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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 August 13, 2020.

Supplement to: Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; published online July 20. http://dx.doi.org/10.1016/S0140-6736(20)31604-4.

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Supplementary tables and figures

Figure S1 Trial Profile

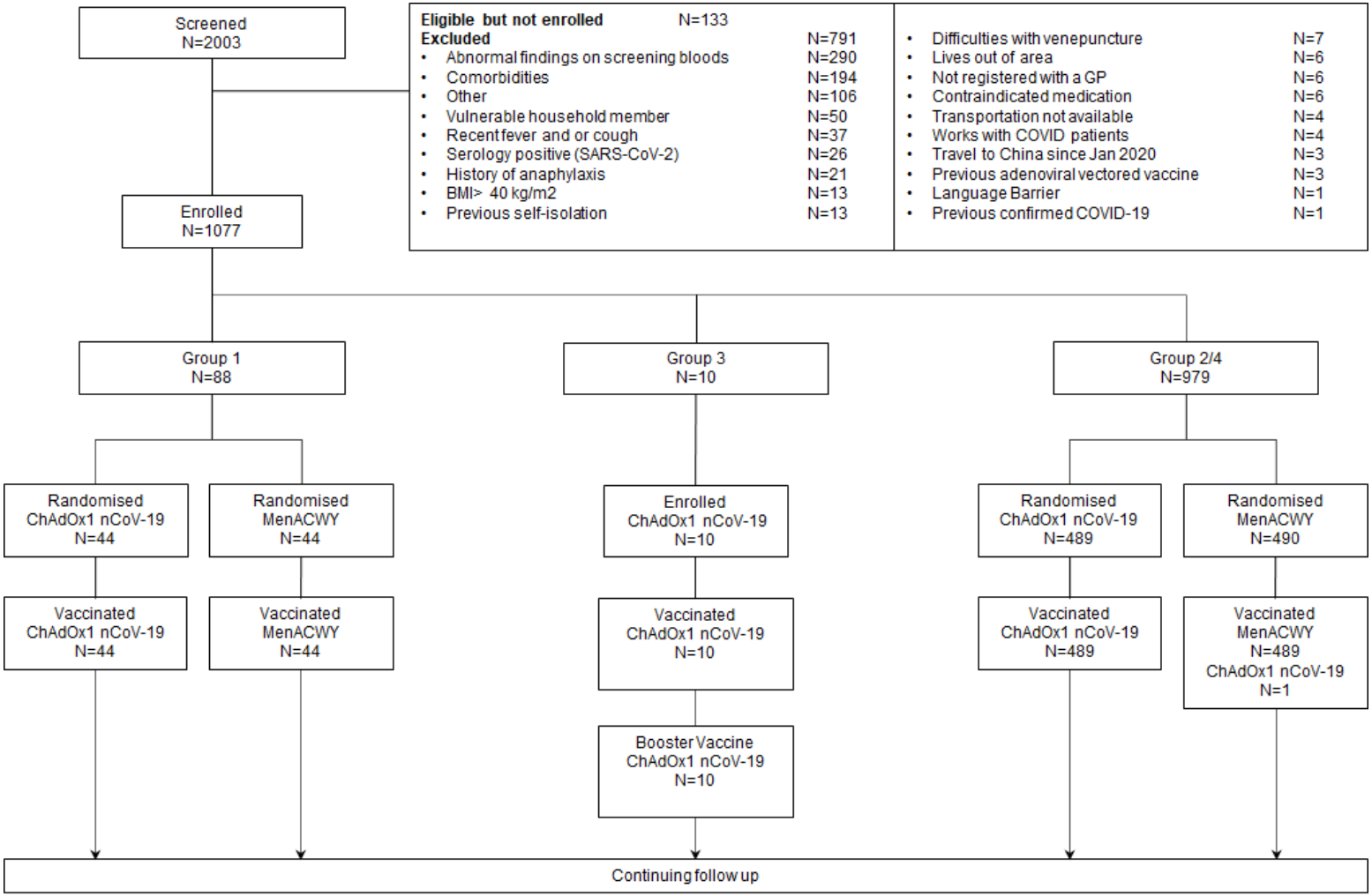


Table S1 Baseline characteristics of enrolled participants

	ChAdOx1 N=543	MenACWY N=534
Female sex (n %)	265 (49%)	271 (51%)
Age, years, median [IQR]	34 [28, 43]	36 [28, 45]
Non-smoker	495 (91%)	485 (91%)
Non-drinker	89 (16%)	60 (11%)
BMI, median [IQR]	24 [22, 27]	24 [22, 27]
Ethnicity		
Arab	2 (<1%)	2 (<1%)
Black	4 (1%)	2 (<1%)
E.Asian	5 (1%)	4 (1%)
S. Asian	15 (3%)	20 (4%)
Mixed	12 (2%)	9 (2%)
Other	11 (2%)	10 (2%)
Not given	1 (<1%)	1 (<1%)
White	493 (91%)	486 (91%)

Table S2 Solicited adverse local and systemic reactions, with and without prophylactic paracetamol by e-diary

Symptom	Vaccine Group	Paracetamol	None	Mild	Moderate	Severe	Hospitalisation	Any
Pain	ChAdOx1 nCoV-19	Paracetamol	28 (50%, 36%-64%)	22 (39%, 26%-53%)	5 (9%, 3%-20%)	1 (2%, 0%-10%)	0 (0%, 0%-6%)	28 (50%, 36%-64%)
		No Paracetamol	159 (33%, 28%-37%)	258 (53%, 48%-57%)	66 (14%, 11%-17%)	4 (1%, 0%-2%)	0 (0%, 0%-1%)	328 (67%, 63%-72%)
	MenACWY	Paracetamol	39 (68%, 55%-80%)	15 (26%, 16%-40%)	3 (5%, 1%-15%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	18 (32%, 20%-45%)
		No Paracetamol	297 (62%, 58%-67%)	161 (34%, 30%-38%)	18 (4%, 2%-6%)	1 (0%, 0%-1%)	0 (0%, 0%-1%)	180 (38%, 33%-42%)
Redness	ChAdOx1 nCoV-19	Paracetamol	55 (98%, 90%-100%)	0 (0%, 0%-6%)	1 (2%, 0%-10%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	1 (2%, 0%-10%)
		No Paracetamol	472 (97%, 95%-98%)	8 (2%, 1%-3%)	6 (1%, 0%-3%)	1 (0%, 0%-1%)	0 (0%, 0%-1%)	15 (3%, 2%-5%)
	MenACWY	Paracetamol	56 (98%, 91%-100%)	0 (0%, 0%-6%)	1 (2%, 0%-9%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	1 (2%, 0%-9%)
		No Paracetamol	467 (98%, 96%-99%)	4 (1%, 0%-2%)	6 (1%, 0%-3%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	10 (2%, 1%-4%)
Warmth	ChAdOx1 nCoV-19	Paracetamol	45 (80%, 68%-90%)	10 (18%, 9%-30%)	1 (2%, 0%-10%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	11 (20%, 10%-32%)
		No Paracetamol	365 (75%, 71%-79%)	121 (25%, 21%-29%)	1 (0%, 0%-1%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	122 (25%, 21%-29%)
	MenACWY	Paracetamol	47 (82%, 70%-91%)	10 (18%, 9%-30%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	10 (18%, 9%-30%)
		No Paracetamol	377 (79%, 75%-83%)	97 (20%, 17%-24%)	3 (1%, 0%-2%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	100 (21%, 17%-25%)
Itch	ChAdOx1 nCoV-19	Paracetamol	49 (88%, 76%-95%)	6 (11%, 4%-22%)	1 (2%, 0%-10%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	7 (12%, 5%-24%)
		No Paracetamol	452 (93%, 90%-95%)	35 (7%, 5%-10%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	35 (7%, 5%-10%)
	MenACWY	Paracetamol	55 (96%, 88%-100%)	2 (4%, 0%-12%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	2 (4%, 0%-12%)
		No Paracetamol	452 (95%, 92%-97%)	23 (5%, 3%-7%)	2 (0%, 0%-2%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	25 (5%, 3%-8%)
Swelling	ChAdOx1 nCoV-19	Paracetamol	55 (98%, 90%-100%)	0 (0%, 0%-6%)	1 (2%, 0%-10%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	1 (2%, 0%-10%)
		No Paracetamol	466 (96%, 93%-97%)	10 (2%, 1%-4%)	10 (2%, 1%-4%)	1 (0%, 0%-1%)	0 (0%, 0%-1%)	21 (4%, 3%-7%)
	MenACWY	Paracetamol	53 (93%, 83%-98%)	3 (5%, 1%-15%)	1 (2%, 0%-9%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	4 (7%, 2%-17%)
		No Paracetamol	463 (97%, 95%-98%)	8 (2%, 1%-3%)	6 (1%, 0%-3%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	14 (3%, 2%-5%)
Induration	ChAdOx1 nCoV-19	Paracetamol	56 (100%, 94%-100%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)
		No Paracetamol	470 (97%, 94%-98%)	13 (3%, 1%-5%)	3 (1%, 0%-2%)	1 (0%, 0%-1%)	0 (0%, 0%-1%)	17 (3%, 2%-6%)

	MenACWY	Paracetamol	54 (95%, 85%-99%)	3 (5%, 1%-15%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	3 (5%, 1%-15%)
		No Paracetamol	468 (98%, 96%-99%)	7 (1%, 1%-3%)	2 (0%, 0%-2%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	9 (2%, 1%-4%)
Tenderness	ChAdOx1 nCoV-19	Paracetamol	13 (23%, 13%-36%)	38 (68%, 54%-80%)	5 (9%, 3%-20%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	43 (77%, 64%-87%)
		No Paracetamol	84 (17%, 14%-21%)	333 (68%, 64%-72%)	66 (14%, 11%-17%)	4 (1%, 0%-2%)	0 (0%, 0%-1%)	403 (83%, 79%-86%)
	MenACWY	Paracetamol	31 (54%, 41%-68%)	26 (46%, 32%-59%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	26 (46%, 32%-59%)
		No Paracetamol	201 (42%, 38%-47%)	258 (54%, 49%-59%)	17 (4%, 2%-6%)	1 (0%, 0%-1%)	0 (0%, 0%-1%)	276 (58%, 53%-62%)
Feverishness	ChAdOx1 nCoV-19	Paracetamol	36 (64%, 50%-77%)	8 (14%, 6%-26%)	12 (21%, 12%-34%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	20 (36%, 23%-50%)
		No Paracetamol	237 (49%, 44%-53%)	99 (20%, 17%-24%)	111 (23%, 19%-27%)	40 (8%, 6%-11%)	0 (0%, 0%-1%)	250 (51%, 47%-56%)
	MenACWY	Paracetamol	52 (91%, 81%-97%)	5 (9%, 3%-19%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	5 (9%, 3%-19%)
		No Paracetamol	439 (92%, 89%-94%)	36 (8%, 5%-10%)	2 (0%, 0%-2%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	38 (8%, 6%-11%)
Fever ≥ 38ºC	ChAdOx1 nCoV-19	Paracetamol	47 (84%, 72%-92%)	6 (11%, 4%-22%)	3 (5%, 1%-15%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	9 (16%, 8%-28%)
		No Paracetamol	400 (82%, 78%-85%)	46 (9%, 7%-12%)	33 (7%, 5%-9%)	8 (2%, 1%-3%)	0 (0%, 0%-1%)	87 (18%, 15%-22%)
	MenACWY	Paracetamol	57 (100%, 94%-100%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)
		No Paracetamol	475 (100%, 98%-100%)	2 (0%, 0%-2%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	2 (0%, 0%-2%)
Chills	ChAdOx1 nCoV-19	Paracetamol	41 (73%, 60%-84%)	10 (18%, 9%-30%)	5 (9%, 3%-20%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	15 (27%, 16%-40%)
		No Paracetamol	215 (44%, 40%-49%)	121 (25%, 21%-29%)	112 (23%, 19%-27%)	39 (8%, 6%-11%)	0 (0%, 0%-1%)	272 (56%, 51%-60%)
	MenACWY	Paracetamol	52 (91%, 81%-97%)	5 (9%, 3%-19%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	5 (9%, 3%-19%)
		No Paracetamol	431 (90%, 87%-93%)	42 (9%, 6%-12%)	4 (1%, 0%-2%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	46 (10%, 7%-13%)
Joint pain	ChAdOx1 nCoV-19	Paracetamol	40 (71%, 58%-83%)	12 (21%, 12%-34%)	4 (7%, 2%-17%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	16 (29%, 17%-42%)
		No Paracetamol	337 (69%, 65%-73%)	97 (20%, 16%-24%)	47 (10%, 7%-13%)	6 (1%, 0%-3%)	0 (0%, 0%-1%)	150 (31%, 27%-35%)
	MenACWY	Paracetamol	51 (89%, 78%-96%)	4 (7%, 2%-17%)	2 (4%, 0%-12%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	6 (11%, 4%-22%)
		No Paracetamol	431 (90%, 87%-93%)	37 (8%, 6%-11%)	8 (2%, 1%-3%)	1 (0%, 0%-1%)	0 (0%, 0%-1%)	46 (10%, 7%-13%)
Muscle ache	ChAdOx1 nCoV-19	Paracetamol	29 (52%, 38%-65%)	14 (25%, 14%-38%)	13 (23%, 13%-36%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	27 (48%, 35%-62%)

		No Paracetamol	193 (40%, 35%-44%)	168 (34%, 30%-39%)	107 (22%, 18%-26%)	19 (4%, 2%-6%)	0 (0%, 0%-1%)	294 (60%, 56%-65%)
	MenACWY	Paracetamol	42 (74%, 60%-84%)	14 (25%, 14%-38%)	1 (2%, 0%-9%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	15 (26%, 16%-40%)
		No Paracetamol	359 (75%, 71%-79%)	104 (22%, 18%-26%)	14 (3%, 2%-5%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	118 (25%, 21%-29%)
Fatigue	ChAdOx1 nCoV-19	Paracetamol	16 (29%, 17%-42%)	23 (41%, 28%-55%)	14 (25%, 14%-38%)	3 (5%, 1%-15%)	0 (0%, 0%-6%)	40 (71%, 58%-83%)
		No Paracetamol	147 (30%, 26%-34%)	176 (36%, 32%-41%)	134 (28%, 24%-32%)	30 (6%, 4%-9%)	0 (0%, 0%-1%)	340 (70%, 66%-74%)
	MenACWY	Paracetamol	31 (54%, 41%-68%)	19 (33%, 21%-47%)	7 (12%, 5%-24%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	26 (46%, 32%-59%)
		No Paracetamol	250 (52%, 48%-57%)	169 (35%, 31%-40%)	57 (12%, 9%-15%)	1 (0%, 0%-1%)	0 (0%, 0%-1%)	227 (48%, 43%-52%)
Headache	ChAdOx1 nCoV-19	Paracetamol	22 (39%, 26%-53%)	25 (45%, 31%-59%)	8 (14%, 6%-26%)	1 (2%, 0%-10%)	0 (0%, 0%-6%)	34 (61%, 47%-74%)
		No Paracetamol	156 (32%, 28%-36%)	168 (34%, 30%-39%)	136 (28%, 24%-32%)	27 (6%, 4%-8%)	0 (0%, 0%-1%)	331 (68%, 64%-72%)
	MenACWY	Paracetamol	36 (63%, 49%-76%)	18 (32%, 20%-45%)	3 (5%, 1%-15%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	21 (37%, 24%-51%)
		No Paracetamol	282 (59%, 55%-64%)	166 (35%, 31%-39%)	26 (5%, 4%-8%)	3 (1%, 0%-2%)	0 (0%, 0%-1%)	195 (41%, 36%-45%)
Malaise	ChAdOx1 nCoV-19	Paracetamol	29 (52%, 38%-65%)	11 (20%, 10%-32%)	14 (25%, 14%-38%)	2 (4%, 0%-12%)	0 (0%, 0%-6%)	27 (48%, 35%-62%)
		No Paracetamol	191 (39%, 35%-44%)	136 (28%, 24%-32%)	124 (25%, 22%-30%)	36 (7%, 5%-10%)	0 (0%, 0%-1%)	296 (61%, 56%-65%)
	MenACWY	Paracetamol	51 (89%, 78%-96%)	5 (9%, 3%-19%)	1 (2%, 0%-9%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	6 (11%, 4%-22%)
		No Paracetamol	394 (83%, 79%-86%)	70 (15%, 12%-18%)	12 (3%, 1%-4%)	1 (0%, 0%-1%)	0 (0%, 0%-1%)	83 (17%, 14%-21%)
Nausea	ChAdOx1 nCoV-19	Paracetamol	37 (66%, 52%-78%)	14 (25%, 14%-38%)	5 (9%, 3%-20%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	19 (34%, 22%-48%)
		No Paracetamol	363 (75%, 70%-78%)	81 (17%, 13%-20%)	33 (7%, 5%-9%)	10 (2%, 1%-4%)	0 (0%, 0%-1%)	124 (25%, 22%-30%)
	MenACWY	Paracetamol	46 (81%, 68%-90%)	10 (18%, 9%-30%)	1 (2%, 0%-9%)	0 (0%, 0%-6%)	0 (0%, 0%-6%)	11 (19%, 10%-32%)
		No Paracetamol	428 (90%, 87%-92%)	41 (9%, 6%-11%)	8 (2%, 1%-3%)	0 (0%, 0%-1%)	0 (0%, 0%-1%)	49 (10%, 8%-13%)

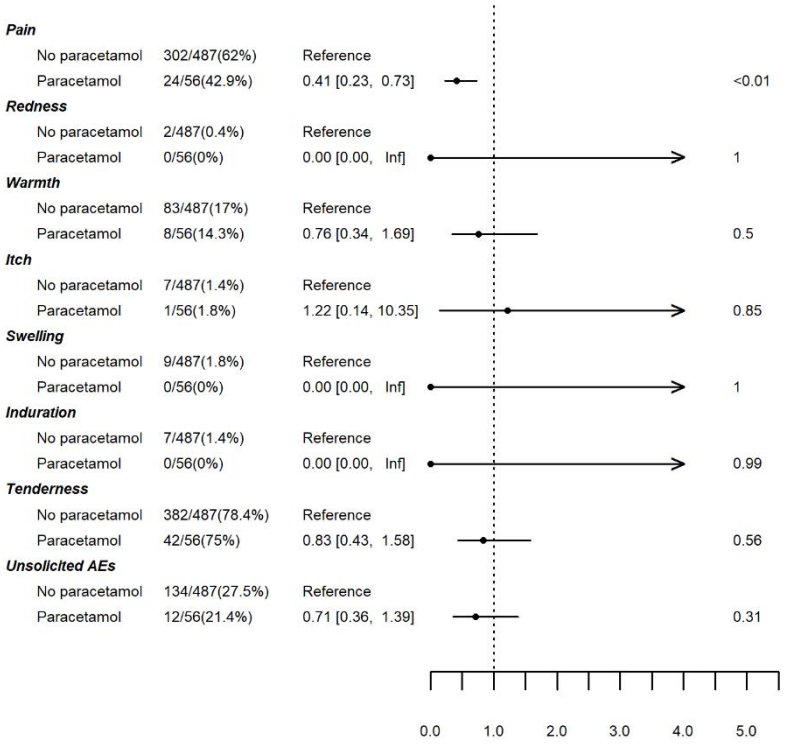
Table S3 Solicited Local and Systemic Reactions after Prime and Boost vaccinations in Group 3 participants

Symptom	1st dose (N=10)					2nd dose (N=10)				
	None	Mild	Moderate	Severe	Hospitalisation	None	Mild	Moderate	Severe	Hospitalisation
Pain	5 (50%, 19%-81%)	4 (40%, 12%-74%)	1 (10%, 0%-45%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	8 (80%, 44%-97%)	2 (20%, 3%-56%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Redness	10 (100%, 69%-100%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	10 (100%, 69%-100%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Warmth	8 (80%, 44%-97%)	2 (20%, 3%-56%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	8 (80%, 44%-97%)	2 (20%, 3%-56%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Itch	9 (90%, 55%-100%)	1 (10%, 0%-45%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	9 (90%, 55%-100%)	1 (10%, 0%-45%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Swelling	10 (100%, 69%-100%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	10 (100%, 69%-100%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Induration	10 (100%, 69%-100%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	10 (100%, 69%-100%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Tenderness	5 (50%, 19%-81%)	4 (40%, 12%-74%)	1 (10%, 0%-45%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	5 (50%, 19%-81%)	5 (50%, 19%-81%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Feverishness	3 (30%, 7%-65%)	2 (20%, 3%-56%)	5 (50%, 19%-81%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	8 (80%, 44%-97%)	1 (10%, 0%-45%)	1 (10%, 0%-45%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Fever >= 38 deg	5 (50%, 19%-81%)	5 (50%, 19%-81%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	10 (100%, 69%-100%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Chills	2 (20%, 3%-56%)	5 (50%, 19%-81%)	3 (30%, 7%-65%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	8 (80%, 44%-97%)	2 (20%, 3%-56%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Joint pain	7 (70%, 35%-93%)	2 (20%, 3%-56%)	1 (10%, 0%-45%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	10 (100%, 69%-100%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Muscle ache	4 (40%, 12%-74%)	4 (40%, 12%-74%)	2 (20%, 3%-56%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	8 (80%, 44%-97%)	2 (20%, 3%-56%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Fatigue	5 (50%, 19%-81%)	4 (40%, 12%-74%)	1 (10%, 0%-45%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	6 (60%, 26%-88%)	3 (30%, 7%-65%)	1 (10%, 0%-45%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)

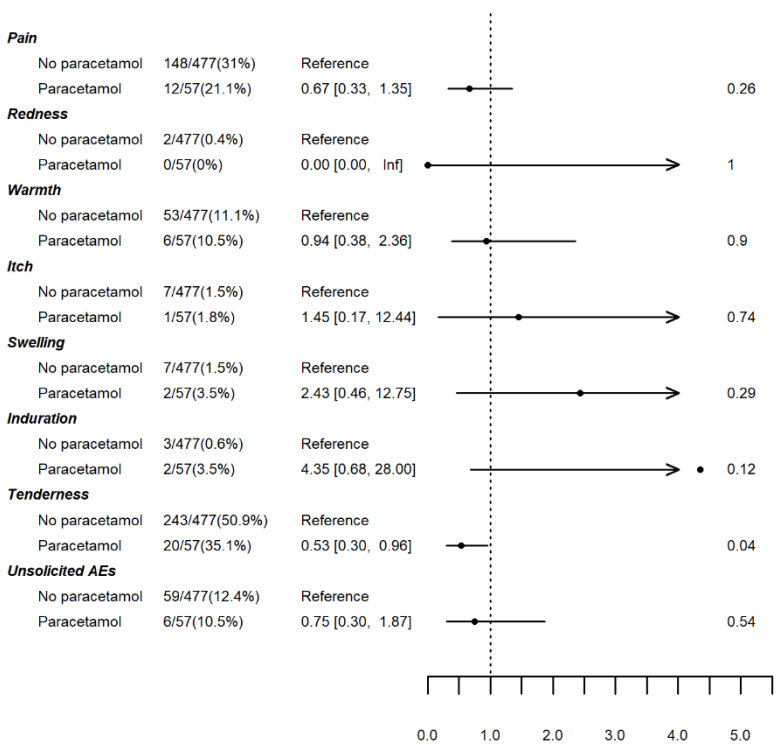
Symptom	1st dose (N=10)					2nd dose (N=10)				
	None	Mild	Moderate	Severe	Hospitalisation	None	Mild	Moderate	Severe	Hospitalisation
Headache	3 (30%, 7%-65%)	3 (30%, 7%-65%)	4 (40%, 12%-74%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	6 (60%, 26%-88%)	4 (40%, 12%-74%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Malaise	6 (60%, 26%-88%)	0 (0%, 0%-31%)	4 (40%, 12%-74%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	8 (80%, 44%-97%)	2 (20%, 3%-56%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)
Nausea	6 (60%, 26%-88%)	1 (10%, 0%-45%)	3 (30%, 7%-65%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	8 (80%, 44%-97%)	2 (20%, 3%-56%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)	0 (0%, 0%-31%)

Figure S2 The effect of prophylactic paracetamol on solicited local reactions in the first 2 days after vaccination with A) ChAdOx1 nCoV-19, B) MenACWY

A

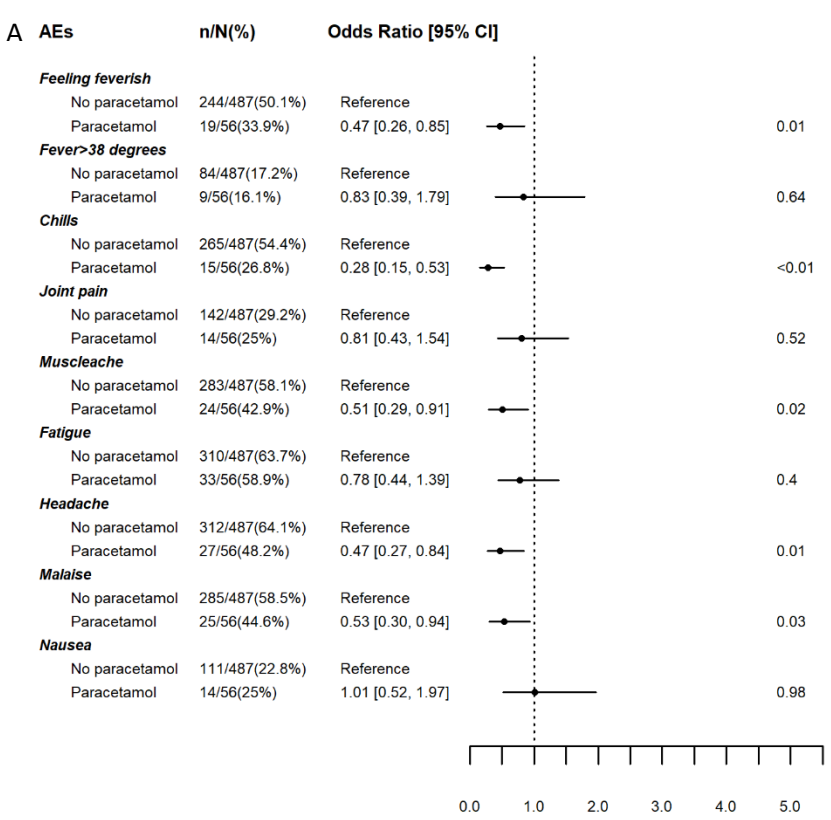


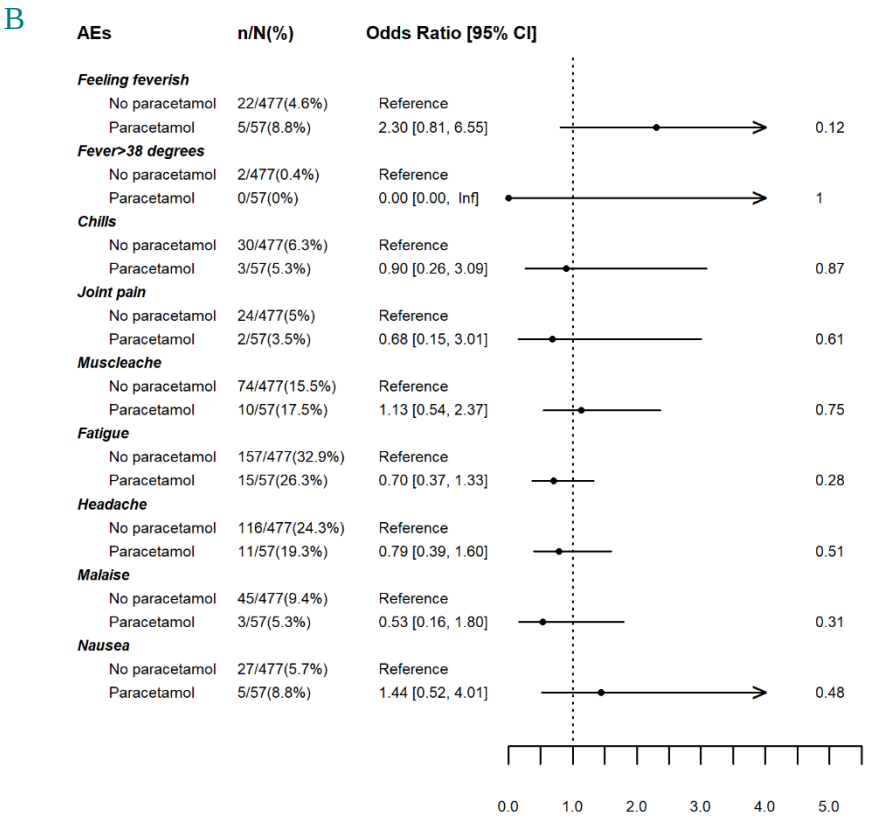
B



* Odds ratios were adjusted for age, sex, occupation (Health care worker or not), smoking, alcohol consumption and BMI

Figure S3 The effect of prophylactic paracetamol on solicited systemic reactions in the first 2 days after vaccination with A) ChAdOx1 nCoV-19, B) MenACWY





* Odds ratios were adjusted for age, sex, occupation (Health care worker or not), smoking, alcohol consumption and BMI

Table S4: Unsolicited adverse events day 0 to day 28 post vaccination by MedDRA Preferred Term, severity and relatedness (Group 1, N=88)

		ChAdOx1 nCOV-19				MenACWY		Total		
		Max Sev				Max Sev				All
		Mild	Mod	Mild	Mod	Mild	Mod	ChAd	Men	
MedDRA System Organ Class	MedDRA Preferred Term									
Un-related Adverse Events										
Eye disorders	Eye irritation				1			1	1	
Gastrointestinal disorders	Abdominal pain upper	.	.	.	.	1	.	.	1	1
	Diarrhoea	.	.	.	.	.	2	.	2	2
	Dyspepsia	.	.	.	1	.	.	.	1	1
	Mouth ulceration	1	.	.	.	.	.	1	.	1
	Nausea	.	.	.	1	.	.	.	1	1
General disorders and administration sit	Chest discomfort	1	.	.	.	.	.	1	.	1
	Fatigue	1	1	.	2	.	.	2	2	4
	Feeling cold	.	.	.	.	1	.	.	1	1
	Hangover	.	1	.	.	.	.	1	.	1
	Malaise	.	.	.	.	.	1	.	1	1
	Pain	.	.	.	.	1	.	.	1	1
	Swelling	.	.	.	.	1	.	.	1	1
Immune system disorders	Seasonal allergy	.	.	.	1	.	.	.	1	1
Injury, poisoning and procedural complic	Arthropod bite	.	.	.	.	2	.	.	2	2
	Arthropod sting	.	1	.	.	.	.	1	.	1

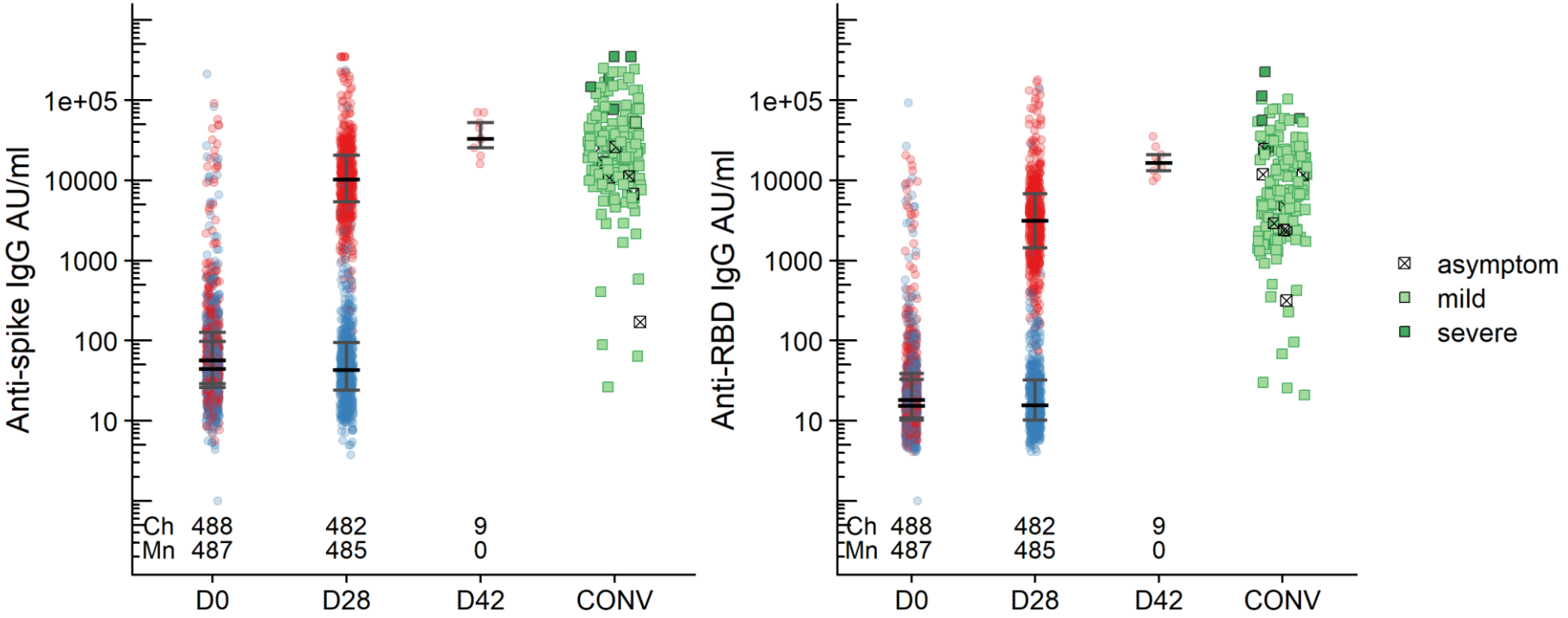
		ChAdOx1 nCOV-19				MenACWY			Total	
		Max Sev				Max Sev				All
		Mild	Mod	Mild	Mod	Mild	Mod	ChAd	Men	
	Vessel puncture site pain	.	.	.	1	.	.	.	1	1
Musculoskeletal and connective tissue di	Back pain	.	1	.	.	2	.	1	2	3
	Myalgia	.	1	.	.	1	.	1	1	2
	Neck pain	.	.	1	.	.	.	1	.	1
	Pain in extremity	.	.	.	.	1	.	.	1	1
	Sciatica	.	1	.	.	.	.	1	.	1
Nervous system disorders	Headache	3	1	.	3	4	2	4	9	13
	Migraine	.	.	.	.	1	.	.	1	1
Psychiatric disorders	Depressed mood	.	1	.	.	1	.	1	1	2
Reproductive system and breast disorders	Dysmenorrhoea	.	1	.	.	.	.	1	.	1
Respiratory, thoracic and mediastinal di	Cough	.	1	.	1	.	.	1	1	2
	Nasal congestion	1	.	.	.	.	.	1	.	1
	Oropharyngeal pain	1	.	.	.	1	.	1	1	2
	Productive cough	1	.	.	.	.	.	1	.	1
	Rhinorrhoea	1	.	.	.	.	.	1	.	1
	Throat irritation	.	.	.	2	.	.	.	2	2
Skin and subcutaneous tissue disorders	Rosacea	.	.	.	1	.	.	.	1	1
Vascular disorders	Dizziness	.	.	.	1	.	.	.	1	1
Related Adverse Events										
Eye disorders	Eye pain	1	.	.	.	.	.	1	.	1
Gastrointestinal disorders	Abdominal distension	.	.	.	1	.	.	.	1	1

		ChAdOx1 nCOV-19				MenACWY			Total	
		Max Sev				Max Sev				All
		Mild	Mod	Mild	Mod	Mild	Mod	ChAd	Men	
	Abdominal pain upper	1	.	.	.	1	.	1	1	2
	Diarrhoea	1	.	.	1	1	.	1	2	3
	Dry mouth	.	.	.	2	.	.	.	2	2
General disorders and administration sit	Axillary pain	.	.	.	.	1	.	.	1	1
	Chills	.	1	1	.	.	.	2	.	2
	Fatigue	1	.	.	.	.	.	1	.	1
	Feeling abnormal	1	.	.	.	.	.	1	.	1
	Feeling jittery	1	.	.	.	.	.	1	.	1
	Malaise	.	1	1	.	.	.	2	.	2
	Night sweats	.	1	.	.	.	.	1	.	1
	Pain	.	1	.	.	.	.	1	.	1
	Pyrexia	.	.	1	.	.	.	1	.	1
	Vaccination site bruising	1	.	.	1	.	.	1	1	2
	Vaccination site pain	2	.	.	.	.	.	2	.	2
Musculoskeletal and connective tissue di	Arthralgia	.	1	.	.	.	.	1	.	1
	Limb discomfort	1	1	.	.	.	.	2	.	2
	Muscle spasms	.	1	.	.	.	.	1	.	1
	Musculoskeletal stiffness	.	1	.	.	.	.	1	.	1
	Neck pain	.	1	.	.	.	.	1	.	1
Nervous system disorders	Abnormal sleep-related event	.	1	.	.	.	.	1	.	1

		ChAdOx1 nCOV-19				MenACWY			Total	
				Max Sev			Max Sev			All
		Mild	Mod	Mild	Mod	Mild	Mod	ChAd	Men	
	Dysgeusia	.	.	.	1	.	.	.	1	1
	Headache	2	1	.	.	.	.	3	.	3
	Insomnia	.	.	.	.	1	.	.	1	1
	Paraesthesia	.	1	.	.	.	.	1	.	1
Psychiatric disorders	Depressed mood	.	1	.	.	.	.	1	.	1
Renal and urinary disorders	Pollakiuria	.	.	.	1	.	.	.	1	1
	Polyuria	1	.	.	.	.	.	1	.	1
Respiratory, thoracic and mediastinal di	Cough	1	.	.	.	.	.	1	.	1
	Nasopharyngitis	1	.	.	.	.	.	1	.	1
	Oropharyngeal pain	3	.	.	.	.	.	3	.	3
	Rhinorrhoea	2	.	.	.	.	.	2	.	2
Skin and subcutaneous tissue disorders	Pruritus	.	1	.	.	1	.	1	1	2
Vascular disorders	Dizziness	1	1	.	.	.	.	2	.	2

Note: The table above describes only unsolicited AEs reported within the 28 day period for participants in Group 1. More than one MedDRA code can apply to the same event therefore the total number of codes does not equal the total number of participants or events experienced.

Figure S4 Multiplex SARS-CoV-2 IgG response by ELISA to A) spike protein and B) receptor binding domain, in trial participants and convalescent PCR+ COVID-19 patients (MIA)



Red: ChAdOx1 nCoV-19 recipients; Blue: MenACWY recipients, Green: convalescent plasma from PCR+ COVID-19 patients. Error bars show median and IQR. Day 42 samples taken in N=9 participants boosted at day 28. AU=arbitrary units

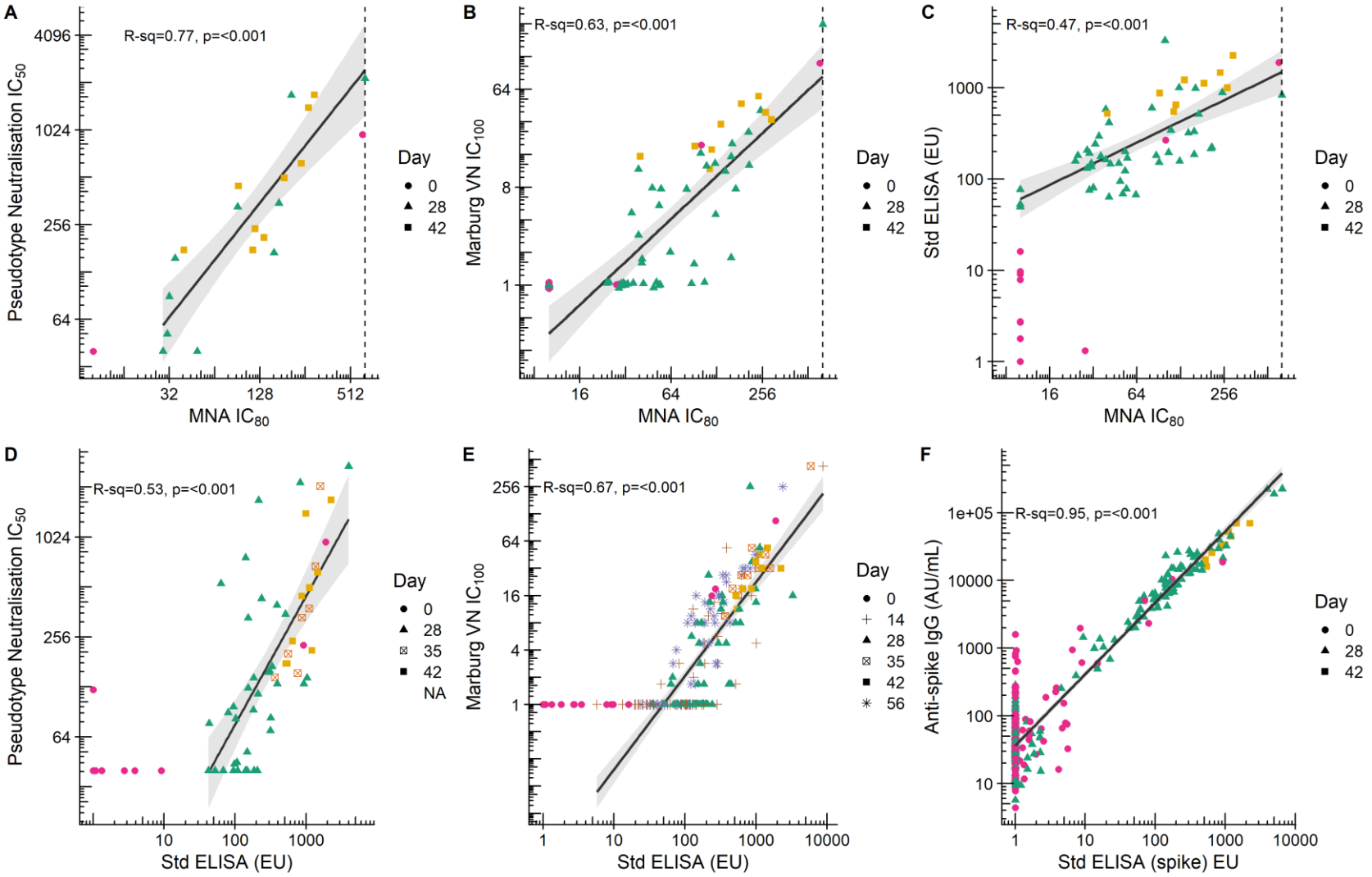
Table S5 Summary statistics for antibody assays and t cell responses

Assay	Study Day		MenACWY		ChAdOx1 Prime		ChAdOx1 Prime-Boost
		N	Median [IQR]	N	Median [IQR]	N	Median [IQR]
Anti-spike IgG using Standardised ELISA (EU)	0	131	1 [1, 1]	129	1 [1, 1]	10	1 [1, 2.3]
	7	44	1 [1, 1]	42	1 [1, 1.8]	10	1 [1, 2.4]
	14	44	1 [1, 1]	44	102.7 [43.7, 186]	10	137 [46.4, 206.8]
	28	130	1 [1, 1]	127	157.1 [96.2, 316.9]	10	210.7 [149.4, 321.6]
	35					10	821.1 [578.1, 1298.4]
	42					9	997.5 [648.5, 1214]
	56	44	1 [1, 2.6]	43	119 [70.3, 203.4]	10	639.2 [360, 792.2]
Multiplex MSD – Anti spike IgG (AU/mL)	0	487	45.5 [26.1, 98.2]	488	57.6 [29.1, 125.8]		
	28	485	43.9 [23.9, 94.5]	482	10471.8 [5378.6, 20517.3]		
	42					9	33830.8 [25674.3, 52251.8]
Multiplex MSD – RBD IgG (AU/mL)	0	487	15.6 [10.1, 32.7]	488	18.5 [10.9, 38.8]		
	28	485	15.8 [10.2, 32.4]	482	3182.5 [1426.3, 6800.4]		
	42					9	16825.4 [13118.9, 20937.9]
Marburg VN	0	44	1 [1, 1]	44	1 [1, 1]	10	1 [1, 1]
	14	44	1 [1, 1]	44	1 [1, 2.2]	10	1 [1, 8.3]
	28	43	1 [1, 1]	44	1 [1, 8]	10	3.2 [1, 14]

Assay	Study Day		MenACWY		ChAdOx1 Prime		ChAdOx1 Prime-Boost
		N	Median [IQR]	N	Median [IQR]	N	Median [IQR]
	35					9	29.5 [21, 41.9]
	42					10	32 [19, 38.1]
	56	25	1 [1, 1]	37	2.8 [1, 8]	10	29.5 [23.7, 32]
PHE MNA_{50}	0	2	10 [10, 10]	35	22 [10, 30]	10	29.5 [23.5, 41]
	28	2	10 [10, 10]	35	201 [141.5, 399.5]	10	256 [119.3, 631.5]
	42					9	372 [326, 640]
PHE MNA_{80}	0	2	10 [10, 10]	35	10 [10, 10]	10	10 [10, 10]
	28	2	10 [10, 10]	35	51 [32, 103]	10	70 [32.8, 168]
	42					9	136 [115, 241]
PHE MNA_{90}	0	2	10 [10, 10]	35	10 [10, 10]	10	10 [10, 10]
	28	2	10 [10, 10]	35	23 [10, 45.5]	10	33 [10, 73.8]
	42					9	81 [58, 126]
PHE $PRNT_{50}$	0	2	36.5 [23.3, 49.8]	35	23 [10, 34]		
	28	2	36.5 [30.8, 42.3]	35	218 [122, 395]		
PseudoNA	D0	30	40 [40, 40]	29	40 [40, 40]	10	40 [40, 40]
	D28	30	40 [40, 40]	28	87.9 [40, 144.5]	10	162.9 [61.2, 345.8]
	D35					10	334.3 [178.6, 529.2]
	D42					9	450.9 [212, 627.5]
IFNγ ELISpot response against SARS-CoV-2 spike peptides (SFC)	0	73	64 [48, 132]	71	60 [48, 114]	10	108 [90.8, 150.2]

Assay	Study Day		MenACWY		ChAdOx1 Prime		ChAdOx1 Prime-Boost
		N	Median [IQR]	N	Median [IQR]	N	Median [IQR]
	7	43	67.3 [48, 113]	40	183.2 [79.5, 345]	10	258 [209.8, 432.2]
	14	44	55.3 [48, 99.3]	43	856 [493.3, 1802]	10	1642.3 [1423.7, 2009.5]
	28	69	61.3 [48, 88]	68	554.3 [311.3, 1017.7]	10	528.7 [376.3, 603]
	35					10	445.3 [651.3, 719.3]
	56	42	66.7 [48, 123.3]	43	424 [221.3, 798.7]	10	614 [437.3, 666]

Figure S5 Relationship between pseudotyped virus neutralisation (PseudoNA), PHE Microneutralisation Assay (IC_{80}), live virus neutralisation (Marburg VN), Standardised ELISA, and Multiplex ELISA (Mesoscale MIA platform)



A: y=Pseudotyped virus neutralisation (Monogram PseudoNA) vs x= Public Health England microneutralisation assay (80% neutralisation),

B: y=Marburg virus neutralisation (Marburg VN (100% neutralisation) vs x= Public Health England microneutralisation assay (80% neutralisation),

C: y=Anti-Spike IgG (Std ELISA) vs x= x= Public Health England microneutralisation assay (80% neutralisation),

D: y=Pseudotyped virus neutralisation (Monogram PseudoNA) vs x= Anti-Spike IgG (Std ELISA),

E: y=Marburg virus neutralisation (Marburg VN (100% neutralisation) vs x= Anti-Spike IgG (Std ELISA),

F: y=Anti-Spike IgG (Mesoscale Multiplex Immunoassay) vs x= Anti-Spike IgG (Std ELISA),

Dotted line shows upper limit of the PHE MNA assay. Solid lines, confidence intervals, R-sq values and p values, from unadjusted linear regression model including post-baseline time points only.

Figure S6 Anti-Spike IgG by Standardised ELISA in those with and without neutralising antibodies to ChAdOx1 vector

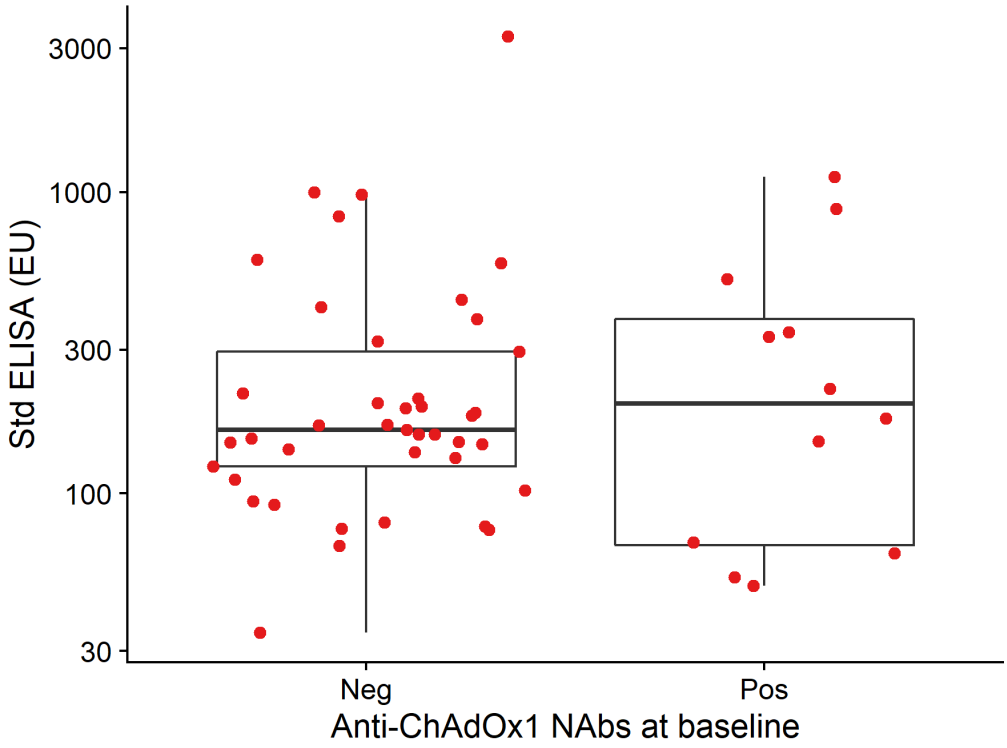


Table S6 Amino acid sequences of SARS-CoV-2 spike peptides used in ELISPOT assays

Peptide number	Amino acid start position	Sequence	Subunit	Pool	No. in peptide pool
1	1	MFVFLVLLPLVSSQC			
2	6	VLLPLVSSQCVNLTT			
3	11	VSSQCVNLTTRTQLP			
4	16	VNLTTRTQLPPAYTN			
5	21	RTQLPPAYTNSFTRG			
6	26	PAYTNSFTRGVYYPD			
7	31	SFTRGVYYPDKVFRS			
8	36	VYYPDKVFRSSVLHS			
9	41	KVFRSSVLHSTQDLF			
10	46	SVLHSTQDLFLPFFS		1	20
11	51	TQDLFLPFFSNVTWF			
12	56	LPFFSNVTWFHAIHV			
13	61	NVTWFHAIHVSGTNG			
14	66	HAIHVSGTNGTKRFD			
15	71	SGTNGTKRFDNPVLP			
16	76	TKRFDNPVLPFNDGV			
17	81	NPVLPFNDGVYFAST	S1		
18	86	FNDGVYFASTEKSNI			
19	91	YFASTEKSNIIRGWI			
20	96	EKSNIIRGWIFGTTL			
21	101	IRGWIFGTTLDSKTQ			
22	106	FGTTLDSKTQSLLIV			
23	111	DSKTQSLLIVNNATN			
24	116	SLLIVNNATNVVIKV			
25	121	NNATNVVIKVCEFQF			
26	126	VVIKVCEFQFCNDPF			
27	131	CEFQFCNDPFLGVYY		2	20
28	136	CNDPFLGVYYHKNNK			
29	141	LGVYYHKNNKSWMES			
30	146	HKNNKSWMESEFRVY			
31	151	SWMESEFRVYSSANN			
32	156	EFRVYSSANNCTFEY			
33	161	SSANNCTFEYVSQPF			

Peptide number	Amino acid start position	Sequence	Subunit	Pool	No. in peptide pool
34	166	CTFEYVSQPFLMDLE			
35	171	VSQPFLMDLEGKQGN			
36	176	LMDLEGKQGNFKNLR			
37	181	GKQGNFKNLREFVFK			
38	186	FKNLREFVFKNIDGY			
39	191	EFVFKNIDGYFKIYS			
40	196	NIDGYFKIYSKHTPI			
41	201	FKIYSKHTPINLVRD			
42	206	KHTPINLVRDLPQGF			
43	211	NLVRDLPQGFSALEP			
44	216	LPQGFSALEPLVDLP			
45	221	SALEPLVDLPIGINI			
46	226	LVDLPIGINITRFQT			
47	231	IGINITRFQTLLALH			
48	236	TRFQTLLALHRSYLT			
49	241	LLALHRSYLTPGDSS			
50	246	RSYLTPGDSSSGWTA			
51	251	PGDSSSGWTAGAAAY		3	22
52	256	SGWTAGAAAYYVGYL			
53	261	GAAAYYVGYLQPRTF			
54	266	YVGYLQPRTFLLKYN			
55	271	QPRTFLLKYNENGTI			
56	276	LLKYNENGTITDAVD			
57	281	ENGTITDAVDCALDP			
58	286	TDAVDCALDPLSETK			
59	291	CALDPLSETKCTLKS			
60	296	LSETKCTLKSFTVEK			
61	301	CTLKSFTVEKGIYQT			
62	306	FTVEKGIYQTSNFRV			
63	311	GIYQTSNFRVQPTES			
64	316	SNFRVQPTESIVRFP			
65	321	QPTESIVRFPNITNL			
66	326	IVRFPNITNLCPFGE			
67	331	NITNLCPFGEVFNAT		4	24
68	336	CPFGEVFNATRFASV			
69	341	VFNATRFASVYAWNR			
70	346	RFASVYAWNRKRISN			
71	351	YAWNRKRISNCVADY			
72	356	KRISNCVADYSVLYN			

Peptide number	Amino acid start position	Sequence	Subunit	Pool	No. in peptide pool
73	361	CVADYSVLYNSASFS			
74	366	SVLYNSASFSTFKCY			
75	371	SASFSTFKCYGVSPT			
76	376	TFKCYGVSPTKLNDL			
77	381	GVSPTKLNDLCFTNV			
78	386	KLNDLCFTNVYADSF			
79	391	CFTNVYADSFVIRGD			
80	396	YADSFVIRGDEVRQI			
81	401	VIRGDEVRQIAPGQT			
82	406	EVRQIAPGQTGKIAD			
83	411	APGQTGKIADYNYKL			
84	416	GKIADYNYKLPDDFT			
85	421	YNYKLPDDFTGCVIA			
86	426	PDDFTGCVIAWNSNN			
87	431	GCVIAWNSNNLDSKV			
88	436	WNSNNLDSKVGGNYN			
89	441	LDSKVGGNYNYLYRL			
90	446	GGNYNYLYRLFRKSN			
91	451	YLYRLFRKSNLKPFE			
92	456	FRKSNLKPFERDIST			
93	461	LKPFERDISTEIYQA			
94	466	RDISTEIYQAGSTPC			
95	471	EIYQAGSTPCNGVEG			
96	476	GSTPCNGVEGFNCYF			
97	481	NGVEGFNCYFPLQSY			
98	486	FNCYFPLQSYGFQPT		5	24
99	491	PLQSYGFQPTNGVGY			
100	496	GFQPTNGVGYQPYRV			
101	501	NGVGYQPYRVVVLSF			
102	506	QPYRVVVLSFELLHA			
103	511	VVLSFELLHAPATVC			
104	516	ELLHAPATVCGPKKS			
105	521	PATVCGPKKSTNLVK			
106	526	GPKKSTNLVKNKCVN			
107	531	TNLVKNKCVNFNFNG			
108	536	NKCVNFNFNGLTGTG			
109	541	FNFNGLTGTGVLTES			
110	546	LTGTGVLTESNKKFL			
111	551	VLTESNKKFLPFQQF			

Peptide number	Amino acid start position	Sequence	Subunit	Pool	No. in peptide pool
112	556	NKKFLPFQQFGRDIA			
113	561	PFQQFGRDIADTTDA			
114	566	GRDIADTTDAVRDPQ			
115	571	DTTDAVRDPQTLEIL			
116	576	VRDPQTLEILDITPC			
117	581	TLEILDITPCSFGGV			
118	586	DITPCSFGGVSVITP			
119	591	SFGGVSVITPGTNTS			
120	596	SVITPGTNTSNQVAV			
121	601	GTNTSNQVAVLYQDV			
122	606	NQVAVLYQDVNCTEV			
123	611	LYQDVNCTEVPVAIH		6	24
124	616	NCTEVPVAIHADQLT			
125	621	PVAIHADQLTPTWRV			
126	626	ADQLTPTWRVYSTGS			
127	631	PTWRVYSTGSNVFQT			
128	636	YSTGSNVFQTRAGCL			
129	641	NVFQTRAGCLIGAEH			
130	646	RAGCLIGAEHVNNSY			
131	651	IGAEHVNNSYECDIP			
132	656	VNNSYECDIPIGAGI			
133	661	ECDIPIGAGICASYQ			
134	666	IGAGICASYQTQTNS			
135	671	CASYQTQTNSPRRAR			
136	676	TQTNSPRRARSVASQ			
137	681	PRRARSVASQSIIAY			
138	686	SVASQSIIAYTMSLG			
139	691	SIIAYTMSLGAENSV			
140	696	TMSLGAENSVAYSNN			
141	701	AENSVAYSNNSIAIP			
142	706	AYSNNSIAIPTNFTI	S2	7	20
143	711	SIAIPTNFTISVTTE			
144	716	TNFTISVTTEILPVS			
145	721	SVTTEILPVSMTKTS			
146	726	ILPVSMTKTSVDCTM			
147	731	MTKTSVDCTMYICGD			
148	736	VDCTMYICGDSTECS			
149	741	YICGDSTECSNLLLQ			
150	746	STECSNLLLQYGSFC			

Peptide number	Amino acid start position	Sequence	Subunit	Pool	No. in peptide pool
151	751	NLLLQYGSFCTQLNR			
152	756	YGSFCTQLNRALTGI			
153	761	TQLNRALTGIAVEQD			
154	766	ALTGIAVEQDKNTQE			
155	771	AVEQDKNTQEVFAQV			
156	776	KNTQEVFAQVKQIYK			
157	781	VFAQVKQIYKTPPIK			
158	786	KQIYKTPPIKDFGGF			
159	791	TPPIKDFGGFNFSQI			
160	796	DFGGFNFSQILPDPS			
161	801	NFSQILPDPSKPSKR			
162	806	LPDPSKPSKRSFIED			
163	811	KPSKRSFIEDLLFNK			
164	816	SFIEDLLFNKVTLAD		8	20
165	821	LLFNKVTLADAGFIK			
166	826	VTLADAGFIKQYGDC			
167	831	AGFIKQYGDCLGDIA			
168	836	QYGDCLGDIAARDLI			
169	841	LGDIAARDLICAQKF			
170	846	ARDLICAQKFNGLTV			
171	851	CAQKFNGLTVLPPLL			
172	856	NGLTVLPPLLTDEMI			
173	861	LPPLLTDEMIAQYTS			
174	866	TDEMIAQYTSALLAG			
175	871	AQYTSALLAGTITSG			
176	876	ALLAGTITSGWTFGA			
177	881	TITSGWTFGAGAALQ			
178	886	WTFGAGAALQIPFAM			
179	891	GAALQIPFAMQMAYR			
180	896	IPFAMQMAYRFNGIG			
181	901	QMAYRFNGIGVTQNV			
182	906	FNGIGVTQNVLYENQ		9	21
183	911	VTQNVLYENQKLIAN			
184	916	LYENQKLIANQFNSA			
185	921	KLIANQFNSAIGKIQ			
186	926	QFNSAIGKIQDSLSS			
187	931	IGKIQDSLSSTASAL			
188	936	DSLSSTASALGKLQD			
189	941	TASALGKLQDVVNQN			

Peptide number	Amino acid start position	Sequence	Subunit	Pool	No. in peptide pool
190	946	GKLQDVVNQNAQALN			
191	951	VVNQNAQALNTLVKQ			
192	956	AQALNTLVKQLSSNF			
193	961	TLVKQLSSNFGAISS			
194	966	LSSNFGAISSVLNDI			
195	971	GAISSVLNDILSRLD			
196	976	VLNDILSRLDKVEAE			
197	981	LSRLDKVEAEVQIDR			
198	986	KVEAEVQIDRLITGR			
199	991	VQIDRLITGRLQSLQ			
200	996	LITGRLQSLQTYVTQ			
201	1001	LQSLQTYVTQQLIRA			
202	1006	TYVTQQLIRAAEIRA			
203	1011	QLIRAAEIRASANLA			
204	1016	AEIRASANLAATKMS			
205	1021	SANLAATKMSECVLG		10	20
206	1026	ATKMSECVLGQSKRV			
207	1031	ECVLGQSKRVDFCGK			
208	1036	QSKRVDFCGKGYHLM			
209	1041	DFCGKGYHLMSFPQS			
210	1046	GYHLMSFPQSAPHGV			
211	1051	SFPQSAPHGVVFLHV			
212	1056	APHGVVFLHVTYVPA			
213	1061	VFLHVTYVPAQEKNF			
214	1066	TYVPAQEKNFTTAPA			
215	1071	QEKNFTTAPAICHDG			
216	1076	TTAPAICHDGKAHFP			
217	1081	ICHDGKAHFPREGVF			
218	1086	KAHFPREGVFVSNGT			
219	1091	REGVFVSNGTHWFVT			
220	1096	VSNGTHWFVTQRNFY			
221	1101	HWFVTQRNFYEPQII			
222	1106	QRNFYEPQIITTDNT		11	20
223	1111	EPQIITTDNTFVSGN			
224	1116	TTDNTFVSGNCDVVI			
225	1121	FVSGNCDVVIGIVNN			
226	1126	CDVVIGIVNNTVYDP			
227	1131	GIVNNTVYDPLQPEL			
228	1136	TVYDPLQPELDSFKE			

Peptide number	Amino acid start position	Sequence	Subunit	Pool	No. in peptide pool
229	1141	LQPELDSFKEELDKY			
230	1146	DSFKEELDKYFKNHT			
231	1151	ELDKYFKNHTSPDVD			
232	1156	FKNHTSPDVDLGDIS			
233	1161	SPDVDLGDISGINAS			
234	1166	LGDISGINASVVNIQ			
235	1171	GINASVVNIQKEIDR			
236	1176	VVNIQKEIDRLNEVA			
237	1181	KEIDRLNEVAKNLNE			
238	1186	LNEVAKNLNESLIDL			
239	1191	KNLNESLIDLQELGK			
240	1196	SLIDLQELGKYEQYI			
241	1201	QELGKYEQYIKWPWY			
242	1206	YEQYIKWPWYIWLGF			
243	1211	KWPWYIWLGFIAGLI			
244	1216	IWLGFIAGLIAIVMV		12	18
245	1221	IAGLIAIVMVTIMLC			
246	1226	AIVMVTIMLCCMTSC			
247	1231	TIMLCCMTSCCSCLK			
248	1236	CMTSCCSCLKGCCSC			
249	1241	CSCLKGCCSCGSCCK			
250	1246	GCCSCGSCCKFDEDD			
251	1251	GSCCKFDEDDSEPVL			
252	1256	FDEDDSEPVLKGVKL			
253	1261	DDSEPVLKGVKLHYT			
254	-	MDAMKRGLCCVLLLC			
255	-	RGLCCVLLLCGAVFV			
256	-	VLLLCGAVFVSASQE	tpa	tpa	5
257	-	GAVFVSASQEIHARF			
258	-	SASQEIHARFRRIHS			

DSMB review timetable

The DSMB primary responsibility is to safeguard the interests of study participants, monitor the main outcome measures, primarily safety, and monitor the overall conduct of the study. The DSMB have periodically assessed safety and immunogenicity data as outlined below.

Meeting 1: 18th March 2020	Before vaccinations
Meeting 2: 15th April 2020	Before vaccinations
Meeting 3: 23rd April 2020	Approval to commence vaccinations
Email review: 24th April 2020	Continued approval following review of safety report on first 2 participants enrolled (COV001)
Email review: 26th April 2020	Continued approval following review of safety report on first 4 participants receiving the IMP (COV001)
Meeting 4: 28th April 2020	Continued approval following review of safety report on first 54 participants receiving the IMP (COV001)
Meeting 5: 5th May 2020	Continued approval following review of safety data (COV001)
Meeting 6: 15th May 2020	Continued approval following review of safety and immunogenicity data (COV001)
Meeting 7: 27th May 2020	Continued approval following review of safety and immunogenicity data (COV001)
Meeting 8: 10th June 2020	Continued approval following review of safety and immunogenicity data (COV001)
Meeting 9: 19th June 2020	Continued approval following review of safety and immunogenicity data (COV001)
Meeting 10: 25th June 2020	Continued approval following review of safety and immunogenicity data (COV001)
Meeting 11: 9th July 2020	Continued approval following review of safety and immunogenicity data (COV001)

Supplementary Methods

Standardised ELISA for detection of SARS-CoV-2 antigen specific total IgG

Total anti-SARS CoV-2 antibodies were determined using an indirect ELISA that uses a standard curve derived from a pool of SARS-COV-2 convalescent plasma samples on every plate. A soluble full-length trimeric S (FL-S) protein of SARS-CoV-2 (GenBank MN908947 Wuhan-Hu-1) construct encoding residues 1-1213 with two sets of mutations that stabilise the protein in a pre-fusion conformation (removal of a furin cleavage site and the introduction of two proline residues; K983P, V984P) was expressed as described [1]. The endogenous viral signal peptide was retained at the N terminus (residues 1-14), a C-terminal T4-foldon domain incorporated to promote association of monomers into trimers to reflect the native transