers, seroconversion rates, neutralising antibody titres and differences in T-cell responses.	Day 0-7 for solicited AEs D28 for seroconversion rates and neutralising antibodies D14 for T-cell immunology readouts
	Compare safety, reactogenicity and immunogenicity between different methods for measuring doses (Abs260, Abs 260 corrected for PS80, and qPCR) of ChAdOx1 nCoV-19	Differences in safety, reactogenicity and immunogenicity profiles between Groups 1, 2, and 5A compared with and Groups, 7, 8 and 5B, C and D respectively (proportion of Grade 3 solicited AEs, occurrence of fevers, seroconversion rates at D28, neutralising antibody titres and differences in T-cell responses at D14).	Day 0-7 for solicited AEs D28 for seroconversion rates and neutralising antibodies D14 for T-cell immunology readouts
	To assess vaccine induced mucosal immunity	Differences in IgA levels in nasal mucosa in a subset of individuals	at D0 and D28 post vaccination
	To compare viral shedding on stool samples of SARS-CoV-2 PCR* positive individuals	Differences in viral shedding on stool between vaccine and comparator arms	At approximately 7 days and beyond post SARS-CoV-2 PCR* positivity.
	To compare immunogenicity of ChAdOx1 nCoV-19 in participants receiving 1 or 2 doses (groups 1, 2, 7 and 8)	a) Differences in antibody titres (ELISA and Neutralising antibodies) in participants who received 1 or 2 doses of ChAdOx1 nCoV-19 (groups 1, 2, 7 and 8)	a) At 28 days post prime and 28 days post boost

		b) Longevity of immune responses in participants who received 1 or 2 doses of ChAdOx1 nCoV-19 (groups 1, 2, 7 and 8)	b) At 6 and 12 months post prime (prime only) and 6 and 12 months post boost
	To describe the impact of previous vaccination with other ChAdOx1 vectored vaccines in immune responses to ChAdOx1 nCoV-19	Differences in antibody titres and T-cell responses between groups 5d and 11 and their relationship with anti-vector neutralising antibody titres.	At day 14 post ChAdOx1 nCoV-19 prime (T-cell responses), day 28 post prime and day 28 post boost.
	To assess the cell-mediated and humoral immunogenicity profile of ChAdOx1 nCoV-19 vaccine in HIV infected adults	Cell-mediated and humoral responses against SARS-Cov-2 These will be measured by the following: a) Proportion of seroconversion to antibodies (Ab) against SARS-CoV-2 spike protein measured by ELISA. b) Interferon-gamma enzyme linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein c) Intracellular Cytokine analyses of CD4 and CD8-specific SARS-CoV-2 spike protein responses d) Further exploratory immunology	a) at all exploratory immunology timepoints described in the schedule of attendances b) at all exploratory immunology timepoints described in the schedule of attendances c) at all exploratory immunology timepoints described in the schedule of attendances d) at all exploratory immunology timepoints described in the schedule of attendances

	To assess whether increasing age and or CD4 nadir are associated with a lack of immune response in HIV infected adults	a) Nadir CD4 count b) Age at enrolment c) Immune responses to ChAdOx1 nCoV-19 (assessed as described above)	a) at all exploratory immunology timepoints described in the schedule of attendances
	To assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in HIV infected adults	a) Occurrence of serious adverse events (SAEs) throughout the study duration b) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination c) occurrence of solicited systemic signs and symptoms for 7 days following each vaccination d) occurrence of unsolicited AEs for 28 days following each vaccination	a) Throughout the study b) Day 0-7 post prime and boost c) Day 0-7 post prime and boost d) Day 0-28 post prime and boost
	To assess Impact of vaccination on HIV reservoirs	Change in Total HIV DNA copies per million CD4 T cells	a) Throughout the study

*or other nucleic acid amplification test

Sample analysis for the completion of exploratory endpoints may be performed under the ethically approved OVC Biobank protocol.

5 TRIAL DESIGN

This is a Phase 2/3, participant-blinded individually randomised controlled trial in adults and healthy children in the UK, administering either a single dose or two-doses of ChAdOx1 nCoV-19 or licensed MenACWY vaccine via IM injection. Additional steps may be taken to keep clinical investigators assessing the primary efficacy endpoint blinded to group allocation, where this is possible and practical to do so. All data from participants with PCR (or other nucleic acid amplification test) -positive swabs will be assessed for inclusion in the primary efficacy analysis by two blinded assessors who will independently review each case according to pre-specified criteria as detailed in the statistical analysis plan, to classify each for inclusion in the primary and secondary outcomes.

After review of all available data from animal studies and at least 4 weeks safety and immunogenicity data from the first 54 participants receiving ChAdOx1 nCoV-19 in COV001, following DSMB review, enrolment into Groups 1, 4, 5 & 6 will commence. A minimum of 7 days safety data from group 1 will be reviewed by the DSMB prior to enrolment of participants into group 2. Participants will be randomised to ChAdOx1 nCoV-19/MenACWY on a 3:1:3:1 ratio in groups 1 and 7, and 5:1:5:1 ratio in groups 2 and 8, 1:1 in groups 3, 4, 5a, 5b, 5c, 6, 9 and 10, and 5:1 in group 5d. Participants in groups 4, 6, 9 and 10 will be advised to take prophylactic paracetamol for 24 hours (1000 mg every 4-6 hours) from the time of vaccination to reduce the likelihood of fever. The sequence of enrolment of participants over the age of 56 years is outlined in section 7.3.2.2. Recruitment into group 3 will not start before a minimum of 4 weeks safety and immunogenicity data from all healthy adult volunteers recruited into COV001 and all participants in groups 1 and 2 and 5, from COV002 are reviewed. Staggered enrolment will apply to group 3 with an interim review after 15 participants have received the IMP (half of the total number of participants expected to receive the IMP in this group). Up to 100 volunteers in group 4 will be invited to receive a booster dose of $2.2x10^{10}$vp (qPCR) 4-6 weeks after prime. All remaining volunteers in group 4 and all participants in group 6 will be invited to receive a booster dose of 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) at least 4 weeks after prime. Participants who were originally randomised to receive a single dose in groups 1 (a1 and a2), 2 (a1 and a2) and 5 (a1 and a2) will be invited to receive a booster dose of 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) at the earliest available opportunity, with a minimum 4 weeks interval from prime.

Safety will be assessed in real time. The DSMB will periodically assess safety and efficacy data every 4-8 weeks and/or as required.

Participants will be followed over the duration of the study to record adverse events and episodes of virologically confirmed symptomatic COVID-19 cases. Participants will be tested for COVID-19 if they present with a new onset of fever (≥37.8 C) OR cough OR shortness of breath OR anosmia/ageusia.

Weekly testing for PCR+ infection with SARS-CoV-2 using home test kits will also be undertaken in partnership with the Department of Health and Social care national community testing programme, subject to testing resource availability.

Moderate and Severe COVID-19 disease will be defined using clinical criteria. Detailed clinical parameters will be collected from medical records and aligned with agreed definitions as they emerge. These are likely to include, but are not limited to, oxygen saturation, need for oxygen therapy, respiratory rate and other vital signs, need for ventilatory support, Xray and CT scan imaging and blood test results, amongst other clinically relevant parameters.

Accumulated safety data from COV001 will be reviewed before commencing enrolment.

To account for the multisite recruitment activity, it is recognised that the number of volunteers enrolled into each group 9 and 10 will be 1000 +/-10%.

HIV -Group 12: open-label

This is a single arm group whereby up to 60 HIV infected individuals who are stable on antiretroviral therapy (ARV) will be recruited and receive ChAdOx1 nCoV-19 vaccination according to the schedule of attendance described in table 14.

5.1 Study groups

Group	Vaccine	Number of Volunteers	Age group of volunteers
Randomised groups			
Group 1 ****	a1) Single dose ChAdOx1 nCOV19 vaccine, 5x1010vp (Abs 260)*, OR a2) Single dose MenACWY a3) Two-dose ChAdOx1 nCoV-19 5x1010vp (Abs 260) prime and 0.5mL (3.5 – 6.5 × 1010 vp, Abs 260, corrected for PS80) boost*, OR a4) Two-dose MenACWY, b1) Two dose ChAdOx1 nCOV19 vaccine, 5x1010vp (Abs 260) prime and 2.2x1010vp (qPCR) boost* (4-6 weeks apart), OR b2) Two-dose MenACWY (4-6 weeks apart)	N=30 N=10 N= up to 30 from 1a1 N= up to 10 from 1a2 N=30 N=10	Adults aged 56 – 69 years
Group 2****	a1) Single dose ChAdOx1 nCOV19 vaccine, 5x1010vp (Abs 260)*, OR a2) Single dose MenACWY (4-6 weeks apart) a3) Two-dose ChAdOx1 nCoV-19 5x1010vp (Abs 260) prime and 0.5mL (3.5 – 6.5 × 1010 vp, Abs 260, corrected for PS80) boost*, OR a4) Two-dose MenACWY b1) Two dose ChAdOx1 nCOV19 vaccine, 5x1010vp (Abs 260) prime and	N=50 N=10 N= up to 50 from 2a1	Adults aged 70 years or older

	2.2x1010vp (qPCR) boost * (4-6 weeks apart), OR b2) Two-dose MenACWY	N= up to 10 from 2a2 N=50 N=10	
Group 3	Single low-dose ChAdOx1 nCoV19 vaccine, 2.5x10^{10}vp (qPCR)* , OR MenACWY	N=30 N=30	Children aged 5 to 12 years (inclusive)
Group 4** (n= up to 3550)	a1) Single dose ChAdOx1 nCoV19 vaccine, 5x10^{10}vp (Abs 260)*OR a2) MenACWY b1) Two dose ChAdOx1 nCOV19 vaccine, 5x10^{10}vp (Abs260) prime and 2.2x10^{10}vp (qPCR) boost* (4-6 weeks apart) OR b2) Two dose MenACWY c1) Two dose ChAdOx1 nCOV19 vaccine, 5x10^{10}vp (Abs260) prime and 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80) boost* OR 5x10^{10}vp (qPCR) boost (at least 4 weeks apart) OR c2) Two dose MenACWY	N=up to 1775 N=up to 1775 N= up to 50 (from 4a1) N= up to 50 (from 4a2) N= up to 1725 (from 4a1) N= up to 1725 (from 4a2)	Adults aged 18 – 55 years
Group 5****	a1) Single dose ChAdOx1 nCoV19 vaccine, 5x10^{10}vp, (Abs 260)* OR a2) MenACWY a3) Two-dose ChAdOx1 nCoV-19 5x1010vp (Abs 260) prime and 0.5mL	N= 50 N=50 N = up to 50 from 5a1	Adults aged 18-55 years

	(3.5 – 6.5 × 1010 vp, Abs 260, corrected for PS80) boost* a4) Two-dose MenACWY b1) Single dose ChAdOx1 nCoV19 vaccine, $5x10^{10}$vp, (qPCR)* OR b2) Men ACWY MenACWY (B-cell immunology only) c1) Single dose ChAdOx1 nCoV19 vaccine, $5x10^{10}$vp, (qPCR)* OR c2) MenACWY (B and T-cell immunology) d1) Two-dose ChAdOx1 nCoV19 vaccine, 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) OR d2) Men ACWY	N = up to 50 from 5a2 N= up to 25 N= up to 25 N= up to 25 N= up to 25 N= up to 50 N= up to 10	
Group 6*** (n= up to 6000)	a1) ChAdOx1 nCoV19 vaccine, $5x10^{10}$vp (qPCR)* OR a2) MenACWY b1) Two dose ChAdOx1 nCoV-19 vaccine, $5x10^{10}$vp (qPCR) prime and 0.5mL (3.5 – 6.5 × 10^{10} vp, Abs 260, corrected for PS80) boost* OR $5x10^{10}$vp (qPCR) boost* (at least 4 weeks apart) OR b2) Two dose MenACWY	N = up to 3000 N = up to 3000 N = up to 3000 (from 6a1) N = up to 3000 (from 6a2)	Adults aged 18 – 55 years
Group 7	a1) Single dose ChAdOx1nCOV19 vaccine, $5x10^{10}$vp (qPCR)*, OR a2) Single dose MenACWY	N=30 N=10 N=30	Adults aged 56 – 69 years

	b1) Two dose ChAdOx1nCOV19 vaccine, $5x10^{10}$vp (qPCR)* (4-6 weeks apart), OR b2) Two-dose MenACWY (4-6 weeks apart)	N=10	
Group 8	a1) Single dose ChAdOx1nCOV19 vaccine, $5x10^{10}$vp (qPCR)*, OR a2) Single dose MenACWY b1) Two dose ChAdOx1nCOV19 vaccine, $5x10^{10}$vp (qPCR) prime and 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80) boost* OR $5x10^{10}$vp (qPCR) boost (4-6 weeks apart), OR b2) Two-dose MenACWY (4-6 weeks apart)	N=50 N=10 N=50 N=10	Adults aged 70 years or older
Group 9	a1)Two dose ChAdOx1 nCOV19 vaccine, 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80)* (4-6 weeks apart) OR a2) Two dose MenACWY	N= approx. 500 N= approx. 500	Adults aged 56 – 69 years
Group 10	a1)Two dose ChAdOx1 nCOV19 vaccine, 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80)* (4-6 weeks apart) OR a2) Two dose MenACWY	N= approx. 500 N= approx. 500	Adults aged 70 years or older
Group 11	Two dose ChAdOx1 nCOV19 vaccine, 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80)* (4-6 weeks apart)	N=up to 60	Adults aged 18-55 who previously received a ChAdOx1 vectored vaccine.
Group 12	Two dose ChAdOx1 nCOV19 vaccine, 0.5mL ($3.5 – 6.5 \times 10^{10}$ vp, Abs 260, corrected for PS80)* (4-6 weeks apart)	N=up to 60	HIV positive adults aged 18-55

* See section 8.5 for further information on dosing

** A subset of up to 100 participants in group 4a will be invited to receive a booster dose in 4b, keeping the overall sample size in group 4 the same. All remaining participants in group 4a will be invited to receive a booster dose in 4c, keeping the overall sample size in group 4 the same.

*** Participants in group 6a will be invited to receive a booster dose in 6b, keeping the overall sample size in group 6 the same

**** Participants in groups 1a (a1 and a2), 2a (a1 and a2) and 5a (a1 and a2) will be invited to receive a booster dose in the respective a3 and a4 groups, keeping the overall sample size in group 1a, 2a and 5a the same.

5.2 Trial volunteers

Adult volunteers aged at least 18 years, and healthy children aged 5 – 12 years (inclusive) will be recruited into the study. Volunteers will be considered enrolled immediately following administration of the vaccine.

5.3 Definition of End of Trial

The end of the trial is the date of the last assay conducted on the last sample collected.

5.4 Potential Risks for volunteers

The potential risks are those associated with phlebotomy, vaccination and disease enhancement

Venepuncture

Adult Groups

Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. These will not be documented as AEs if they occur. The total volume of blood drawn over a 12 month period will be 105-621.5mL in the adult groups (blood volumes may vary slightly for volunteers at different investigator sites due to use of different volume vacutainers, following local Trust SOPs). The total volume of blood drawn over a 12 month period in the HIV group will be 1077.5mL. This should not compromise these otherwise healthy volunteers, as they would donate 470mL during a single blood donation for the National Blood transfusion Service over a 3-4 month period. Volunteers will be asked to refrain from blood donation for the duration of their involvement in the trial.

Group 3

In the paediatric group maximum blood volumes per visit are based on 0.8ml/kg. This is in line with guidance given by the European Commission of Public Health which are tabled below in table 3. The weights for each age group are based on the 0.4th centile on the female UK-WHO growth chart. These volumes should not compromise these otherwise healthy paediatric participants to ensure < 3% total blood volume sampling over a 3 month period.

Table 7 Paediatric maximum blood volumes per visit based on guidance by European Commission of public health

Age	Maximum (target) volume of blood (ml)
5-7 years	10ml
8-11 years	15ml
12 years	20ml

Allergic reactions

Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product's preparation. Anaphylaxis is extremely rare (about 1 in 1,000,000 vaccine doses) but can occur in response to any vaccine or medication.

Vaccination

Local reaction from IM vaccination

The typical local reaction as a result of IM injection is temporary pain, tenderness, redness, and swelling at the site of the injection.

Systemic reactions

Constitutional influenza-like symptoms such as fatigue, headache, malaise, feverishness, and muscle aches can occur with any vaccination and last for approximately 2-3 days. In the phase 1 COV001 study, approximately 30-40% of participants not taking prophylactic paracetamol felt feverishness, or had chills, muscle ache, malaise, fatigue, or headache which they rated as moderate to severe. (See the investigator brochure for further details). Presyncopal and syncopal episodes may occur at the time of vaccination which rapidly resolve. As with many vaccines, temporary ascending paralysis (Guillain-Barré syndrome, GBS) or immune mediated reactions that can lead to organ damage may occur, but this should be extremely rare (1 in 100,000-1,000,000 vaccine doses).

Transient neutropenia, lymphopenia and thrombocytopenia has been described following immunization with other adenoviral-vectored vaccines, and is not perceived to be of clinical significance.

Control participants will receive one or two doses of a licensed MenACWY vaccine, the risks of which are described in these vaccines SmPC.

Disease Enhancement

The risks of inducing disease enhancement and lung immunopathology in the event of COVID-19 disease following ChAdOx1 nCoV-19 vaccination are unknown as described above. Two NHP challenge studies have shown no evidence of disease enhancement from immunisation with ChAdOx1 nCoV-19 or inactivated SARS-CoV-2 virus, but caution should be taken when interpreting these negative findings. . All pre-clinical data from challenge studies using ChAdOx1 nCoV-19 and other vaccine candidates (when available) will inform decisions on risk/benefit to participants receiving the IMP. Any safety signals associated with disease enhancement potentially observed in COV001 will also inform these decisions.

5.5 Known Potential Benefits

Volunteers enrolled into the control groups will receive 1 or 2 doses of MenACWY, a licensed vaccine that has been administered to teenagers in the UK routine schedule since 2015 and is used as a travel vaccine for high risk areas. The majority of participants in this study will not have had this vaccine previously, and therefore will gain the benefit of protection against group A, C, W and Y meningococcus. Those participants who have previously had MenACWY vaccines will have their immunity against these organisms boosted. Recipients of ChAdOx1 nCoV-19 do not have any guaranteed benefit, however it is hoped that the information gained from this study will contribute to the development of a safe and effective vaccine against COVID-19.

6 RECRUITMENT AND WITHDRAWAL OF TRIAL VOLUNTEERS

6.1 Identification of Trial Volunteers

Volunteers will be recruited by use of an advertisement +/- registration form formally approved by the ethics committee(s) and distributed or posted in the following places:

- In public places, including buses and trains, with the agreement of the owner / proprietor.
- In newspapers or other literature for circulation.
- On radio via announcements.
- On a website or social media site operated by our group or with the agreement of the owner or operator (including on-line recruitment through our website).
- By e-mail distribution to a group or list only with the express agreement of the network administrator or with equivalent authorisation.
- By email distribution to individuals who have already expressed an interest in taking part in any clinical trial at the Oxford Vaccine Centre and at trial sites.
- On stalls or stands at exhibitions or fairs.
- Via presentations (e.g. presentations at lectures or invited seminars).
- Direct mail-out: This will involve obtaining names and addresses of adults via the most recent Electoral Roll. The contact details of individuals who have indicated that they do not wish to receive postal mail-shots would be removed prior to the investigators being given this information. The company providing this service is registered under the General Data Protection Regulation 2016/679. Investigators would not be given dates of birth or ages of individuals but the list supplied would only contain names of those aged ≥18 years (as per the inclusion criteria).
- Direct mail-out using National Health Service databases: These include the National Health Applications and Infrastructure Services (NHAIS) via a NHAIS data extract or equivalent. Initial contact to potential participants will not be made by the study team. Instead study invitation material will be sent out on our behalf by an external company, CFH Docmail Ltd, in order to preserve the confidentiality of potential participants. CFH Docmail Ltd is accredited as having exceeded standards under the NHS Digital Data Security and Protection Toolkit (ODS ID – 8HN70).
- Oxford Vaccine Centre databases and study site databases: We may contact individuals from databases of groups within the CCVTM (including the Oxford Vaccine Centre database) and other study

sites of previous trial participants who have expressed an interest in receiving information about all future studies for which they may be eligible.

- Using local GP practices or Trusts as Participant Identification Centres (PICs)

Recruitment of those with likely higher exposure to SARS-CoV-2 will be prioritised, in order to increase the likelihood of obtaining efficacy endpoints in the context of a waning epidemic. These priority groups will mainly consist of, but are not limited to, COVID-19 patient facing frontline healthcare workers (e.g. those working in ICU, A&E, COVID-19 wards, Paramedics, Care Homes, GP COVID-19 hubs, dentists, COVID-19 testing centres), non-healthcare staff working in COVID-19 clinical areas (e.g. hospital porters, receptionists, cleaners, other hospital workers), and other public facing keyworkers with no access to personal protective equipment, amongst others.

6.2 Informed consent

The parent/legal guardian of the participant or the participant themselves (when aged 18 or over) will personally sign and date the latest approved version of the Informed Consent form. A written version and verbal explanation of the Study Information leaflet and Informed Consent will be presented to the participant/parent/legal guardian of the participant detailing:

• the exact nature of the study

• what it will involve for the participant

• the implications and constraints of the protocol

• the known side effects and any risks involved in taking part

• sample handling – participants will be informed that anonymised samples taken during the course of the study may be shared with study collaborators.

• Individual results will not be shared with participants

The Study Information leaflet will be made available to the participant and/or parent/legal guardian for an appropriate amount of time (where possible this will a minimum of 24 hours) prior to consent being obtained. A video presentation of the Study Information leaflet may be screened to an audience, or made available for them to access it remotely. However, participants will have the opportunity to individually question an appropriately trained and delegated researcher before signing consent. Assent will also be sought from children 7 years of age or older, to participate in the trial.

The following general principles will be emphasised:

- Participation in the study is entirely voluntary
- Refusal to participate involves no penalty or loss of medical benefits
- The volunteer may withdraw from the study at any time.
- The volunteer is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- The study involves research of an investigational vaccine
- There is no direct benefit to the volunteer from participating

- The volunteer's GP will be contacted to corroborate their medical history (Groups 1, 2 , 7 and 8 only, except group 12 where GPs can be replaced by their HIV consultant). Written or verbal information regarding the volunteer's medical history will be sought from the GP or other sources. This can either be via the study team accessing patient's electronic care summaries from local systems, by contacting the GP practice, or volunteers bringing their medical care summaries from the GP to the study clinicians. However, volunteers in all remaining groups may be enrolled based on medical information obtained during screening and/or enrolment visit, at the physician's discretion..
- Blood samples taken as part of the study may be sent outside of the UK and Europe to laboratories in collaboration with the University of Oxford. These will be de-identified. Volunteers will be asked if they consent to indefinite storage of any leftover samples for use in other ethically approved research, this will be optional.

The parent/legal guardian of the participant or adult participant will be allowed as much time as wish to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of the adult participant or the parent/legal guardian of the participant dated signature, and dated signature of the person who presented and obtained the Informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator and listed on the delegation log. A copy of the signed informed consent will be given to the participant or parent/legal guardian of the participant. The original signed form will be retained at the research study site, in the case report form (CRF).

Updated information that require volunteers to be re-consented will be sent to participants and written re-consent requested at the earliest scheduled visit. If the earliest visit to occur is in the symptomatic pathway, the participant may consent using an electronic signature for infection control purposes. Where appropriate, and when re-consenting in person is not possible (e.g. participants in self-isolation), volunteers may be contacted over the phone and an appropriately trained and delegated researcher will obtain re-consent. In this instance the re-consent discussion will be documented by the researcher, the participant will sign the form (electronic or paper) and a copy will be signed by the researcher. The dates of signature may be different and a fully signed copy will be provided to the participant at the next scheduled visit. The participant may re-consent using an electronic signature.

6.3 Inclusion and exclusion criteria

This study will be conducted in adults and children, who meet the following inclusion and exclusion criteria:

6.3.1 Inclusion Criteria

The volunteer must satisfy all the following criteria to be eligible for the study:

- Adults aged 18 - 55 years (groups 4, 5, 6 and 11)
- Adults aged 56-69 years (groups 1, 7, and 9)
- Adults aged 70 years and older (groups 2, 8, and 10)

- Children aged 5-12 years inclusive (group 3)
- Able and willing (in the Investigator's opinion) to comply with all study requirements.
- Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
- For females of childbearing potential only, willingness to practice continuous effective contraception (see below) during the study and a negative pregnancy test on the day(s) of screening and vaccination.
- Agreement to refrain from blood donation during the course of the study.
- Provide written informed consent.
- Parent/Guardian provides informed consent

Additional Inclusion criteria to Group 12 (HIV sub-study):

- HIV positive
- Receiving antiretroviral therapy
- Undetectable HIV viral load
- CD4>350 cells/mL

6.3.2 Exclusion Criteria

The volunteer may not enter the study if any of the following apply:

- Participation in COVID-19 prophylactic drug trials for the duration of the study.

  Note: Participation in COVID-19 treatment trials is allowed in the event of hospitalisation due to COVID-19. The COV002 study team should be informed as soon as possible.

- Participation in SARS-CoV-2 serological surveys where participants are informed of their serostatus for the duration of the study.

  Note: Disclosure of serostatus post enrolment may accidently unblind participants to group allocation. Participation in COV002 can only be allowed if volunteers are kept blinded to their serology results from local/national serological surveys

- Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination, with the exception of the licensed seasonal influenza vaccination and the licensed pneumococcal vaccination. Participants will be encouraged to receive these vaccinations at least 7 days before or after their study vaccine.
- Prior or planned receipt of an investigational or licensed vaccine or product likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines). This

exclusion criteria will not apply to group 11, as recruitment will be targeted at those volunteers who previously received a ChAdOx1 vectored vaccine.

- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate.
- Any confirmed or suspected immunosuppressive or immunodeficient state (except group 12, where HIV infected participants are allowed); asplenia; recurrent severe infections and use of immunosuppressant medication within the past 6 months, except topical steroids or short-term oral steroids (course lasting ≤14 days)
- History of allergic disease or reactions likely to be exacerbated by any component of ChAdOx1 nCoV-19 or MenACWY
- Any history of angioedema.
- Any history of anaphylaxis.
- Pregnancy, lactation or willingness/intention to become pregnant during the study.
- Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
- History of serious psychiatric condition likely to affect participation in the study.
- Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
- Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
- Suspected or known current alcohol or drug dependency.
- Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data.
- Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well controlled comorbidities are allowed)
- History of laboratory confirmed COVID-19 (except groups 5d, 9, 10 and 11).
  - Seropositivity to SARS-CoV-2 before enrolment (except groups 5d, 9, 10 and 11)
  - NB: volunteers with previous NAAT positive results are also allowed in groups 9, 10 and 11

Additional Exclusion criteria to Groups 4, 6, 9 and 10

- History of allergic disease or reactions likely to be exacerbated by Paracetamol

- Note: Caution should be taken when recommending paracetamol to adults who already take paracetamol chronically

Additional Exclusion Criteria to Group 3

- Chronic medical conditions such as chronic lung disease, chronic liver disease, chronic renal failure, chronic heart disease, congenital genetic syndromes (e.g. Trisomy 21)
- Fulfil any of the contraindications to vaccination as specified in The Green Book

6.3.3 Re-vaccination exclusion criteria (two-dose groups only)

The following AEs associated with any vaccine, or identified on or before the day of vaccination constitute absolute contraindications to further administration of an IMP to the volunteer in question. If any of these events occur during the study, the subject will not be eligible to receive a booster dose and will be followed up by the clinical team or their GP until resolution or stabilisation of the event:

- Anaphylactic reaction following administration of vaccine
- Pregnancy
- Any AE that in the opinion of the Investigator may affect the safety of the participant or the interpretation of the study results

Participants who develop COVID-19 symptoms and have a positive NAAT test after the first vaccination can only receive a booster dose after a minimum 4 weeks interval from their first NAAT positive test, provided their symptoms have significantly improved. The decision to proceed with booster vaccinations in those cases will be at clinical discretion of the investigators. For participants who are asymptomatic and have a positive NAAT test, a minimum of 2 weeks from first NAAT positivity will be required before boosting.

6.3.4 Effective contraception for female volunteers

Female volunteers of childbearing potential are required to use an effective form of contraception during the course of the study.

Acceptable forms of contraception for female volunteers include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Total hysterectomy.
- Bilateral Tubal Occlusion
- Barrier methods of contraception (condom or occlusive cap with spermicide).
- Male sterilisation, if the vasectomised partner is the sole partner for the subject.

- True abstinence, when this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence and withdrawal are not acceptable methods of contraception).

6.3.5 Withdrawal of Volunteers

In accordance with the principles of the current revision of the Declaration of Helsinki and any other applicable regulations, a volunteer has the right to withdraw from the study at any time and for any reason, and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the volunteer at any time in the interests of the volunteer's health and well-being. In addition, the volunteer may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator.
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).
- Significant protocol deviation.
- Volunteer non-compliance with study requirements.
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures.

The reason for withdrawal will be recorded in the CRF. If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the volunteer, until the AE has resolved, stabilised or a non-trial related causality has been assigned. Any volunteer who is withdrawn from the study may be replaced, if that is possible within the specified time frame. The DSMB or DSMB chair may recommend withdrawal of volunteers.

If a volunteer withdraws from the study, data and blood samples collected before their withdrawal will still be used on the analysis. Storage of blood samples will continue unless the participant specifically requests otherwise.

In all cases of subject withdrawal, long-term safety data collection, including some procedures such as safety bloods, will continue as appropriate if subjects have received one or more vaccine doses, unless they decline any further follow-up.

6.4 Pregnancy

Should a volunteer become pregnant during the trial, no further study IMP will be administered. She will be followed up for clinical safety assessment with her ongoing consent and in addition will be followed until pregnancy outcome is determined. We would not routinely perform venepuncture in a pregnant volunteer unless there is clinical need.

7 CLINICAL PROCEDURES

This section describes the clinical procedures for evaluating study participants and follow-up after administration of study vaccine.

7.1 Schedule of Attendance

All volunteers will have clinic attendances and procedures as indicated in the schedule of attendances below (tables 5-12). Subjects will receive either the ChAdOx1 nCoV-19 vaccine or MenACWY, and undergo follow-up for a total of 12 months from the last vaccination visit. Additional visits or procedures may be performed at the discretion of the investigators, e.g., further medical history and physical examination, or additional blood tests and other investigations if clinically relevant.

7.2 Observations, medical history and physical examination

Temperature will be routinely measured at the time-points indicated in the schedule of procedures. Respiratory rate, oxygen saturation, pulse, blood pressure and temperature will be measured at the COVID-19 testing visits and if clinically required. All subjects will undergo medical history and a targeted physical examination if considered necessary at screening or pre-enrolment on D0. The purpose of this examination is to assess and document the subject's baseline health status so that any later change can be determined. Vital signs (temperature, heart rate, respiratory rate, blood pressure +/- oxygen saturation) will be measured at screening or pre-enrolment on D0 as part of baseline assessments. Further medical history, physical examination and observations may be done throughout the study based on clinical discretion. A targeted physical examination, including neurological assessment, must be conducted, when appropriate, in the event of a SAE.

Blood tests, Nose/Throat Swabs, Saliva samples and urinalysis

Blood will be drawn for the following laboratory tests and processed at contractually agreed NHS Trust laboratories using NHS standard procedures:

- **Haematology;** Full Blood Count
- **Biochemistry;** Sodium, Potassium, Urea, Creatinine, Albumin, Liver Function Tests (ALT, ALP, Bilirubin)
- **Diagnostic serology;** HBsAg, HCV antibodies, HIV antibodies in groups 1, 2, 5a, 5b, 5c and 5d, 7 and 8 only (specific consent will be gained prior to testing blood for these blood-borne viruses). HBsAg and HCV antibodies will be in group 12 with HIV antibodies only done at the investigators discretion.
- **Immunology;** Human Leukocyte Antigen (HLA) typing (groups 5a, 5b, 5c only)
- **COVID-19;** A nose/throat swab and/or saliva sample will be taken for COVID-19 NAAT testing
- **CD4 count and HIV viral load;** volunteers in group 12 only, before enrolment.

Additional safety blood tests may be performed if clinically relevant at the discretion of the medically qualified investigators, including potential prognostic indicators or markers of severe COVID-19 disease

At University of Oxford research laboratories or at designated specialist laboratories:

- **Immunology**; Immunogenicity will be assessed by a variety of immunological assays. This may include antibodies to SARS-CoV-Spike and non-Spike antigens by ELISA, ex vivo ELISpot assays for interferon gamma and flow cytometry assays, neutralising and other functional antibody assays and B cell analyses, virus neutralising Ab (NAb) assays against live and/or pseudotype SARS-CoV-2 virus. Other exploratory immunological assays including cytokine analysis and other antibody assays, DNA analysis

of genetic polymorphisms potentially relevant to vaccine immunogenicity and gene expression studies amongst others may be performed at the discretion of the Investigators. Further exploratory immunology assays may be performed at the discretion of the Investigators on HIV and non-HIV cohorts, including, but not limited to: T cell Proliferative responses to SARS-CoV-2 antigen; T cell cross-reactivity to circulating common cold coronaviruses; Multiparameter immunophenotyping by CyTOF; BCR and TCR repertoire analysis; Serum analysis by Luminex (including inflammatory, anti-inflammatory and adaptive cytokines, chemokines, growth factors and antimicrobial proteins); HIV viral reservoir; amongst others.

- **Stool samples**; SARS-CoV-2 NAAT, infectivity assays, calprotectin, and other exploratory immunology and microbiology assays may be conducted in a subset of participants, subject to site capacity, sample and test availability
- **Mucosal Immunity Swabs (Synthetic Absorptive Matrix [SAM])**; an assessment of mucosal immunity will be conducted in a subset of participants, subject to site capacity, sample and test availability.
- **SARS-CoV-2 weekly PCR sample**; weekly nose/throat swabs will be processed via the Department of Health and Social Care's community testing programme.

At each site:

- **Urinalysis;** For female volunteers of child bearing potential only, urine will be tested for beta-human chorionic gonadotrophin (β-HCG) at screening (when applicable) and immediately prior to vaccination. Where local policies require, a serum β-HCG may replace urinary test.
- **Serum;** Samples may be centrifuged at local sites and shipped to University of Oxford laboratories or elsewhere for analysis.

SARS-CoV-2 serology will be conducted at screening (except in groups 5d, 9, 10 and 11). These may be conducted at appropriate university research or NHS trust laboratories facilities at sites. SARS-CoV-2 screening serology samples and or COVID-19 related immunology samples taken, may also be shipped from sites to a central laboratory facility at the University of Oxford or elsewhere.

Collaboration with other specialist laboratories in the UK, Europe and outside of Europe for further exploratory tests may occur. This would involve the transfer of serum, urine, stool or plasma, PBMC and/or other study samples to these laboratories, but these would remain anonymised. Informed consent for this will be gained from volunteers. Samples collected for the purposes of COVID-19 diagnosis might be sent to reference labs in the UK alongside their personal data. This would be in line with the national guidance and policy for submitting samples for testing at reference labs.

Immunological assays will be conducted according to local SOPs.

Subjects will be informed that there may be leftover samples of their blood (after all testing for this study is completed), and that such samples may be stored indefinitely for possible future research (exploratory immunology), including genotypic testing of genetic polymorphisms potentially relevant to vaccine immunogenicity. Subjects will be able to decide if they will permit such future use of any leftover samples.

With the volunteers' informed consent, any leftover cells, urine, stool and serum/plasma will be frozen indefinitely for future analysis of COVID-19 and other coronaviruses related diseases or vaccine-related responses. If a subject elects not to permit this, all of that subject's leftover samples will be discarded after the required period of storage to meet Good Clinical Practice (GCP) and regulatory requirements.

Samples that are to be stored for future research will be transferred to the OVC Biobank (REC 16/SC/0141).

7.3 Study visits

The study visits and procedures will be undertaken by one of the clinical trials team. The procedures to be included in each visit are documented in the schedule of attendances (tables 5-12). Each visit is assigned a time-point and a window period, within which the visit will be conducted.

7.3.1 Screening visit

Participants will be required to complete an online questionnaire as an initial confirmation of eligibility.

In order to minimise the risks of COVID-19 exposure in clinic, participants may be asked to provide verbal permission or electronic consent to collect and record details of their medical history over the phone, ahead of their screening visit (for the purpose of the eligibility assessment and if enrolled the recording of baseline health records). This will be recorded on their Pre-screening questionnaire (either directly completed by the volunteer or on behalf of the volunteer by a member of the study team with the volunteers verbal consent) or on the reply slip. This will reduce the amount of time participants have with the clinical team during their screening procedures.

All potential volunteers will have a screening visit, which may take place up to 90 days prior to vaccination. At the screening visit, a video presentation of the aims of the study and all tests to be carried out may be screened to an audience or accessed remotely. Individually each volunteer will have the opportunity to question an appropriately trained and delegated researcher before signing the consent. Informed consent will be taken before screening/enrolment, as described in section 6.2.

If written consent is obtained, the procedures indicated in the schedule of attendances will be undertaken including a medical history (if not already collected by phone), physical examination (if required), height and weight and blood tests including a SARS-CoV-2 screening test (all groups except 4c, 6b, 5d, 9, 10 and 11) and safety bloods (groups 1, 2, 5, 7 and 8) will be done. To avoid unnecessary additional venepuncture, if the appropriate blood test results for screening are available for the same volunteer from a screening visit for another study, these results may be used for assessing eligibility (provided the results date is within the 6 months preceding enrolment in COV002).

We will aim to contact the subject's general practitioner with the permission of the subject after screening to corroborate medical history when possible and practical to do so (Groups 1, 2, 7 and 8 only, except group 12 where GPs can be replaced by their HIV consultant). GPs will be notified that the subject has volunteered for the study (all study groups,).

Abnormal clinical findings from blood tests at screening (Groups 1, 2, 5, 7 and 8 only) will be assessed by a medically qualified study member. Abnormal blood tests following screening will be assessed according to site-specific laboratory adverse event grading tables. Any abnormal test result deemed clinically significant may be repeated to ensure it is not a single occurrence. If an abnormal finding is deemed to be clinically significant, the volunteer will be informed and appropriate medical care arranged with the permission of the volunteer.

The eligibility of the volunteer will be reviewed at the end of the screening visit and again when all results from the screening visit have been considered. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator. If eligible, a day 0 visit will be scheduled for the volunteer to receive the vaccine and subsequent follow-up.

7.3.2 Day 0: Enrolment and vaccination visit

The parent(s)/legal guardian(s) of participants in group 3 and participants in all remaining groups will have informed consent taken as per section 6.2. Volunteers will be considered enrolled in to the trial at the point of vaccination. Before vaccination/trial intervention, the eligibility of the volunteer will be reviewed. Temperature will be observed and if necessary, a medical history and physical examination maybe undertaken to determine need to postpone vaccination or withdraw the participant. Vaccinations/trial intervention will be administered as described below.

7.3.2.1 Vaccination

All vaccines will be administered intramuscularly according to specific SOPs. The injection site will be covered with a sterile dressing and the volunteer will stay in the trial site for observation for a minimum of 15 minutes (+15 minutes), in case of immediate adverse events. The sterile dressing will be removed and injection site inspected.

In groups 1-3, 5, 7, 8, 11 and 12 and in a subset of volunteers in groups 4, 6, 9 and 10 (n=up to 1000, in each groups 4 and 6 and approximately 500 in each of groups 9 and 10), participants will be given an oral thermometer, tape measure and diary card (paper or electronic), with instructions on use. The approximate 3000 participants in groups 4, 6, 9 and 10 that are required to complete diaries will be allocated according to site. The allocation will ensure distribution of ages. All participants will be given the emergency 24 hour telephone number to contact the on-call study physician if needed. Volunteers will be instructed on how to self-assess the severity of these AEs. There will also be space on the diary card to self-document unsolicited AEs, and whether medication was taken to relieve the symptoms. Participants in groups 4, 6, 9 and 10 will be advised to take prophylactic paracetamol for 24 hours after vaccination and will record this in the e-diary (up to 1,000 participants in each of groups 4 and 6, and approximately 500 in each of groups 9 and 10 only). Participants in groups 1-3 and 5, 7, 8 and 11 will be asked to report on solicited AEs for 7 days and unsolicited AEs for 28 days. The subset of approximately 3000 participants in groups 4, 6, 9, and 10 will be asked to report solicited and unsolicited AEs for 7 days only. Participants in group 12 will be asked to report on solicited local and systemic AEs for 7 days and unsolicited AEs for 28 days.

Diary cards will collect information on the timing and severity of the following solicited AEs:

*Table 8**. Solicited AEs as collected on post vaccination diary cards***

Local solicited AEs	Systemic solicited AEs
Pain	Fever
Tenderness	Feverishness
Redness	Chills
Warmth	Joint pains
Itch	Muscle pains
Swelling	Fatigue
Induration	Headache
	Malaise
	Nausea
	Vomiting

7.3.2.2 Sequence of Enrolment and Vaccination of Volunteers

Prior to initiation of the study, any newly available safety data will be reviewed from animal studies or clinical trials of coronavirus vaccines being tested in the UK (COV001) or elsewhere, and discussed with the DSMB and/or MHRA as necessary. Recruitment of groups 1, 4, 5, 6, 11 and 12 may occur simultaneously. However, older adults aged 56 and above will only be recruited into groups 4, 6, 7 and 8 following a safety review of participants enrolled in groups 1 and 2. This review will include the profile of AEs observed following a single dose of ChAdOx1 nCoV-19. Adults aged 56 and above will only be recruited into group 9 following safety review of groups 1 and 7, and into group 10 following safety review of groups 2 and 8.

7.3.3 Subsequent visits

Follow-up visits will take place as per the schedule of attendances described in tables 5-12 with their respective windows. Volunteers in groups 1-3 and 5, 7 and 8 will be assessed for local and systemic adverse events, interim history, physical examination, review of diary cards (paper or electronic) and blood tests at these time points as detailed in the schedule of attendances. Blood will also be taken for immunology purposes.

If volunteers experience adverse events (laboratory or clinical), which the investigator (physician), CI and/or DSMB chair determine necessary for further close observation, the volunteer may be admitted to an NHS hospital for observation and further medical management under the care of the Consultant on call.

Table 9 Schedule of attendances for participants in groups 1a, 2a, 7a and 8a (single dose)

Attendance Number	1[S]	2	3	4	5	6	7	8	9	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive + 7 days	COVID-19 Follow-up
Timeline**(days)	≤ 90	0	3	7	14	28	56	182	364	As required	3-5 days post symptom onset	7 days post NAAT positive	
Time window (days)			±1	±2	±3	±7	±7	±14	±30	N/A	+2	±2	
Verbal Consent to discuss medical history over the phone	(X)												
Informed Consent	X												
Review contraindications, inclusion and exclusion criteria	X	X											
Vaccination		X											
Vital signs^	X	X	X	X	X	X	X	X	X	X	(X)	X	
Telephone/Video call													As required
Ascertainment of adverse events		X	X	X	X	X	X	X	X	X	(X)	X	X
Diary cards provided		X											X
Diary cards collected						X							X
Weekly household exposure questionnaire	ongoing												
Medical History, Physical Examination	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Biochemistry, Haematology (mL)	5	(5)*	5	5		5				5	(5)	5	

Attendance Number	1[S]	2	3	4	5	6	7	8	9	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive + 7 days	COVID-19 Follow-up
SARS-CoV-2 Serology	5												
Exploratory immunology (mL)		up to 55		up to 50	up to 50	up to 50	up to 50	up to 50	up to 50	up to 50		up to 50	
PAXgenes		2.5								2.5		2.5	
Nose/Throat Swab and/or Saliva Sample										X	(X)	(X)	
Stool sample[a,b]												(X)	(X)
Weekly PCR sample[a]	ongoing												
Urinary bHCG (women of childbearing potential only)	X	X											
HBsAg, HCV Ab, HIV serology (mL)	5												
Blood volume per visit	Up to 15	Up to 57.5	Up to 5	Up to 55	Up to 50	Up to 55	Up to 50	Up to 50	Up to 50	up to 57.5		up to 57.5	
Cumulative blood volume[%]	15	72.5	77.5	132.5	182.5	237.5	287.5	337.5	387.5	445		502.5	

S = screening visit; (X) = if considered necessary; ** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window. ^Vital signs at screening or pre-enrolment assessment on D0 include pulse, blood pressure, temperature, respiratory rate +/- oxygen saturation. Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set of observations will be taken, including respiratory rate and oxygen saturation. % Cumulative blood volume for volunteers if blood taken as per schedule, and excluding any repeat safety blood test that may be necessary. Blood volumes may vary according to local site equipment and practices. *Safety bloods should only be repeated at vaccination day if there is a period greater than 2 weeks between screening and vaccination visit; an extra 5mL of blood should be added to the overall cumulative blood volume. [a] Subject to site capacity, sample and test availability. [b] Optional Stool sample at approximately 7 days after onset of symptoms for those who have a positive SARS-CoV-2 NAAT test result and possibly again at 14 days after symptom onset if necessary.

Table 10 Schedule of attendances for participants in groups 1b, 2b,5d, 7b and 8b (two dose)

Attendance Number	1[$]	2 (V1)	3	4	5	6 (V2)	7	8	9	10	11	12	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Timeline** (days)	≤ 90	0	3	7	14	28	31 (3 days post boost)	35 (7 days post boost)	42 (14 days post boost)	56 (28 days post boost	182	364	As required	3-5 days post symptom onset	7 days post NAAT positive	
Time window (days)			±1	±3	±3	+14	±1	±2	±3	±7	±14	±30	N/A	+2	±2	
Verbal Consent to discuss medical history over the phone	(X)															
Informed Consent	X															
Review contraindications, inclusion and exclusion criteria	X	X				X										
Vaccination		X				X										
Vital signs^	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X	
Telephone/Video call																As required
Ascertainment of adverse events		X	X	X	X	X	X	X	X	X	X	X	X	(X)	X	X
Diary cards provided		X				X										X
Diary cards collected						X				X						X
Weekly household exposure questionnaire			ongoing													
Medical History, Physical Examination	X[c]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Biochemistry[$], Haematology (mL)	5	(5)*	5	5		5	5	5		5			5	(5)	5	
SARS-CoV-2 Serology (mL)	(5)															
Exploratory immunology[£] (mL)		up to 55		up to 50	up to 50	up to 50		up to 50	up to 50	up to 50	up to 50	up to 50	up to 50		up to 50	
PAXgenes		2.5											2.5		2.5	

Attendance Number	1[S]	2 (V1)	3	4	5	6 (V2)	7	8	9	10	11	12	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Nasal/Throat Swab, and/or Saliva sample													X	(X)	(X)	
Stool sample [a,b]															(X)	(X)
Weekly PCR sample			ongoing													
Urinary bHCG (women of childbearing potential only)	X	X				X										
HBsAg, HCV Ab, HIV serology (mL)	5															
Blood volume per visit	Up to 15	Up to 57.5	Up to 5	Up to 55	Up to 50	Up to 55	Up to 5	Up to 55	Up to 50	Up to 55	Up to 50	Up to 50	up to 57.5		up to 57.5	
Cumulative blood volume[%]	15	72.5	77.5	132.5	182.5	237.5	242.5	297.5	347.5	402.5	452.5	502.5	560		617.5	

S = screening visit; (X) = if considered necessary; ** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window. Where a second dose is administered, the window will apply to the time their last vaccination took place ^Vital signs at screening or pre-enrolment assessment on D0 include pulse, blood pressure, temperature, respiratory rate +/- oxygen saturation. Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set observations will be taken, including respiratory rate and oxygen saturation. % Cumulative blood volume for volunteers if blood taken as per schedule, and excluding any repeat safety blood test that may be necessary. Blood volumes may vary according to local site equipment and practices. *Safety bloods should only be repeated at vaccination day if there is a period greater than 2 weeks between screening and vaccination visit; an extra 5mL of blood should be added to the overall cumulative blood volume. [a] Subject to site capacity, sample and test availability. [b] Optional Stool sample at approximately 7 days after onset of symptoms for those who have a positive SARS-CoV-2 NAAT test result and possibly again at 14 days after symptom onset if necessary. [c] Targeted physical examination if considered necessary for group 5d.

Table 11: Schedule of attendances for participants in group 3

Attendance Number	1S	1	2	3	4	5	6	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Timeline**(days)		0	3	7	28	182	364	As required	3-5 days post symptom onset	7 days post COVID-19 Testing	
Time window (days)			±1	±2	±7	±14	±30	N/A	+2	±2	
Informed Consent	X										
Review contraindications, inclusion and exclusion criteria	X	X									
Vaccination		X									
Vital Signs ^	X	X	(X)	(X)	(X)	(X)	(X)	X	(X)	X	
Telephone/Video call											As required
Ascertainment of adverse events		X	X	X	X	X	X	X	(X)	X	X
Diary cards provided		X									X
Diary cards collected					X						X
Weekly household exposure questionnaire			ongoing								
Medical History, Physical Examination	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Biochemistry, Haematology (mL)		4	4[a]	4[b]	4			4	(5)	4	
SARS-CoV-2 Serology (mL)	3.5										
Exploratory immunology (mL)		up to 6 -16			up to 6 - 16	up to 10 -20	up to 10 - 20	up to 6 - 16		up to 6-16	
Nasal/Throat Swab and/or Saliva sample								X	(X)	(X)	
Weekly PCR sample[c]			ongoing								

Blood volume per visit (mL)	3.5	10-20	4	4	10 - 20	10 -20	10 - 20	10 – 20		10-20	
Cumulative blood volume[%]	3.5	13.5-23.5	17.5 - 27.5	17.5 - 27.5	27.5 – 47.5	37.5 – 67.5	47.5 – 87.5	57.5 – 107.5		67.5-127.5	

S = screening visit (X) = if considered necessary ^ = Vital signs includes temperature, a full set of observations will be done if clinically required; ** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window. [a,b,] Participants will have blood taken for safety and immunogenicity at one of 2 time points as outlined. Half of the participants will be bleed at D3 and half a t D7. [c] Subject to site capacity and test availability % Cumulative blood volume for volunteers if blood taken as per schedule and excluding any repeat safety blood test that may be necessary.

Table 12 Schedule of attendances for participants in group 4a and 6a

Attendance Number	1	2	3	4	5	6	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Timeline** (days)		0	28	90	182	364	As required	3-5 days post symptom onset	7 days post NAAT positive	
Time window (days)			-7/+14	±14	±14	±30	N/A	+2	±2	
Informed Consent	X	X								
Review contraindications, inclusion and exclusion criteria	X	X								
Vaccination		X								
Vital signs^	X	X	(X)	(X)	(X)	(X)	X	(X)	X	
Telephone/Video call										As required
Ascertainment of adverse events		X	X	X	X	X	X	(X)	X	X
Diary Cards[$]		X								
Symptoms diary										X
Weekly household exposure questionnaire			ongoing							
Medical History (required at 1 timepoint prior to enrolment),	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Physical Examination (if necessary)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Biochemistry, Haematology (mL)							5	(5)	5	
Exploratory immunology (mL)		up to 15	up to10	up to 10	up to 10	up to 10	up to 50[d]		up to 50[d]	
Mucosal Immunity[a,c]		(X)	(X)							
PAXgenes						(2.5)[P]	2.5		2.5	
SARS-CoV-2 Serology	5									

Attendance Number	1	2	3	4	5	6	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Nose/Throat Swab and/or saliva sample							X	(X)	(X)	
Stool sample [a,b]									(X)	(X)
Weekly PCR sample[a]			ongoing							
Urinary bHCG (women of childbearing potential only)	X	X								
Blood volume per visit	5	15	10	10	10	10	up to 57.5		up to 57.5	
Cumulative blood volume[%]	5	20	30	40	50	60	117.5		175	

S = screening visit; (X) = if considered necessary; ** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window. ^Vital signs at screening or pre-enrolment assessment on D0 include pulse, blood pressure, temperature, respiratory rate +/- oxygen saturation. Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set observations will be taken, including respiratory rate and oxygen saturation. % Cumulative blood volume for volunteers if blood taken as per schedule, and excluding any repeat safety blood test that may be necessary. Blood volumes may vary according to local site equipment and practices. [a] Subject to site capacity, sample and test availability. [d] Optional and subject to site capacity. [$] A subset of up to 1000 volunteers will be asked to fill an e-diary with reactogenicity symptoms for 7 days only in groups 4, 6, 9 and 10. [P] Pax genes sample at D364 to be done only on participants with positive SARS-CoV-2 NAAT at COVID-19 testing visits, an extra 2.5mL should be added to the cumulative blood volume when this applies. [b] Optional Stool sample at approximately 7 days after onset of symptoms for those who have a positive SARS-CoV-2 NAAT test result and possibly again at 14 days after symptom onset if necessary. [c] Mucosal immunity assessments to be done in a subset of group 6 individuals only.

Table 13: Schedule of attendances for participants in group 4b

Attendance Number	1	2	3	4	5	6	7	8	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Timeline** (days)		0	28	42 (14 days post boost)	56 (28 days post boost)	118 (90 days post boost)	210 (182 days post boost)	392 (364 days post boost)	As required	3-5 days post symptom onset	7 days post NAAT positive	
Time window (days)			+14	±7	±7	±14	±14	±30	N/A	+2	±2	
Informed Consent	X	X										
Review contraindications, inclusion and exclusion criteria	X	X										
Vaccination		X	X									
Vital signs^	X	X	(X)	(X)	(X)	(X)	(X)	(X)	X	(X)	X	
Telephone/Video call												As required
Ascertainment of adverse events		X	X	X	X	X	X	X	X	(X)	X	X
Diary Cards[$]		X	X									
Symptoms diary												X
Weekly household exposure questionnaire				ongoing								
Medical History (required at 1 timepoint prior to enrolment),	X	X	(X)	(X)		(X)	(X)	(X)	(X)	(X)	(X)	
Physical Examination (if necessary)	(X)	(X)	(X)	(X)		(X)	(X)	(X)	(X)	(X)	(X)	
Biochemistry, Haematology (mL)									5	(5)	5	
Exploratory immunology (mL)		up to 15	up to 20	up to 20	up to 20	up to 20	up to 20	up to 20	up to 50[d]		up to 50[d]	

Attendance Number	1	2	3	4	5	6	7	8	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
PAXgenes								(2.5)[P]	2.5		2.5	
SARS-CoV-2 Serology	5											
Nose/Throat Swab and/or saliva sample									X	(X)	(X)	
Stool sample [a,b]											(X)	(X)
Weekly PCR sample[a]			ongoing									
Urinary bHCG (women of childbearing potential only)	X	X										
Blood volume per visit	5	15	20	20	20	20	20	20	up to 57.5		up to 57.5	
Cumulative blood volume[%]	5	20	40	60	80	100	120	140	197.5		255	

S = screening visit; (X) = if considered necessary; ** Timeline is approximate only. Exact timings of visits relate to the day. Where a second dose is administered, the window will apply to the time their last vaccination took place . ^Vital signs at screening or pre-enrolment assessment on D0 include pulse, blood pressure, temperature, respiratory rate +/- oxygen saturation. Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set observations will be taken, including respiratory rate and oxygen saturation. % Cumulative blood volume for volunteers if blood taken as per schedule, and excluding any repeat safety blood test that may be necessary. Blood volumes may vary according to local site equipment and practices. [a] Subject to site capacity, sample and test availability. [d] Optional and subject to site capacity. [$] A subset of up to 1000 volunteers will be asked to fill an e-diary with reactogenicity symptoms for 7 days only in groups 4, 6, 9 and 10. [P] Pax genes sample at D364 to be done only on participants with positive SARS-CoV-2 NAAT at COVID-19 testing visits, an extra 2.5mL should be added to the cumulative blood volume when this applies. [b] Optional Stool sample at approximately 7 days after onset of symptoms for those who have a positive SARS-CoV-2 NAAT test result and possibly again at 14 days after symptom onset if necessary.

Table 14 Schedule of attendances for participants in group 5a1,5a2, 5b and 5c

Attendance Number	1[S]	2	3	4	5	6	7	8	9	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive + 7 days	COVID-19 Follow-up
Timeline**(days)	≤ 90	0	3	7	14	28	56	182	364	As required	3-5 days post symptom onset	7 days post NAAT positive	
Time window (days)			±1	±2	±3	±7	±7	±14	±30	N/A	+2	±2	
Informed Consent	X												
Review contraindications, inclusion and exclusion criteria	X	X											
Vaccination		X											
Vital signs	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	(X)	X	
Telephone/Video call													As required
Ascertainment of adverse events		X	X	X	X	X	X	X	X	X	(X)	X	X
Diary cards provided		X											X
Diary cards collected						X							X
Weekly household exposure questionnaire			ongoing										
Medical History, Physical Examination	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Biochemistry, Haematology (mL)	5	(5)*	5	5		5				5	(5)	5	
Hep B, C and HIV serology	5												
Exploratory immunology (mL)[e]		up to 55		up to 50	up to 50	up to 50	up to 50	up to 50	up to 50	up to 50		up to 50	
SARS-CoV-2 Serology	5												
PAXgenes		2.5								2.5		2.5	

Attendance Number	1[S]	2	3	4	5	6	7	8	9	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive + 7 days	COVID-19 Follow-up
Nose/Throat Swab and/or Saliva Sample										X	(X)	(X)	
Stool sample [a,b]												(X)	(X)
Weekly PCR sample			ongoing										
Urinary bHCG (women of childbearing potential only)	X	X											
HLA typing (mL)		4											
Blood volume per visit	15	61.5	5	55	50	55	50	50	50	up to 57.5		up to 57.5	
Cumulative blood volume[%]	15	76.5	81.5	136.5	186.5	241.5	291.5	341.5	391.5	449		506.5	

S = screening visit; (X) = if considered necessary; ** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window. ^Vital signs at screening or pre-enrolment assessment on D0 include pulse, blood pressure, temperature, respiratory rate +/- oxygen saturation. Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set observations will be taken, including respiratory rate and oxygen saturation. % Cumulative blood volume for volunteers if blood taken as per schedule, and excluding any repeat safety blood test that may be necessary. Blood volumes may vary according to local site equipment and practices. *Safety bloods should only be repeated at vaccination day if there is a period greater than 2 weeks between screening and vaccination visit; an extra 5mL of blood should be added to the overall cumulative blood volume. [a] Subject to site capacity, sample and test availability. [b] Optional Stool sample at approximately 7 days after onset of symptoms for those who have a positive SARS-CoV-2 NAAT test result and possibly again at 14 days after symptom onset if necessary. [e] Participants enrolled in group 5b will only have B-cell immunology assessments whereas those in group 5c will have both B and T-cell immunology assessments.

Table 15 Schedule of attendances for participants in group 4c, 1a3, 1a4, 2a3, 2a4, 5a3, 5a4 and 6b (booster)

Attendance Number (boost)	1 V2 (booster)	2	3	4	5	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive + 7 days	COVID-19 Follow-up
Timeline** (days)	> 4 weeks post prime	28 post boost	90 post boost	182 post boost	364 post boost	As required	3-5 days post symptom onset	7 days post NAAT positive	
Time window (days)	+14	±7	±14	±14	±30	N/A	+2	±2	
Informed Consent	X								
Review contraindications, inclusion and exclusion criteria	X								
Vaccination	X								
Vital signs^	(X)	(X)	(X)	(X)	(X)	X	(X)	X	
Telephone/Video call									As required
Ascertainment of adverse events	X	X	X	X	X	X	(X)	X	X
Diary Cards[$]	X								
Symptoms diary									X
Weekly household exposure questionnaire		ongoing							
Medical History	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Physical Examination (if necessary)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Biochemistry, Haematology (mL)						5	(5)	5	
Exploratory immunology (mL)	up to 20	up to 20	up to 20	up to 20	up to 20	up to 50[d]		up to 50[d]	
PAXgenes					(2.5)[P]	2.5		2.5	

Attendance Number (boost)	1 V2 (booster)	2	3	4	5	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive + 7 days	COVID-19 Follow-up
Nose/Throat Swab and/or saliva sample						X	(X)	(X)	
Stool sample [a,b]								(X)	(X)
Weekly PCR sample[a]		ongoing							
Urinary bHCG (women of childbearing potential only)	X								
Blood volume per visit	20	20	20	20	20	up to 57.5		up to 57.5	
Cumulative blood volume[%]	20	40	60	80	100	157.5		215	

S = screening visit; (X) = if considered necessary; ** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window. Where a second dose is administered, the window will apply to the time their last vaccination took place . ^Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set observations will be taken, including respiratory rate and oxygen saturation. % Cumulative blood volume for volunteers if blood taken as per schedule, and excluding any repeat safety blood test that may be necessary. Blood volumes may vary according to local site equipment and practices. [a] Subject to site capacity, sample and test availability. [d] Optional and subject to site capacity. [$] A subset of up to 1000 volunteers will be asked to fill an e-diary with reactogenicity symptoms for 7 days only in groups 4, 6, 9 and 10. [P] Pax genes sample at D364 to be done only on participants with positive SARS-CoV-2 NAAT at COVID-19 testing visits, an extra 2.5mL should be added to the cumulative blood volume when this applies. [b] Optional Stool sample at approximately 7 days after onset of symptoms for those who have a positive SARS-CoV-2 NAAT test result and possibly again at 14 days after symptom onset if necessary.

Table 16. Schedule of attendances for participants in groups 9 and 10.

Attendance Number	1	2 V1	3 V2	4	5	6	7	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive+ 7 days	COVID-19 Follow-up
Timeline** (days)		0	28	56 (28 post boost)	118 (90 post boost	210 (182 post boost)	392 (364 post boost)	As required	3-5 days post symptom onset	7 days post NAAT positive	
Time window (days)			+14	±7	±14	±14	±30	N/A	+2	±2	
Informed Consent	X	X									
Review contraindications, inclusion and exclusion criteria	X	X									
Vaccination		X	X								
Vital signs^	X	X	(X)	(X)	(X)	(X)	(X)	X	(X)	X	
Telephone/Video call											As required
Ascertainment of adverse events		X	X	X	X	X	X	X	(X)	X	X
Diary Cards[$]		X	X								
Symptoms diary											X
Weekly household exposure questionnaire				ongoing							
Medical History (required at 1 timepoint prior to enrolment),	X	X	(X)		(X)	(X)	(X)	(X)	(X)	(X)	
Physical Examination (if necessary)	(X)	(X)	(X)		(X)	(X)	(X)	(X)	(X)	(X)	
Biochemistry, Haematology (mL)								5	(5)	5	
Exploratory immunology (mL)		up to 50	up to 50	up to 50	up to 50	up to 50	up to 50	up to 50[d]		up to 50[d]	

Attendance Number	1	2 V1	3 V2	4	5	6	7	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive+ 7 days	COVID-19 Follow-up
PAXgenes							(2.5)[P]	2.5		2.5	
Nose/Throat Swab and/or saliva sample								X	(X)	(X)	
Stool sample [a,b]										(X)	(X)
Weekly PCR sample[a]				ongoing							
Urinary bHCG (women of childbearing potential only)	X	X									
Blood volume per visit		50	50	50	50	50	50	up to 57.5		up to 57.5	
Cumulative blood volume[%]		50	100	150	200	250	300	357.5		415	

S = screening visit; (X) = if considered necessary; ** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window. Where a second dose is administered, the window will apply to the time their last vaccination took place. ^Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set observations will be taken, including respiratory rate and oxygen saturation. % Cumulative blood volume for volunteers if blood taken as per schedule, and excluding any repeat safety blood test that may be necessary. Blood volumes may vary according to local site equipment and practices. [a] Subject to site capacity, sample and test availability. [d] Optional and subject to site capacity. [$] A subset of up to 1000 volunteers will be asked to fill an e-diary with reactogenicity symptoms for 7 days only in groups 4, 6, 9 and 10. [P] Pax genes sample at D364 to be done only on participants with positive SARS-CoV-2 NAAT at COVID-19 testing visits, an extra 2.5mL should be added to the cumulative blood volume when this applies. [b] Optional Stool sample at approximately 7 days after onset of symptoms for those who have a positive SARS-CoV-2 NAAT test result and possibly again at 14 days after symptom onset if necessary.

Table 17 Schedule of attendances for participants in group 11.

Attendance Number	1	2 V1	3	4 V2	5	6	7	8	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Timeline** (days)		0	14	28	56 (28 days post boost)	118 (90 days post boost	210 (182 days post boost)	392 (364 days post boost)	As required	3-5 days post symptom onset	7 days post NAAT positive	
Time window (days)			±3	+14	±7	±14	±14	±30	N/A	+2	±2	
Informed Consent	X	X										
Review contraindications, inclusion and exclusion criteria	X	X										
Vaccination		X		X								
Vital signs^	X	X		(X)	(X)	(X)	(X)	(X)	X	(X)	X	
Telephone/Video call												As required
Ascertainment of adverse events		X		X	X	X	X	X	X	(X)	X	X
Diary Cards		(X)		(X)								
Symptoms diary												X
Weekly household exposure questionnaire		ongoing										

Attendance Number	1	2 V1	3	4 V2	5	6	7	8	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Medical History (required at 1 timepoint prior to enrolment),	X	X		(X)		(X)	(X)	(X)	(X)	(X)	(X)	
Physical Examination (if necessary)	(X)	(X)		(X)		(X)	(X)	(X)	(X)	(X)	(X)	
Biochemistry, Haematology (mL)									5	(5)	5	
Exploratory immunology (mL)		up to 50	up to 50	up to 50	up to 50	up to 50	up to 50	up to 50	up to 50[d]		up to 50[d]	
PAXgenes								(2.5)[p]	2.5		2.5	
Nose/Throat Swab and/or saliva sample									X	(X)	(X)	
Stool sample [a,b]											(X)	(X)
Weekly PCR sample[a]			Ongoing									
Urinary bHCG (women of childbearing potential only)	X	X										
Blood volume per visit		50	50	50	50	50	50	52.5	up to 57.5	5	up to 57.5	
Cumulative blood volume[%]	0	50	100	150	200	250	300	352.5	410	415	472.5	472.5

S = screening visit; (X) = if considered necessary; ** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window. Where a second dose is administered, the window will apply to the time their last vaccination took place. ^Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set observations will be taken, including respiratory rate and oxygen saturation. % Cumulative blood volume for volunteers if blood taken as per schedule,

and excluding any repeat safety blood test that may be necessary. Blood volumes may vary according to local site equipment and practices. [a] Subject to site capacity, sample and test availability. [d] Optional and subject to site capacity. [P] Pax genes sample at D364 to be done only on participants with positive SARS-CoV-2 NAAT at COVID-19 testing visits, an extra 2.5mL should be added to the cumulative blood volume when this applies. [b] Optional Stool sample at approximately 7 days after onset of symptoms for those who have a positive SARS-CoV-2 NAAT test result and possibly again at 14 days after symptom onset if necessary.

Table 18 Schedule of attendances for participants in group 12 (two dose)

Attendance Number	1[S]	2 (V1)	3	4	5	6 (V2)	7	8	9	10	11	12	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Timeline** (days)	≤ 90	0	3	7	14	28	31 (3 days post boost)	35 (7 days post boost)	42 (14 days post boost)	56 (28 days post boost)	182	364	As required	3-5 days post sympto m onset	7 days post NAAT positive	
Time window (days)			±1	±3	±3	+14	±1	±2	±3	±7	±14	±30	N/A	+2	±2	
Verbal Consent to discuss medical history over the phone	(X)															
Informed Consent	X															
Review contraindications, inclusion and exclusion criteria	X	X				X										
Vaccination		X				X										
Vital signs^	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X	
Telephone/Video call																As required
Ascertainment of adverse events		X	X	X	X	X	X	X	X	X	X	X	X	(X)	X	X
Diary cards provided		X				X										X
Diary cards collected						X				X						X
Weekly household exposure questionnaire			ongoing													

Attendance Number	1[$]	2 (V1)	3	4	5	6 (V2)	7	8	9	10	11	12	COVID-19 Testing	COVID-19 Testing +3-5 days	COVD-19 NAAT positive +7 days	COVID-19 Follow-up
Medical History, Physical Examination	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
SARS-CoV-2 Ab	5															
Biochemistry[$], Haematology (mL)	5	(5)*	5	5		5	5	5		5			5	(5)	5	
Exploratory immunology[£] (mL)		up to 95		up to 95	up to 95	up to 95		up to 95	up to 95	up to 95	up to 95	up to 95	up to 95		up to 95	
PAXgenes		2.5											2.5		2.5	
Nasal/Throat Swab, and/or Saliva sample													X	(X)	(X)	
Stool sample [a,b]															(X)	(X)
Weekly PCR sample			ongoing													
Urinary bHCG (women of childbearing potential only)	X	X				X										
HBsAg, HCV Ab, (mL)	5															
HIV serology (at investigators discretion)	(X)															
CD4 count and Viral Load	Up to 20mL															
Blood volume per visit	Up to 35	Up to 102.5	Up to 5	Up to 100	Up to 95	Up to 100	Up to 5	Up to 100	Up to 95	Up to 100	Up to 95	Up to 95	up to 102.5		up to 102.5	
Cumulative blood volume[%]	35	137.5	142.5	242.5	337.5	437.5	442.5	542.5	637.5	737.5	832.5	927.5	1030		1132.5	

S = screening visit; (X) = if considered necessary; ** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, ie, each visit must occur at indicated number of days after enrolment ± time window. ^Vital signs at screening or pre-enrolment assessment on D0 include pulse, blood pressure, temperature, respiratory rate +/- oxygen saturation. Only temperature will be routinely measured at subsequent follow-up visits. At COVID-19 testing visits a full set observations will be taken, including respiratory rate and oxygen saturation. % Cumulative blood volume for volunteers if blood taken as per schedule, and excluding any repeat safety blood test that may be necessary. Blood volumes may vary according to local site equipment and practices. *Safety bloods should only be repeated at vaccination day if there is a period greater than 2 weeks between screening and vaccination visit; an extra 5mL of blood should be added to the overall cumulative blood volume. [a] Subject to site capacity, sample and test availability. [b] Optional Stool sample at approximately 7 days after onset of symptoms for those who have a positive SARS-CoV-2 NAAT test result and possibly again at 14 days after symptom onset if necessary.

7.3.4 Participants under quarantine

Given the evolving epidemiological situation both globally and in the UK, should a participant be under quarantine and unable to attend any of the scheduled visits, a telephone/video consultation will be arranged in order to obtain core study data where possible.

7.3.5 Symptomatic volunteers

Participants who become symptomatic during follow-up will be instructed to call the study team who will then advise on how to proceed with clinical testing for COVID-19 if necessary, as per the trial working instructions. Participants will get weekly reminders (email or text messages) to get in touch with the study team if they present with a fever or cough or shortness of breath or anosmia/ageusia, experience any new event requiring medical attendance, or if they are admitted to hospital for any reason. At the COVID-19 testing visit, a nose/throat swab and/or saliva sample, blood samples for safety (FBC, Biochemistry, CRP and others if deemed clinically relevant) and immunology (paxgenes, cytokine profile, PBMCs, serum and others), vital signs and other clinical data will be taken. Symptomatic volunteers may be regularly reviewed over the phone or via video call using a smartphone or computer app if clinically appropriate.

Participants will be asked to attend a follow-up visit at 3-5 days post symptoms onset (+2 days) for clinical review and further testing or will be given a kit with instructions for a self-swab instead of a clinic visit. Participants will be asked to record information on COVID-19 related symptoms in an electronic diary for safety monitoring until symptom resolution or for at least 14 days. Participants who have a positive NAAT at S0, will not be required to attend a S3-5 visit (or provide a self-swab), but will be reviewed for safety at 7 days post positive swab. Clinical data, and additional blood samples for safety and immunology purposes will be taken at the S7 visit. Participants who have a positive swab at S3-5 will be reviewed for safety at 7 days post positive swab where clinical data, and additional blood samples for safety and immunology purposes will be taken. Participants who have 2 negative NAAT results from S0 and either a S3-5 visit or a self-swab will not be required to attend for an S7 visit. Closer follow-up and safety monitoring may be carried out by local trial teams if felt this is clinically indicated. If breathlessness is the only symptom that triggers a swab, further testing at S3-5 or S7 will be conducted at clinical discretion if there is no objective signs of respiratory distress (e.g. tachypnea, desaturation). Immunology samples from symptomatic volunteers will be optional at their COVID-19 testing visits and will be subject to local site capacity.

Participants who develop COVID-19 symptoms and have a positive NAAT test after the first vaccination can only receive a booster dose after a minimum 4 weeks interval from their first NAAT positive test, provided their symptoms have significantly improved. The decision to proceed with booster vaccinations in those cases will be at clinical discretion of the investigators. For participants who are asymptomatic and have a positive NAAT test, a minimum of 2 weeks from first NAAT positivity will be required before boosting.

7.3.6 Weekly PCR samples

Participants may be asked provide a saliva and/or a nose/throat self-swab sample every week from the date of enrolment, which will be posted and processed in the Department of Health and Social Care's community testing programme. . This process will be detailed in trial specific instructions. Weekly PCR samples will be collected and processed depending on test availability, laboratory capacity, and other local screening programmes, which will determine the number of participants asked to provide weekly samples.

Participants with a positive test result from home testing (self-swabbing) will be notified of their test results by the Department of Health and Social Care community testing programme and advised to self-isolate as per current government guidance. No additional trial follow up of these participants will occur at this time unless they become symptomatic. Symptomatic volunteers will then be reviewed follow the procedures outlined in section 7.3.5 above.

7.3.7 Stool samples

Those participants who have a SARS-CoV-2 positive NAAT test result, may be asked to provide a stool sample at approximately 7 days after symptom onset or positive NAAT result if asymptomatic and 14 days after the first sample if necessary, as per trial specific instructions. Samples will be processed to look at differences in viral shedding between the investigational vaccine and control arms, and to measure calprotectin levels as a marker of gastrointestinal inflammation. These samples will be collected and processed depending on test availability, laboratory capacity, and will not be compulsory to the volunteers. Further exploratory immunology and microbiology tests may be conducted at the investigators' discretion.

7.4 Household Weekly Questionnaire (optional)

Participants will be asked to record information on a weekly basis about illnesses amongst household contacts and friends, their contact with the general public, and infection control procedures. This will be optional.

Volunteers will be asked to enter data in a diary from baseline to the end of the follow-up period. This will be recorded via a web-based electronic diary to which participants will be provided access at baseline. Participants working in clinical areas will be exempt from this questionnaire to reduce the study load on these participants whose exposure to COVID-19 is likely to be in the workplace rather than the home or community.

7.4.1 Medical notes review

With the participant's consent, the study team will request access to medical notes or submit a data collection form for completion by attending clinical staff on any medically attended COVID-19 episodes. Any data which are relevant to ascertainment of efficacy endpoints and disease enhancement (AESI) will be collected. These are likely to include, but not limited to, information on ICU admissions, clinical parameters such as oxygen saturation, respiratory rates and vital signs, need for oxygen therapy, need for ventilatory support, imaging and blood tests results, amongst others.

7.4.2 Randomisation, blinding and code-breaking

Participants will be randomised to investigational vaccine or MenACWY in a 3:1:3:1 (Groups 1 and 7), 5:1:5:1 (Groups 2 and 8) and 1:1 (groups 3, 4, 5a, 5b, 5c, 6, 9 and 10) and 5:1 (group 5d) allocation, using block randomisation. Group 11 will be open-label and randomisation to investigational vaccine or comparator will not apply.

Participants will be blinded to the arm they have been allocated to, whether investigational vaccine or MenACWY. The trial staff administering the vaccine will not be blinded. Vaccines will be prepared out of sight of the participant and syringes will be covered with an opaque object/material until ready for administration to ensure blinding.

If the clinical condition of a participant necessitates breaking the code, this will be undertaken according to a trial specific working instruction and group allocation sent to the attending physician, if unblinding is thought to be relevant and likely to change clinical management.

Additional steps may be taken to keep clinical investigators assessing primary endpoints blinded to group allocation, where this is possible and practical to do so. A designated member of the clinical team may be unblinded for the purposes of safety reporting procedures. All data from participants with NAAT-positive swabs will be assessed for inclusion in the primary efficacy analysis by two blinded assessors who will independently review each case according to pre-specified criteria as detailed in the statistical analysis plan, to classify each for inclusion in the primary and secondary outcomes.

8 INVESTIGATIONAL PRODUCT

8.1 Description of ChAdOx1 nCoV-19

ChAdOx1 nCoV-19 vaccine consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigens of SARS-CoV-2.

8.2 Supply

ChAdOx1 nCoV-19 has been formulated and vialed at Advent S.r.I. (Pomezia, Italy). Labelling has been done at the Clinical BioManufacturing Facility (University of Oxford) or Advent S.r.I. (Pomezia, Italy). It will be certified by a Qualified Person (QP) at the Clinical BioManufacturing Facility (University of Oxford) before release and transfer to the clinical site.

ChAdOx1 nCoV-19 (AZD1222) has been formulated at Cobra Biologics Ltd, vialed at Symbiosis Pharmaceutical Services, and labelled and packaged at Thermo Fisher Scientific (Hertfordshire, United Kingdom). It will be certified by a Qualified Person (QP) at the MedImmune Pharma, BV (Nijmegen, The Netherlands) or MedImmune Ltd (Cambridge, United Kingdom) before release and transfer to the clinical site.

8.3 Storage

The vaccine manufactured by Advent is stored at nominal -80°C (+/- 20°C) in a secure freezer, at the clinical site. The vaccine manufactured by Cobra Biologics Ltd is stored at 2-8°C in a secure fridge, at the clinical site. All movements of the study vaccines will be documented in accordance with existing standard operating procedure (SOP). Vaccine accountability, storage, shipment and handling will be in accordance with relevant SOPs and forms. To allow for large number of participants to receive the vaccine in a short time period, additional clinic locations may be used. In this instance vaccines will be transported in accordance with local SOP's and approvals as required

8.4 Administration

On vaccination day, ChAdOx1 nCoV-19 will be allowed to thaw to room temperature and will be administered in accordance with trial specific instructions or stored at 2-8 for a maximum of 6 hours, where multiple doses are required from a single vial The vaccine manufactured by Cobra Biologics is a multi-dose vial which is stored at 2-8 degrees and does not require thawing. If the vaccine is stored outside of 2-8 it must be used within 6 hours. The vaccine will be administered intramuscularly into the deltoid of the non-dominant arm (preferably). All volunteers will be observed in the unit for a minimum of 15 minutes (+15 minutes) after vaccination. During administration of the investigational products, Advanced Life Support drugs and resuscitation equipment will be immediately available for the management of anaphylaxis. Vaccination will be performed and the IMPs handled according to the relevant SOPs.

8.5 Rationale for selected dose

The dose to be administered in this trial have been selected on the basis of clinical experience with the ChAdOx1 adenovirus vector expressing different inserts and other similar adenovirus vectored vaccines (eg. ChAd63).

A first-in-man dose escalation study using the ChAdOx1 vector encoding an influenza antigen (FLU004), safely administered ChAdOx1 NP+M1 at doses ranging from 5 x 10^8 to 5 x 10^{10} vp. Subsequent review of the data identified an optimal dose of 2.5 x 10^{10} vp balancing immunogenicity and reactogenicity. This dose has subsequently been given to over hundreds of volunteers in numerous larger phase 1 studies at the Jenner Institute. ChAdOx1 vectored vaccines have thus far demonstrated to be very well tolerated. The vast majority of AEs have been mild-moderate and there have been no SARs until this date.

Another simian adenovirus vector (ChAd63) has been safely administered at doses up to 2 x 10^{11} vp with an optimal dose of 5 x 10^{10} vp, balancing immunogenicity and reactogenicity.

MERS001 was the first clinical trial of a ChAdOx1 vectored expressing the full-length Spike protein from a separate, but related betacoronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5x10^9 vp to 5x10^{10} vp. Despite higher reactogeniticy observed at the 5x10^{10} vp, this dose was safe, with self-limiting AEs and no SARs recorded. The 5x10^{10} vp was the most immunogenic, in terms of inducing neutralising antibodies against MERS-CoV using a live virus assay [16]. Given the immunology findings and safety profile observed with a ChAdOx1 vectored vaccine against MERS-CoV, the 5x10^{10} vp dose was chosen for ChAdOx1 nCoV-19.

For children, a lower-dose of 2.5x10^{10} VP will be administered as the lower dose is likely to be less reactogenic and therefore more acceptable given the lower risk of severe illness in this age group.

The Clinical BioManufacturing Facility (CBF), who manufactured and tested batches 02P20-01 and 02P20-02 for the COV001 trial, determined vp/mL for Advent manufactured batch(es). This was done using a spectrophotometry-based methodology documented in their internal SOP (SOP A104). The doses to be administered in COV002, on Advent manufactured batches, will be determined by both methods (Abs260 and qPCR). Overseas studies conducted on Advent batch(es) will be dosed based on Advent's qPCR method. The University of Oxford is also performing a number of for information only tests for ChAdOx1 nCoV-19 batch(es) manufactured by Advent to demonstrate comparability between the different manufacturing processes and suitability of a reconstitution process involving dilution of the product with 0.9 % (w/v) saline that will be managed using local clinical trial SOPs available at each site/location.

For Advent Lot Number K.0007 the concentration is 1.7x10^{11} vp/mL (qPCR) which has been assessed by the CBF as equivalent to 3.89x10^{11} vp (Abs 260).

An analytical comparability assessment of ChAdOx1 nCoV-19 (AZD1222) manufactured by CBF, Advent and Cobra Biologics was conducted using a comprehensive set of physiochemical and biological release and characterization tests. In order to support the analytical comparability assessment, A260 testing of Advent's process (K.0007, K.0008, and K.0009 lots) was performed, where corrections to the absorbance due to excess polysorbate 80 were made to compensate for polysorbate 80 concentrations above the formulation target of 0.1% (w/v).

Differences in strength related attributes (ie, virus particle concentration, virus genome concentration, and infectious virus concentration) are noted. These differences in strength is further examined for potential impact on clinical dosing. The target clinical dosage of CBF's product is 5 × 10^{10} viral particles per dose based on vp/mL concentration determined by UV spectroscopy (A260), whereas that of Advent's product is 5 × 10^{10} viral genome copies per dose based on vg/mL concentration determined by qPCR. The target clinical dosage of Symbiosis' product is 3.5 – 6.5 × 10^{10} viral particles per dose based on the vp/mL concentration determined by A260, with a 0.5 mL dosing volume. This dosing range is based on a target 5 × 10^{10} viral particles per dose and a ± 30% range to take into account process and method variabilities. The planned

clinical dosage of Symbiosis' product is compared to that of CBF and Advent products, the resulting Symbiosis' product dosage at 0.5 mL for lot 20481A is somewhat lower in total viral particle per dose (20% from the lower range limit), slightly higher in total viral genome copies per dose (12% from the higher range limit), and slightly lower in total infectious particle per dose (8% from the lower range limit). These differences are considered to be comparable to or within the variabilities from the analytical methods used in concentration determination (A260, qPCR, and infectivity) and the dosing volumes during clinical administration. In summary, with a 0.5 mL dosing volume for Symbiosis' product, strength difference from CBF and Advent products is not expected to have significant clinical impact in terms of reactogenicity and immunogenicity/efficacy.

Table 19 Clinical Strengths of ChAdOx1 nCoV-19 (AZD1222) Drug Product

Strength Attribute	CBF		Advent			Cobra
	Lot 02P20-01	Lot 02P20-02	Lot K.0007	Lot K.0008	Lot K.0009	Lot 20481A
Concentration						
Virus particle concentration (A_{260}) (vp/mL)	1.49×10^{11}	1.22×10^{11}	3.12×10^{11}	3.16×10^{11}	2.45×10^{11}	0.8×10^{11}
Virus genome concentration (qPCR) (vg/mL)	1.7×10^{11}	Not tested	1.7×10^{11}	2.1×10^{11}	1.4×10^{11}	1.3×10^{11}
Infectious particle concentration (ifu/mL) [a]	2.6×10^{9}	Not tested	2.9×10^{9}	3.0×10^{9}	2.4×10^{9}	1.3×10^{9}
Target Clinical Dosage						
Equivalent DP volume per dose (mL)	0.34	0.41	0.294	0.235	0.356	0.50
Dosing of virus particle (vp/dose)	5.1×10^{10}	5.0×10^{10}	9.2×10^{10}	7.4×10^{10}	8.7×10^{10}	4.0×10^{10}
Dosing of viral genome (vg/dose)	5.8×10^{10}	NA	5.0×10^{10}	4.9×10^{10}	5.0×10^{10}	6.5×10^{10}
Dosing of infectious particle (ifu/dose)	8.8×10^{8}	NA	8.5×10^{8}	7.1×10^{8}	8.5×10^{8}	6.5×10^{8}

[a] ifu = infectious units; NA = not applicable; vp = virus particle; vg = virus genome

[a] **Testing performed using the Advent infectivity assay.**

8.6 Minimising environmental contamination with genetically modified organisms (GMO)

The study will be performed in accordance with the current version of the UK Genetically Modified Organisms (Contained Use) Regulations. Approved SOPs will be followed to minimise dissemination of the recombinant vectored vaccine virus into the environment. GMO waste will be inactivated according to approved SOPs.

8.7 Control vaccine

Participants who are allocated to the control groups will receive one or two injections of MenACWY vaccine instead of ChAdOx1 nCoV-19. Either of the two licensed quadrivalent protein - polysaccharide conjugate vaccine MenACWY vaccines will be used, i.e.:

- Nimenrix (Pfizer). The licensed posology of this vaccine for those over 6 months of age is a single (0.5ml) intramuscular dose, containing 5mcg each of *Neisseria meningitidis* group A, C, W and Y polysaccharide, each conjugated to 44 mcg tetanus toxoid carrier protein.
- Menveo (Glaxosmithkline). The licensed posology of this vaccine for those 2 years of age and over is a single (0.5ml) intramuscular dose, containing
    - 10 mcg meningococcal group A polysaccharide, conjugated to 16.7 to 33.3 mcg *Corynebacterium diphtheriae* CRM_{197} protein
    - 5mcg meningococcal group C polysaccharide, conjugated to 7.1 to 12.5 mcg *C. diphtheriae* CRM_{197} protein
    - 5mcg meningococcal group W polysaccharide, conjugated to 3.3 to 8.3 mcg *C. diphtheriae* CRM_{197} protein
    - 5mcg meningococcal group Y polysaccharide, conjugated to 5.6 to 10.0 mcg *C. diphtheriae* CRM_{197} protein

The summary of product characteristics for both vaccines allows for administration of a booster dose if indicated by ongoing risk, therefore allows for the two doses administered to a subset of participants in this study. Similarly, previous receipt of either vaccine (or a plain polysaccharide quadrivalent meningococccal A, C, W and Y vaccine) will not be a contraindication to receiving a further vaccine in this study.

Participants will be blinded as to which injection they are receiving. A vaccine accountability log of MenACWY will be maintained at each trial site. There will be no additional labelling of these vaccines beyond their licensed packaging.

MenACWY will be stored in a locked (or access controlled) refrigerator (2°C – 8°C) at the sites, as per SmPC.

8.8 Compliance with Trial Treatment

All vaccinations will be administered by the research team and recorded in the CRF. The study medication will be at no time in the possession of the participant and compliance will not, therefore, be an issue.

8.9 Accountability of the Trial Treatment

Accountability of the IMP and MenACWY will be conducted in accordance with the relevant SOPs.

8.10 Concomitant Medication

As set out by the exclusion criteria, volunteers may not enter the study if they have received: any vaccine in the 30 days prior to enrolment, any investigational product within 30 days prior to enrolment or if receipt is planned during the study period, or if there is any chronic use (>14 days) of any immunosuppressant medication within 6 months prior to enrolment or if receipt is planned at any time during the study period (topical steroids are permitted).

Participants on continuous use of oral anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban) will be excluded from this trial, as per the exclusion criteria.

Participants in groups 4 and 6 will be advised to take Paracetamol after vaccination at 1g every 4-6 hours for the first 24 hours (maximum dose 4g within 24 hours). This will not be a requirement for study participation, and participants will have the option to not follow the advice.

8.11 Provision of Treatment for Controls

If this vaccine is proven to be efficacious following analysis of the primary endpoint and if the DSMB agrees, participants allocated to MenACWY group may be offered the IMP, should extra doses become available.

9 ASSESSMENT OF SAFETY

Safety will be assessed by the frequency, incidence and nature of AEs and SAEs arising during the study.

9.1 Definitions

9.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a volunteer, which may occur during or after administration of an IMP and does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavourable and unintended sign (including any clinically significant abnormal laboratory finding or change from baseline), symptom or disease temporally associated with the study intervention, whether or not considered related to the study intervention.

9.1.2 Adverse Reaction (AR)

An AR is any untoward or unintended response to an IMP. This means that a causal relationship between the IMP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by the reporting medical Investigator as having a reasonable suspected causal relationship to an IMP (i.e. possibly, probably or definitely related to an IMP) will qualify as AR.

Adverse events that may be related to the IMP are listed in the Investigator's Brochure for each product.

9.1.3 Serious Adverse Event (SAE)

An SAE is an AE that results in any of the following outcomes, whether or not considered related to the study intervention.

- Death
- Life-threatening event (i.e., the volunteer was, in the view of the Investigator, at immediate risk of death from the event that occurred). This does not include an AE that, if it occurred in a more severe form, might have caused death.
- Persistent or significant disability or incapacity (i.e., substantial disruption of one's ability to carry out normal life functions).
- Hospitalisation or prolongation of existing hospitalisation, regardless of length of stay, even if it is a precautionary measure for continued observation. Hospitalisation (including inpatient or outpatient hospitalisation for an elective procedure) for a pre-existing condition that has not worsened unexpectedly does not constitute a serious AE.
- An important medical event (that may not cause death, be life threatening, or require hospitalisation) that may, based upon appropriate medical judgment, jeopardise the volunteer and/or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic reaction requiring intensive treatment in an emergency room or clinic, blood dyscrasias, or convulsions that do not result in inpatient hospitalisation.
- Congenital anomaly or birth defect.

9.1.4 Serious Adverse Reaction (SAR)

An AE that is both serious and, in the opinion of the reporting Investigator or Sponsors, believed to be possibly, probably or definitely due to an IMP or any other study treatments, based on the information provided.

9.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the IB.

9.2 Expectedness

No IMP related SAEs are expected in this study. All SARs will therefore be reported as SUSARs.

9.3 Foreseeable Adverse Reactions:

The foreseeable ARs following vaccination with ChAdOx1 nCoV-19 include injection site pain, tenderness, erythema, warmth, swelling, induration, pruritus, myalgia, arthralgia, headache, fatigue, fever, feverishness, chills, malaise, nausea and vomiting.

9.4 Adverse Events of Special Interest

Disease enhancement following vaccination with ChAdOx1 nCoV-19 will be monitored. Severe COVID-19 disease will be defined using clinical criteria. Detailed clinical parameters will be collected from medical records and aligned with agreed definitions as they emerge. These are likely to include, but are not limited to, oxygen saturation, need for oxygen therapy, respiratory rate, need for ventilatory support, imaging and blood test results, amongst other clinically relevant parameters.

Acute respiratory distress, pneumonitis, acute cardiac injury, arrhythmia, septic-shock like syndrome and acute kidney injury related with COVID-19 disease will be monitored from medical records review of hospitalised participants.

Kawasaki-like disease and other hyperinflammatory syndromes will be monitored and recorded as AESI in the paediatric group.

Eosinophilia as a marker skewed Th2 responses will be routinely monitored in participants attending their COVID-19 testing and follow-up visits. Marked eosinophilia of ≥ 1.5 x109/L will be reported as an SAE.

AESI relevant to vaccination in general will also be monitored such as: generalised convulsion, Guillain-Barre Syndrome (GBS), Acute Disseminated Encephalomyelitis (ADEM), Thrombocytopenia, Anaphylaxis, Vasculitides in addition to serious solicited AEs will be monitored.

9.5 Causality

For every AE, an assessment of the relationship of the event to the administration of the vaccine will be undertaken by the CI-delegated clinician. An interpretation of the causal relationship of the intervention to the AE in question will be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of the vaccine therapy (Table 13). Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination will be considered and investigated. Causality assessment will take place during planned safety reviews, interim analyses (e.g. if a holding or stopping rule is activated) and at the final safety analysis, except for SAEs, which should be assigned by the reporting investigator, immediately, as described in SOP OVC005 Safety Reporting for CTIMPs.

0	**No Relationship**	No temporal relationship to study product ***and*** Alternate aetiology (clinical state, environmental or other interventions); ***and*** Does not follow known pattern of response to study product
1	**Unlikely**	Unlikely temporal relationship to study product ***and*** Alternate aetiology likely (clinical state, environmental or other interventions) ***and*** Does not follow known typical or plausible pattern of response to study product.
2	**Possible**	Reasonable temporal relationship to study product; ***or*** Event not readily produced by clinical state, environmental or other interventions; ***or*** Similar pattern of response to that seen with other vaccines
3	**Probable**	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions ***or*** Known pattern of response seen with other vaccines
4	**Definite**	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions; ***and*** Known pattern of response seen with other vaccines

Table 20. Guidelines for assessing the relationship of vaccine administration to an AE.

9.6 Reporting Procedures for All Adverse Events

All local and systemic AEs occurring in the 28 days following each vaccination observed by the Investigator or reported by the volunteer, whether or not attributed to study medication, will be recorded in electronic diaries or study database. Participants in a subset of groups 4 and 6 will be asked to record local and systemic AE's for 7 days following vaccination in the electronic diary. Any unsolicited AEs reported by participants in any group at subsequent routine visits will be documented on the eCRF until at least 6 months of safety data has accrued for ChAdOx1 nCOV19. All AEs that result in a volunteer's withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if the volunteer consents to this). SAEs and Adverse Events of Special Interest will be collected throughout the entire trial period.

9.7 Assessment of severity

The severity of clinical and laboratory adverse events will be assessed according to scales based on FDA toxicity grading scales for healthy and adolescent volunteers enrolled in preventive vaccine clinical trials, listed in the study specific working instructions and tables 14-16 below.

Adverse Event	Grade	Intensity
Pain at injection site	1	Pain that is easily tolerated
	2	Pain that interferes with daily activity
	3	Pain that prevents daily activity
	4	A&E visit or hospitalization
Tenderness	1	Mild discomfort to touch
	2	Discomfort with movement
	3	Significant discomfort at rest
	4	A&E visit or hospitalization
Erythema at injection site*	1	2.5 - 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis or exfoliative dermatitis
Induration/Swelling at injection site	1	2.5 – 5 cm and does not interfere with activity
	2	5.1 - 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
	4	Necrosis

Table 21. ***Severity grading criteria for local adverse events*** **erythema ≤2.5cm is an expected consequence of skin puncture and will therefore not be considered an adverse event*

Vital Signs	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 Potentially Life threatening
Fever (oral)	38.0°C - 38.4°C	38.5°C – 38.9°C	39.0°C - 40°C	> 40°C
Tachycardia (bpm)*	101 - 115	116 – 130	>130	A&E visit or hospitalisation for arrhythmia
Bradycardia (bpm)**	50 – 54	45 – 49	<45	A&E visit or hospitalisation for arrhythmia
Systolic hypertension (mmHg)	141 - 150	151 – 155	≥155	A&E visit or hospitalization for malignant hypertension

Diastolic hypertension (mmHg)	91 - 95	96 – 100	>100	A&E visit or hospitalization for malignant hypertension
Systolic hypotension (mmHg)***	85 - 89	80 – 84	<80	A&E visit or hospitalization for hypotensive shock
Respiratory Rate –breaths per minute	17 - 20	21-25	>25	Intubation

*Table 22**. Severity grading criteria for physical observations (applies to adults only).***
**Taken after ≥10 minutes at rest **When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterising bradycardia among some healthy subject populations, for example, conditioned athletes. ***Only if symptomatic (e.g. dizzy/ light-headed)*

GRADE 0	None
GRADE 1	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
GRADE 2	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
GRADE 4	Potentially Life-threatening: requires assessment in A&E or hospitalisation

Table 23. Severity grading criteria for local and systemic AEs. NB: A&E assessment in itself does not constitute a SAE. Refer to 9.1.3 for SAE definition

9.8 Reporting Procedures for Serious AEs

In order to comply with current regulations on SAE reporting to regulatory authorities, the event will be documented accurately and notification deadlines respected. SAEs will be reported on the SAE forms to members of the study team immediately the Investigators become aware of their occurrence, as described in SOP OVC005 Safety Reporting for CTIMPs. Copies of all reports will be forwarded for review to the Chief Investigator (as the Sponsor's representative) within 24 hours of the Investigator being aware of the suspected SAE. The DSMB will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the chair of DSMB will be notified immediately (within 24 hours) of the sponsor being aware of their occurrence. SAEs will not normally be reported immediately to the ethical committee(s) unless there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial volunteers, at the discretion of the Chief Investigator and/or DSMB. In addition to the expedited reporting above, the Investigator shall include all SAEs in the annual Development Safety Update Report (DSUR) report.

Grade 4 laboratory AEs should be reported as SAEs and under the category of outcome of an important medical event. A&E attendances should not routinely be reported as SAEs unless they meet the SAE definition described above.

Cases falling under the Hy's Law should be reported as SAEs. A Hy's Law Case is defined by FDA Guidance for Industry "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (2009). Any study participant with an increase in Aspartate Aminotransferase (AST) or **Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin ≥2xULN**, **where no other reason can be found to explain the combination of these abnormal results**, e.g., elevated serum alkaline phosphatase (ALP) indicating cholestasis, viral hepatitis A, B or C, another drug capable of causing the observed injury, amongst others.

9.9 Reporting Procedures for SUSARS

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional

relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

9.10 Development Safety Update Report

A Development Safety Update Report (DSUR) will be prepared annually, within 60 days of the anniversary of the first approval date from the regulatory authority for each IMP. The DSUR will be submitted by the CI to the Competent Authority, Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

9.11 Procedures to be followed in the event of abnormal findings

Eligibility for enrolment in the trial in terms of laboratory findings will be assessed by clinically qualified staff. Abnormal clinical findings from medical history, examination or blood tests will be assessed as to their clinical significance throughout the trial. Laboratory AEs will be assessed using specific toxicity grading scales adapted from the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Paediatric laboratory AEs will be assessed using site specific paediatric laboratory reference ranges, values outside of these age specific ranges will be reviewed by a study clinician to determine clinical significance. If a test is deemed clinically significant, it may be repeated, to ensure it is not a single occurrence. If a test remains clinically significant, the volunteer will be informed and appropriate medical care arranged as appropriate and with the permission of the volunteer. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator

9.12 Interim Safety Reviews

The safety profile will be assessed on an on-going basis by the Investigators. The CI and relevant Investigators (as per the trial delegation log) will also review safety issues and SAEs as they arise.

Immunopathology data from pre-clinical and phase 1 studies will be assessed by the CI, relevant investigators and the DSMB as soon as they are available and before any volunteers receive a dose of the IMP.

The DSMB will evaluate frequency of events, safety and efficacy data every 4-8 weeks and/or as required. The DSMB will make recommendations concerning the conduct, continuation or modification of the study.

In particular, the DSMB will review the data at the following key timepoints:

- Before vaccination of the first participant (all accumulated data available will be reviewed from COV001, with a minimum 4 weeks safety and immunogenicity data from the first 54 participants receiving the IMP and all accumulated data from the animal studies)

- Prior to expansion of the recruitment of groups 4 and 6 in those aged older than 55 years (data will be reviewed from groups 1 and 2)
- Prior to enrolment of the first child (all data available will be reviewed from both studies, with a minimum 4 weeks safety data from groups 1 and 2 in COV002 and 4 weeks safety data from all volunteers recruited into COV001)

9.13 Data Safety Monitoring Board

The Data Safety Monitoring Board that is in place for COV001 will also oversee COV002 and review data from both studies combined

The chair of the DSMB may be contacted for advice and independent review by the Investigator or trial Sponsor in the following situations:

• Following any SAE deemed to be possibly, probably or definitively related to a study intervention.

• Any other situation where the Investigator or trial Sponsor feels independent advice or review is important.

The DSMB will review SAEs deemed possibly, probably or definitively related to study interventions. The DSMB will be notified within 24 hours of the Investigators' being aware of their occurrence. The DSMB can recommend placing the study on hold if deemed necessary following a study intervention-related SAE.

The DSMB will only be able to judge the short-term safety of the ChAdOx1 nCoV-19 vaccine. Given the complexity of the underlying immunology and the minimal immunological data that will be available for review early in the study, the DSMB will not be in a position to comment on the effects of a later wave of SARS-CoV-2 as vaccine-induced immunity wanes and the theoretical risk of immune enhancement increases.

9.14 Safety Group Holding Rules

These safety holding rules apply to ChAdOx1 nCoV-19 vaccine only. Staggered enrolment will apply to group 3 where half of the overall number of participants allocated to the IMP arm will be vaccinated first and their safety data reviewed after 7 days before enrolment of the remainder. Solicited, unsolicited and laboratories adverse events will be systematically collected in groups 1, 2, 3, 5, 7 and 8. Only a sub-set of up to 1000 participants in each of Groups 4 and 6 will be asked to record solicited and unsolicited AEs for 7 days.

- **Solicited local adverse events:**
    - If more than 25% of doses of the vaccine at a given time point (e.g. Day 0, Day 28) in a study group are followed by the same Grade 3 solicited local adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at Grade 3 for >72 hrs
- **Solicited systemic adverse events:**

- If more than 25% of doses of the vaccine at a given time point (e.g. Day 0, Day 28) in a study group are followed by the same Grade 3 solicited systemic adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at Grade 3 for >72 hrs

- **Unsolicited adverse events:**
  - If more than 25% of doses of the vaccine at a given time point (e.g. Day 0, Day 28) in a study group are followed by the same Grade 3 unsolicited adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at Grade 3 for >72 hrs

- **Laboratory adverse event:**
  - If more than 25% of doses of the vaccine at a given time point (e.g. Day 0, Day 28) in a study group are followed by the same Grade 3 laboratory adverse event beginning within 3 days after vaccination and persisting at Grade 3 for >72 hrs

- **A serious adverse event considered possibly, probably or definitely related to vaccination occurs**
  - If an SAE occurs in any one individual, which is possibly, probably or definitely related to vaccination this would trigger a holding rule. There are two exemptions from this rule, which would not activate a holding rule. These include:
    - COVID-19 related hospital admissions considered to be at least possibly related to ChAdOx1 nCoV-19 (e.g. if considered to be a clinical presentation of a disease enhancement episode). COVID-19 related SAEs will be regularly reviewed by the DSMB, and a single event will not trigger a holding rule.
    - SAEs reported under the Hy's Law requirement will not necessarily trigger a holding rule. These cases will also be reviewed by the DSMB

If any of the above holding rules are activated, then further vaccinations in any of the groups will not occur until a safety review by the DSMB, study sponsor and the chief investigator has been conducted and it is deemed appropriate to restart dosing. The Regulatory Authority will be informed and a request to restart dosing with pertinent data will be submitted as a substantial amendment. The safety review will consider:

- The relationship of the AE or SAE to the vaccine.
- The relationship of the AE or SAE to the vaccine dose, or other possible causes of the event.
- If appropriate, additional screening or laboratory testing for other volunteers to identify those who may develop similar symptoms and alterations to the current Participant Information Sheet (PIS) are discussed.

- New, relevant safety information from ongoing research programs on the various components of the vaccine.

The local ethics committee and vaccine manufacturers will also be notified if a holding rule is activated or released.

All vaccinated volunteers will be followed for safety until resolution or stabilisation (if determined to be chronic sequelae) of their AEs.

9.14.1 Individual stopping rules (will apply to prime-boost groups only)

In addition to the above stated group holding rules, stopping rules for individual volunteers will apply (i.e., indications to withdraw individuals from further vaccinations). Study participants who present with at least one of the following stopping rules will be withdrawn from further vaccination in the study:

- **Local reactions:** Injection site ulceration, abscess or necrosis

- **Laboratory AEs:**

  the volunteer develops a Grade 3 laboratory AE considered possibly, probably or definitely related within 7 days after vaccination and persisting continuously at Grade 3 for > 72hrs.

- **Systemic solicited adverse events:**
  - the volunteer develops a Grade 3 systemic solicited AE considered possibly, probably or definitely related within 2 days after vaccination (day of vaccination and one subsequent day) and persisting continuously at Grade 3 for > 72hrs.

- **Unsolicited adverse events:**
  - the volunteer has a Grade 3 adverse event, considered possibly, probably or definitely related to vaccination, persisting continuously at Grade 3 for >72hrs.
  - the volunteer has a SAE considered possibly, probably or definitely related to vaccination.
  - the volunteer has an acute allergic reaction or anaphylactic shock following the administration of vaccine investigational product.

If a volunteer has an acute respiratory illness (moderate or severe illness with or without fever) or a fever (oral temperature greater than 37.8°C) at the scheduled time of administration of investigational product/control, the volunteer will not be enrolled and will be withdrawn from the study.
All vaccinated volunteers will be followed for safety until the end of their planned participation in the study or until resolution or stabilisation (if determined to be chronic sequelae) of their AEs, providing they consent to this.

In addition to these pre-defined criteria, the study can be put on hold upon advice of the DSMB, Chief Investigator, Study Sponsor, regulatory authority, Ethical Committee(s), for any single event or

combination of multiple events which, in their professional opinion, jeopardise the safety of the volunteers or the reliability of the data.

10 STATISTICS

10.1 Description of Statistical Methods

Both a fully detailed study level statistical analysis plan (SAP) as well as a separate Statistical Analysis Plan for the Marketing Authorisation Application (MAA SAP) will be written and signed off before any interim data analyses are conducted.

The data from this study will be included in prospective pooled analyses of studies for efficacy and safety of ChAdOx1 nCoV-19 to provide greater precision of both efficacy and safety outcomes.

10.1.1 Efficacy Outcomes

The primary efficacy endpoint is PCR* positive symptomatic COVID-19.

This is defined as a participant with a PCR+* swab and at least one of the following symptoms: cough, fever ≥ 37.8, shortness of breath, anosmia, or ageusia.

Where possible, sensitivity analyses will be conducted using common alternative definitions of virologically-confirmed COVID-19 disease, including those in use in other phase 3 protocols (including but not limited to: USA AstraZeneca phase 3 trial, South Africa COV005 trial, WHO solidarity trial, CEPI definition). This will aid in comparisons between various studies and meta-analyses. These alternative definitions will be detailed in the statistical analysis plan as exploratory analyses.

*or other nucleic acid amplification test

10.2 Primary efficacy

The primary and secondary analyses will be conducted on participants who are seronegative at baseline. A sensitivity analysis will be conducted including all participants regardless of baseline serostatus.

Analysis of the primary endpoint will be computed as follows:

1. **Efficacy of two doses of vaccine** where the booster vaccine was a high-dose ChAdOx1 nCoV-19. Only participants who received two doses will be included (LD/SD or SD/SD) and only cases occurring more than 14 days after the second vaccine will be included.

Secondary analysis
2. **Efficacy of at least one standard-dose** of any ChAdOx1 nCoV-19. Cases occurring more than 21 days after the first vaccination will be included if the first vaccine was a high-dose vaccine. For
participants who received a low-dose as their first vaccine, only cases occurring more than 14 days after a standard-dose booster will be included. Participants receiving only low-dose vaccines will be excluded.

3. **Efficacy of two standard-doses of vaccine**. Only participants who received two standard-dose vaccines will be included and only cases occurring more than 14 days after the second vaccine will be included.

Proportions will be compared between ChAdOx1 nCoV-19 and MenACWY groups using a Poisson regression model with robust variance (Zou 2004). The model will contain terms including treatment group, and age group at randomization if there is a sufficient sample size within each age category. The logarithm of the period at risk for primary endpoint will be used as an offset variable in the model to adjust for volunteers having different follow up times during which the events occur. Vaccine efficacy (VE) will be calculated as (1 – RR) x 100%, where RR is the relative risk of symptomatic infection (ChADOx1 nCoV-19: Control) and 95% confidence intervals will be presented.

If the Poisson regression model with robust variance fails to converge, the exact conditional method for stratified poisson regression will be used.

Cumulative incidence of symptomatic infections will be presented using the Kaplan-Meier method.

Secondary efficacy endpoints will be analysed in the same way as the primary efficacy endpoint.

Analyses will conducted for all adults combined as well as conducting analyses stratified by age cohorts.

All data from participants with PCR-positive swabs will be assessed for inclusion in the efficacy analyses by two blinded assessors who will independently review each case according to pre-specified criteria as detailed in the statistical analysis plan, to classify each for inclusion in the primary and secondary outcomes. A separate CRF will be designed for this purpose.

All PCR-positive results will be assessed for the primary outcome, including those with symptoms swabbed by trial staff, those with positive throat swabs from weekly home-testing, and other potential sources of information such as health-care workers who are tested at their workplace as either a routine test procedure or due to developing symptoms.

PCR+ swabs from outside the trial (for example, a workplace routine swab result in a healthcare worker) will be reviewed by blinded staff and only included as a potential endpoint if the test was conducted in 1) a medical laboratory with ISO 15189 accreditation (provided by UKAS in UK) AND 2) an assay that is either CE marked or that has a derogation authorisation from the MHRA.

*or other nucleic acid amplification test

10.3 Safety & Reactogenicity

Counts and percentages of each local and systemic solicited adverse reaction from diary cards, and all unsolicited AEs and SAEs will be presented for each group.

10.4 Immunogenicity

Highly skewed antibody data will be log-transformed prior to analysis. The geometric mean concentration and associated 95% confidence interval will be summarised for each group at each timepoint, by computing the anti-log of the mean difference of the log-transformed data.

The geometric mean concentration at day 28 and the proportion of participants seroconverting to the S-spike protein from day 0 to day 28 will be computed. Comparisons between ChAdOx1 nCoV-19 vaccine and MenACWY groups will be made using a Mann Whitney U test due to the low titres expected in the control group which will cause a non-normal distribution.

In addition, those aged 56 years or older receiving either a single-dose or two-doses of ChAdOx1 nCoV-19 vaccine will be compared with those in phase 1 (COV001) aged 18-55 years who received single-dose ChAdOx1 nCoV-19.

Spike-specific T cell responses (ELISpot) will be presented as means and confidence intervals, or medians and interquartile ranges if non-normally distributed at all post vaccination time points. Comparisons between ChAdOx1 nCoV-19 vaccine and MenACWY groups will be made using a Mann Whitney U test due to the low responses expected in the control group which will cause a non-normal distribution. Comparison between two different dose levels of ChAdOx1 nCoV-19 will be made using t-tests. In addition, those aged 56 years or older receiving either a single-dose or two-doses of ChAdOx1 nCoV-19 vaccine will be compared with those in phase 1 (COV001) aged 18-55 years who received single-dose ChAdOx1 nCoV-19.

10.5 Subgroup analyses

Subgroup comparisons of efficacy, and safety will be conducted by incorporating vaccine-group by subgroup interaction terms into appropriate regression models. Subgroup comparisons will only be conducted if there are at least 5 cases in all subgroups.

Comparisons will include:
1. Males vs females

2. Age (18 to 55 years vs 56-<70 years vs 70+ years)

3. Seropositive to S-spike or non-spike proteins at baseline vs not seropositive

4. Health care workers and highly-exposed participants versus others

5. Standard dose versus low dose

10.6 Interim and primary analyses of the primary outcome

It is planned that the primary evidence of efficacy and safety for the ChADOx1 nCoV-19 vaccine will be based on global analyses utilizing studies COV001 (the UK P1/2 study), COV002 (the UK P2/3 study), COV003 (the Brazil P3 study) and COV005 (the South Africa P1/2 study) including a pooled analysis across the studies. As such the interim and primary analyses for the primary outcome will be based on cases accumulated across multiple studies, details of which will be specified within the MAA SAP rather than for each individual study. Interim and primary data cuts from this study will therefore be carried out to support the pooled analysis.

The global MAA SAP allows for interim and primary analyses to be conducted once sufficient eligible cases have accumulated, where the overall type 1 error is controlled at the 5% level using a flexible alpha–spending approach that accounts for the incorporation of data from this study into pooled interim analyses under the global MAA SAP.

Evidence of efficacy will be determined if the lower bound of the multiplicity adjusted confidence interval is greater than a 20% threshold. The primary analysis will have approximately 90% power assuming a vaccine efficacy of 60%. A flexible alpha spending approach will be implemented to allow an earlier primary analysis in the situation where accumulation of eligible cases were lower than expected.

Evidence of efficacy at an interim or primary analysis of pooled data will not be considered a reason to stop the trial, but instead will be interpreted as early evidence of efficacy. However if an interim analysis demonstrates evidence of efficacy then a study level analysis according to the study SAP may be used to support study level evidence of efficacy.

10.7 Final Analysis

A final analysis will be conducted at the end of the study. The final study-specific analysis will incorporate all data from the study, including data that has previously contributed to global efficacy estimates under the pooled analysis strategy. The final analysis will be considered a supportive analysis to the global efficacy analysis. Alpha at the final study-specific analysis will be adjusted to incorporate the number of previous global analyses to which the study contributed data in order to control the overall study level type 1 error at 5%. Details will be specified in the study level SAP.

10.8 Procedure for Accounting for Missing, Unused, and Spurious Data.

All available data will be included in the analysis

10.9 Inclusion in Analysis

All vaccinated participants will be included in the analysis unless otherwise specified in the SAP.

10.10 Interim analysis for the combined DSMB

The independent DSMB will meet regularly to review safety data from all available studies of ChAdOx1 nCoV-19 and will assess whether the assumptions underlying the sample size calculation are in line with the observed cases. Additionally the independent DSMB will make recommendations based on the interim analyses to assess evidence of efficacy.

11 DATA MANAGEMENT

11.1 Data Handling

The Chief Investigator will be responsible for all data that accrues from the study.

All study data including participant diary will be recorded directly into an Electronic Data Capture (EDC) system (e.g. OpenClinica, REDCap, or similar) or onto a paper source document for later entry into EDC if direct entry is not available. This includes safety data, laboratory data and outcome data. Any additional information that needs recording but is not relevant for the CRF (such as signed consent forms etc.) will be recorded on a separate paper source document. All documents will be stored safely and securely in confidential conditions.

All adverse event data (both solicited and unsolicited) reported by the volunteer will be entered onto a volunteer's electronic diary card (eDiary) for a maximum of 28 days following administration of the IMP. The eDiary provides a full audit trial of edits and will be reviewed at time-points as indicated in the schedule of events. Any adverse event continuing beyond the period of the diary will be copied into the eCRF and followed to resolution, if there is a causal relationship to the IMP, or to the end of the study if there is no causal relationship.

The participants will be identified by a unique trial specific number and code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file, with the exception of the electronic diaries and household questionnaire, for which consent will be obtained to store the participant email address for quality control purposes. Only site research staff and sponsor data managers have access to view the email address.

The EDC system (CRF data) uses a relational database (MySQL/ PostgreSQL) via a secure web interface with data checks applied during data entry to ensure data quality. The database includes a complete suite of features which are compliant with GCP, EU and UK regulations and Sponsor security policies, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL and PostgreSQL database and the webserver will both be housed on secure servers maintained by the University of Oxford IT personnel. The servers are in a physically secure location in Europe. Backups will be stored in accordance with the IT department schedule of daily, weekly, and monthly retained for one month, three months, and six months, respectively. The IT servers provide a stable, secure, well-maintained, and high capacity data storage environment. REDCap and OpenClinica are widely-used, powerful, reliable, well-supported systems. Access to the study's database will be restricted to the members of the study team by username and password.

If participants consent to provide stool samples; the stool sample (in an anonymised form) will be collected from them by a courier and processed in a laboratory by International Health Management Associates (IHMA), an accredited central laboratory. The sample will then be shipped for analysis by Astra Zeneca in a laboratory in the US. The participant would need to provide their name and address to the courier company.

11.2 Record Keeping

The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, co-Investigators and clinical research nurses will have access to records. The Investigators will permit authorised representatives of the Sponsor(s), as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Identifiable information such as contact details will be stored for a minimum of 5 years and until the youngest participant turns 21 years. De-identified research data maybe be stored indefinitely. If volunteers consent to be contacted for future research, information about their consent form will be recorded, retained and stored securely and separately from the research data. If volunteers consent to have their samples stored and used in future research, information about their consent form will be recorded, retained and stored securely as per Biobanking procedures and SOP.

11.3 Source Data and Case Report Forms (CRFs)

All protocol-required information will be collected in CRFs designed by the Investigator. All source documents will be filed in the CRF. Source documents are original documents, data, and records from which the volunteer's CRF data are obtained. For this study, these will include, but are not limited to, volunteer consent form, blood results, GP response letters, laboratory records, diaries, medical records and correspondence. In the majority of cases, CRF entries will be considered source data as the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). In this study this will include, but is not limited to medical history, medication records, vital signs, physical examination records, urine assessments, blood results, adverse event data and details of vaccinations. All source data and volunteer CRFs will be stored securely.

To prevent withdrawal of a participant due to relocation, if there is a nearby participating site and with the consent of the participant, copies of relevant participant research records (such as ICF, paper source documents) will be transferred to the local site using secure email addresses such as nhs.net or by password protected sheets. The electronic research data stored on REDCap will also be transferred to the new site. The original records will be retained by the recruiting site.

11.4 Data Protection

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the sponsor.

11.5 Data Quality

Data collection tools will undergo appropriate validation to ensure that data are collected accurately and completely. Datasets provided for analysis will be subject to quality control processes to ensure analysed data is a true reflection of the source data.

Trial data will be managed in compliance with local data management SOPs. If additional, study specific processes are required, an approved Data Management Plan will be implemented

11.6 Archiving

Study data may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the site. All essential documents will be retained for a minimum of 5 years after the study has finished. The need to store study data for longer in relation to licensing of the vaccine will be subject to ongoing review. For effective vaccines that may be licensed, we may store research data securely at the site at least 15 years after the end of the study, subject to adjustments in clinical trials regulations. Where relevant participants' bank details will be stored for 7 years in line with the site financial policy. De-identified research data maybe be stored indefinitely

General archiving procedures will be conducted in compliance to SOP OVC020 Archiving.

12 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

12.1 Investigator procedures

Approved site-specific standard operating procedures (SOPs) will be used at all clinical and laboratory sites.

12.2 Trial Steering Committee

A Trial Steering Committee will be appointed and will consist of an independent Chairman, not less than two other independent members and the Chief Investigator. All significant operational matters relating to the research will be decided upon by the trial steering committee that would have as main objectives:

- provide advice, through its chair, to the investigators, the trial sponsor, the collaborators on all appropriate aspects of the trial
- concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
- agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments

The trial steering committee will meet regularly and as required.

12.3 Monitoring

Regular monitoring will be performed according to GCP by the monitor. Following written SOPs, the monitor will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The site will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the Sponsor and inspection by local and regulatory authorities.

12.4 Protocol deviation

Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file. Each deviation will be assessed as to its impact on volunteer safety and study conduct. Significant protocol deviations will be listed in the end of study report.

12.5 Audit & inspection

The QA manager conducts systems based internal audits to check that trials are being conducted according to local procedures and in compliance with study protocols, departmental SOPs, GCP and applicable regulations.

The Sponsor, trial sites, and ethical committee(s) may carry out audit to ensure compliance with the protocol, GCP and appropriate regulations.

GCP inspections may also be undertaken by the MHRA to ensure compliance with protocol and the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended. The Sponsor will assist in any inspections and will support the response to the MHRA as part of the inspection procedure.

13 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a potential serious breach is suspected the Sponsor will be informed as soon as possible, to allow preliminary assessment of the breach and reporting to the MHRA within the required timelines.

14 ETHICS AND REGULATORY CONSIDERATIONS

14.1 Declaration of Helsinki

The Investigators will ensure that this study is conducted according to the principles of the current revision of the Declaration of Helsinki.

14.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3 Ethical and Regulatory Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. No amendments to this protocol will be made without consultation with, and agreement of, the Sponsor.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for which regulatory and ethical committee(s) approval has already been given, are not initiated without regulatory and ethical committee(s)' review and approval except to eliminate apparent immediate hazards to the subject (i.e. as an Urgent Safety Measure).

14.4 Volunteer Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of informed consent forms, participant ID logs, electronic diaries and the Household Questionnaire. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. A separate confidential file containing identifiable information will be stored in a secured location in accordance with the current data protection legislation. Photographs taken of vaccination sites (if required, with the volunteer's written, informed consent) will not include the volunteer's face and will be identified by the date, trial code and subject's unique identifier. Once developed, photographs will be stored as confidential records, as above. This material may be shown to other professional staff, used for educational purposes, or included in a scientific publication.

If participants have a positive swab result for COVID-19 during the course of the study then the Public Health Authority will be notified as COVID-19 is a "notifiable disease" and this is a legal requirement in the UK. This may mean participants personal information from their health records will be shared with Public Health either by the processing lab or the study site. Participants may also be contacted by the NHS Test and Trace service. Samples collected using home swab kits may be processed at laboratories within and outside the UK, as determined by the community testing programme. These laboratories provide a test result for the barcode to NPEx (National Pathology Exchange) and this result is then recombined with participant identifiable information by NHS Digital. NHS Digital provide lab results to the Sponsor (University of Oxford) who will match this with personal data including identifying contact information sent to them by the site in order to centralise the processing of weekly surveillance results. Participants will be required to separately consent to the terms and conditions of the national community swabbing programme, each time they perform a self-swab. This is available at: https://www.gov.uk/government/publications/coronavirus-covid-19-testing-privacy-information/testing-for-coronavirus-privacy-information

15 FINANCING AND INSURANCE

15.1 Financing

The study is funded by the UK Government through the National Institute for Health Research (NIHR). AstraZeneca have provided funding for some exploratory objectives.

15.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

15.3 Compensation

Volunteers in groups 1, 2, 5, 7, 8 and 12 will be compensated for their time, the inconvenience of having blood tests and procedures, and their travel expenses. The total amount compensated will be approximately £390-555 depending on the exact number of visits, and whether any repeat or additional visits are necessary. They will be compensated £25 for attending the screening visit. For all other trial visits as outlined in Tables 5-14, compensation will be calculated according to the following:

- Travel expenses: £15 per visit
- Inconvenience of blood tests: £10 per blood donation
- Time required for visit: £20 per hour

Paediatric volunteers in group 3 will be compensated approximately £50 depending on the exact number of visits, and whether any repeat or additional visits are necessary. They will receive a £10 voucher for each study visit which will be given on completion of the trial. Should a volunteer from any group decide to withdraw from the trial before it is completed, payment will be pro rata.

Participants in Groups 4, 6, 9, 10 and 11 will not be compensated.

15.4 Publication Policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Data from the study may also be used as part of a thesis for a PhD or MD.

16 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University rests in the University. The protection and exploitation of any new IP is managed by the University's technology transfer office, Oxford

University Innovations. Investigators in this study may benefit from the royalty sharing policy of the University if new intellectual property is generated from the trial. Several investigators are applicants or co-inventors on previous patent filings or patents related to ChAdOx1 vaccines. The University of Oxford, which is partnered with the Oxford University Hospitals NHS Foundation Trust in the NIHR Oxford Biomedical Research Centre, is committed to the translational progress and commercial development of healthcare products potentially meeting medical and global health needs, and does and will work with commercial partners towards these goals.

References

1 Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine* **382**, 727-733, doi:10.1056/NEJMoa2001017 (2020).

2 Lu, R. *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* **395**, 565-574, doi:10.1016/S0140-6736(20)30251-8 (2020).

3 Li, F. Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annual review of virology* **3**, 237-261, doi:10.1146/annurev-virology-110615-042301 (2016).

4 Zhou, P. *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, doi:10.1038/s41586-020-2012-7 (2020).

5 Alharbi, N. K. *et al.* ChAdOx1 and MVA based vaccine candidates against MERS-CoV elicit neutralising antibodies and cellular immune responses in mice. *Vaccine* **35**, 3780-3788, doi:10.1016/j.vaccine.2017.05.032 (2017).

6 Tseng, C. T. *et al.* Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. *PLoS One* **7**, e35421, doi:10.1371/journal.pone.0035421 (2012).

7 Weingartl, H. *et al.* Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. *J Virol* **78**, 12672-12676, doi:10.1128/JVI.78.22.12672-12676.2004 (2004).

8 Liu, L. *et al.* Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI insight* **4**, e123158, doi:10.1172/jci.insight.123158 (2019).

9 Agrawal, A. S. *et al.* Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. *Hum Vaccin Immunother* **12**, 2351-2356, doi:10.1080/21645515.2016.1177688 (2016).

10 Munster, V. J. *et al.* Protective efficacy of a novel simian adenovirus vaccine against lethal MERS-CoV challenge in a transgenic human DPP4 mouse model. *NPJ vaccines* **2**, 28, doi:10.1038/s41541-017-0029-1 (2017).

11 Alharbi, N. K. *et al.* Humoral Immunogenicity and Efficacy of a Single Dose of ChAdOx1 MERS Vaccine Candidate in Dromedary Camels. *Scientific reports* **9**, 16292, doi:10.1038/s41598-019-52730-4 (2019).

12 Gao, Q. *et al.* Development of an inactivated vaccine candidate for SARS-CoV-2. *Science*, eabc1932, doi:10.1126/science.abc1932 (2020).

13 Antrobus, R. D. *et al.* Clinical assessment of a novel recombinant simian adenovirus ChAdOx1 as a vectored vaccine expressing conserved Influenza A antigens. *Molecular therapy : the journal of the American Society of Gene Therapy* **22**, 668-674, doi:10.1038/mt.2013.284 (2014).

14 Coughlan, L. *et al.* Heterologous Two-Dose Vaccination with Simian Adenovirus and Poxvirus Vectors Elicits Long-Lasting Cellular Immunity to Influenza Virus A in Healthy Adults. *EBioMedicine*, doi:https://doi.org/10.1016/j.ebiom.2018.02.011 (2018).

15 Wilkie, M. *et al.* A phase I trial evaluating the safety and immunogenicity of a candidate tuberculosis vaccination regimen, ChAdOx1 85A prime - MVA85A boost in healthy UK adults. *Vaccine* **38**, 779-789, doi:10.1016/j.vaccine.2019.10.102 (2020).
16 Folegatti, P. M. *et al.* Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: a dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial. *The Lancet Infectious Diseases*, doi:https://doi.org/10.1016/S1473-3099(20)30160-2 (2020).
17 Modjarrad, K. MERS-CoV vaccine candidates in development: The current landscape. *Vaccine* **34**, 2982-2987, doi:10.1016/j.vaccine.2016.03.104 (2016).
18 Afolabi, M. O. *et al.* Safety and Immunogenicity of ChAd63 and MVA ME-TRAP in West African Children and Infants. *Molecular therapy : the journal of the American Society of Gene Therapy* **24**, 1470-1477, doi:10.1038/mt.2016.83 (2016).
19 Tiono, A. B. *et al.* First field efficacy trial of the ChAd63 MVA ME-TRAP vectored malaria vaccine candidate in 5-17 months old infants and children. *PloS one* **13**, e0208328, doi:10.1371/journal.pone.0208328 (2018).
20 She, J., Liu, L. & Liu, W. COVID-19 epidemic: Disease characteristics in children. *J Med Virol*, doi:10.1002/jmv.25807 (2020).
21 Dong, Y. *et al.* Epidemiology of COVID-19 Among Children in China. *Pediatrics*, doi:10.1542/peds.2020-0702 (2020).
22 Ludvigsson, J. F. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*, doi:10.1111/apa.15270 (2020).
23 Zimmermann, P. & Curtis, N. Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. *The Pediatric Infectious Disease Journal* **39**, 355-368, doi:10.1097/inf.0000000000002660 (2020).
24 Verdoni, L. *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *The Lancet*, doi:https://doi.org/10.1016/S0140-6736(20)31103-X (2020).
25 Parmigiani, A. *et al.* Impaired antibody response to influenza vaccine in HIV-infected and uninfected aging women is associated with immune activation and inflammation. *PLoS One* **8**, e79816, doi:10.1371/journal.pone.0079816 (2013).
26 Shive, C. L. *et al.* Pre-vaccine plasma levels of soluble inflammatory indices negatively predict responses to HAV, HBV, and tetanus vaccines in HCV and HIV infection. *Vaccine* **36**, 453-460, doi:10.1016/j.vaccine.2017.12.018 (2018).

APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	1.0	03 APR 2020	Pedro Folegatti, Andrew Pollard, Merryn Voysey, Sarah Gilbert	N/A
1	2.0	14 APR 2020	Emma Plested	Addition of North Bristol NHS Trust as a site.
N/A	3.0	30 APR 2020	Pedro Folegatti	Added rationale for recruiting paediatric groups; Added stopping/holding rules to groups 1, 2 and 3; Specified minimum safety and immunogenicity data required from COV001 prior to start of COV002; Specified minimum safety data required prior to enrolment into older participants in group 4 and enrolment of children into group 3; Added staggered enrolment with interim reviews for groups 1, 2 and 3.
2	4.0	14 May 2020	Pedro Folegatti	Added Dr Angela Minassian as an Investigator; 1 year follow-up as standard trial procedures; added group 5 for batch safety and immunogenicity comparison with COV001; increased sample size to up to 10,260 and adjusted statistical analysis section to reflect this; changes and clarifications to exclusion criteria; added priority groups for recruitment; added anosmia/ageusia as part of the trigger for swabbing criteria; added efficacy against infection as tertiary/exploratory endpoint; weekly PCR samples subject to test availability and site capacity; HCW exemption from filling-out weekly COVID-19 exposure diaries; adjusted blood volumes; added a section on changes to group numbers in the event of further different batches being required in order to complete dosing; clarifications to storage conditions of the IMP; harmonised AESI section with COV001 and as per Brighton Collaboration suggestions; introduced prophylactic paracetamol in group 4;

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Changes to funding arrangements; added multiple sites.
3	5.0	26 May 2020	Merryn Voysey, Pedro Folegatti, Maheshi Ramasamy	Addition of age stratification in randomisation to group 4 (<55years and ≥56years); Corrections to site addresses; updated information on pre-clinical data and disease enhancement/immunopathology; expanded on rationale for recruiting children; addition of exploratory endpoint for batch comparison between COV001 and COV002; Groups 1 and 2 to be recruited sequentially instead of in parallel following request from the DSMB with a minimum of 7 days interval; updated section on potential risks to volunteers following preliminary pre-clinical and clinical data on ChAdOx1 nCoV-19; removed potential benefit from taking part in the study as participants in group 4 won't necessarily undergo physical examination; clarification to recruitment strategy on priority groups; clarification to additional exclusion criteria in group 4 where caution to be taken when advising Paracetamol to participants on chronic use; Added PAXgene sample to last follow-up visit in participants who had a positive COVID-19 PCR sample at diagnosis visit; removed baseline PCR swab; additional text to encourage participants to contact study team for any medical attended event; clarification to weekly swab procedures; Swab testing to be undertaken by DHSC and data from this and any COVID-19 testing will be shared with lead site for central analysis; Nasopharyngeal swab to be conducted at 7 days post COVID-19 diagnosis visit only if considered necessary or if first sample is negative; added Kawasaki-like disease and other hyperinflammatory syndromes as AESI in the paediatric group; clarification to holding rule procedures, so it applies to all groups if a holding rule is met; clarifications to statistical analysis section; added information on volunteer confidentiality regarding weekly swabs

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				data processing; clarification that participants in Group 4 will not be compensated; correction of formatting and typographical errors throughout the document; added information blinding for efficacy endpoints; clarification of the groups required to report AEs; Option for participants to transfer to existing sites if relocating
4	6.0	05-JUN-2020	Pedro Folegatti	Reduced number of participants recruited into group 4; Added group 6 for comparison between dosing on Abs260 and qPCR methods.
5	7.0	18 Jun 2020	Pedro Folegatti, Merryn Voysey, Hannah Robinson	Addition of groups 5 A, B/C, 7 A and B & 8 A and B (reactogenitiicy and immunogenicity comparison between different doses given with different methods for measuring doses); Increase in sample size to up to 10,560;Group 4b has been added to provide immunogenicity data on homologous prime-boost at $5x10^{10}$vp (Abs260) prime and 2.2x1010vp (qPCR) boost, where up to 100 volunteers aged 18-55 initially recruited into group 4a will receive a booster dose of the vaccine 4-6 weeks apart Addition of process should a participant who wishes to continue in the trial, relocate and to an area with a study site; Inclusion of a mucosal immunity swabs in a subset of participants Addition of optional stool samples; Clarification to AE grading table where not all A&E assessments should be recorded as SAEs; clarification on which PCR positive tests conducted outside the study procedures would be acceptable and included in primary endpoint analysis. Change of PI at Cambridge site.
6	8.0	22 Jun 2020	Pedro Folegatti	Added day 42 visit in group 4b and increased the volume of serum taken. Clarification that the mucosal immunity

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				assessments is to be done in a subset of group 6 individuals only.
9	9.0	20 Jul 2020	Pedro Folegatti, Merryn Voysey	Increased overall sample size; Added groups 5d (batch comparison group on Cobra material) and 9 and 10 (efficacy groups in participants aged 56 and above); Addition of diary completion for 7 days for groups 9 and 10 and 28 days for group 11; Groups 9 and 10 will be recommended to take paracetamol post vaccination; Removed participants aged 56 and above from groups 4 and 6; Added booster doses to groups 4 and 6; updated study endpoints to reflect comparisons of 1 vs 2 doses (groups 1, 2, 7 and 8); added information on Cobra material and product comparability and administration; updated primary efficacy analysis to reflect changes above; expanded the number of volunteers filling out diaries.; clarifications to holding/stopping rules; added Hy's law cases to be reported as SAEs; removed the requirement for SARS-CoV-2 serology prior to enrolment in groups 5d, 9 , 10 and 11.; added group 11 to recruit participants who previously received a ChAdOx1 vectored vaccine,; Paola Cicconi added as Investigator
Minor Amendment	9.1	31 Jul 2020	Pedro Folegatti,	Correction of errors with blood volumes for participants in groups 9, 10 and 11; Clarification of dose batches; clarification that the physical examination for group 5d is only if required.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
10	10.0	06 Aug 2020	Pedro Folegatti, Merryn Voysey, Emma Plested, Hannah Robinson, Maheshi Ramasamy	Inclusion of D14 visit for group 11, changed swabbing pathway (S7 to be conducted only on positive cases, added S3-5 visit for second swab or home testing); an update to the 'Planned receipt of any vaccine other than the study intervention within 30 days before and after each study vaccination' exclusion criteria to allow an exception for the seasonal flu vaccine; clarifications made to visit time points; Re-consent may be collected with electronic signatures if required for infection control purposes; Confirmation that 15 minutes is a minimum time for post vaccine observations; clarification on the collection of AEs. ; addition of word 'boost' in group description; Clarification of the criteria for exclusion or delay of booster vaccination; Correction of length of study missed in previous amendment; Clarification of the process for information sharing following diagnosis with COVID-19; additional exclusion criteria for boosting doses to include AEs post prime that may affect the safety of the participant or the interpretation of the study results and SARS-CoV-2 PCR positivity within 4 weeks if symptomatic, or 2 weeks if asymptomatic; clarification to length of follow-up (i.e. 12 months from last vaccination); clarification to the process for sharing of information with public health authorities on COVID-19 positive cases; changes to the analysis procedures on the primary endpoint to reflect the new 2 dose schedule proposed

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
11	11.0	15 SEP 2020	Pedro Folegatti, Merryn Voysey, Andrew Pollard, Julie Fox	Clarifications to which groups are entitled to receive financial compensation; Clarification to efficacy objectives to include efficacy against severe disease; Clarification to exclusion criteria where only licensed seasonal influenza vaccines will be allowed within 30 days of vaccine administration, inclusion of HIV volunteers into sub-study, clarification to inclusion of participants with previous laboratory confirmed SARS-CoV-2 infection ; Clarifications to the statistical analysis section on primary, secondary and exploratory analysis; Clarifications to symptomatic pathway; Addition of boosting doses to groups 1a, 2a and 5a; Addition of HIV cohort sub-study; Correction of formatting and typographical errors; Changes to re-consent process to allow re-consent over the phone and electronic signatures when is not possible to have a physical visit; .Updated exploratory immunology assays to reflect inclusion of HIV group (Group 12); Increase in time to vaccine administration from 4 to 6 hours; clarification to window for booster vaccinations.
12	12.0	20 – OCT -2020	K Emary	Clarification that home swabs may be processed outside UK; Clarification of the flow of information from home swabbing results to sponsor Clarification that stool may be collected at approximately 7 days post PCR positive result in those who are asymptomatic; Inclusion of CD4 count for screening of group 12; HIV serology is at investigators discretion for group 12; AstraZeneca have provided funding for some exploratory objectives; Clarification to exclusion criteria where licensed pneumococcal vaccines will be allowed within 7 days of study vaccine administration; increase in G12 sample volume to allow sufficient volume for exploratory objectives.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
13 (SA16)	V13.0		Merryn Voysey Pedro Folegatti	Updated statistical analysis section; statistician signature space; Number of participants recruited in groups 9 and 10 will be 1000 +/- 10% each, to account for the multiple site recruitment activity and recognizing the potential for over recruitment. The overall sample size is unchanged.
14 (SA17)	V14.0		Maheshi Ramasamy, Emma Plested	Updated diagnostic PCR to NAAT (nucleic acid amplification assay) for purposes of endpoint definition; The number of diaries for Group 9 and 10 have been listed as approximately 500 in each group given the concurrent recruitment across multiple sites.

List details of all protocol amendments here whenever a new version of the protocol is produced.

17 Appendix

Investigator Agreement and Notification of Conflict of Interest

I approve this protocol for use in the above named clinical trial and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Chief Investigator	Signature	Date

Site: **Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare the following conflict of interest. AH is a cofounder of and minor shareholder in an Oxford University spin-off company, Vaccitech Ltd, that has some non-exclusive rights to the vector, ChAdOx1, used in the vaccine to be tested, that may be of commercial value"

Principal Investigator Prof Adrian Hill	Signature	Date:

Site: **NIHR WTCRF**
I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Prof Saul Faust	Signature	Date:

Site: **NIHR Imperial CRF**
I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Katrina M. Pollock	Signature	Date:

Site: **Oxford University Hospital Foundation Trust**
I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Maheshi Ramasamy	Signature	Date:

Site: **St Georges University Hospital NHS Foundation Trust**
I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Prof Paul Heath	Signature	Date:

Site: **University Hospitals Bristol and Weston NHS Foundation Trust**
I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Prof Adam Finn	Signature	Date:

Site: **North Bristol NHS Trust**
I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Rajeka Lazarus	Signature	Date:

Site: **University of Nottingham Health Service and Nottingham University Hospitals NHS Trust**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr David Turner	Signature	Date:

Site: **Sheffield Teaching Hospitals**
I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr. Thomas Darton	Signature	Date:

Site: **University Hospitals Birmingham NHS Foundation Trust (UHB)**
I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Christopher Green	Signature	Date:

Site: **Wales (Public Health Wales)**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Chris J Williams	Signature	Date:

Site: **Castle Hill Hospital**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Patrick Lillie	Signature	Date:

Site: **NHS Greater Glasgow & Clyde Hospitals**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Professor Emma Thomson	Signature	Date:

Site: **Guy's and St Thomas' NHS Foundation Trust**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Anna Goodman	Signature	Date:

Site: **Liverpool School of Tropical Medicine (LSTM)**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Andrea Collins	Signature	Date:

Site: **The Newcastle upon Tyne Hospitals NHS Foundation Trust**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Christopher Duncan	Signature	Date:

Site: **UCLH**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Prof Vincenzo Libri	Signature	Date:

Site: **NHS Lothian**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Rebecca Sutherland	Signature	Date:

Site: **Cambridge**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Mark Toshner	Signature	Date:

Site: **Northwick Park**

I have read this protocol and agree to abide by all provisions set forth therein.

According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/~~the following (delete as appropriate)~~ conflict of interest

Principal Investigator Dr Alastair McGregor	Signature	Date: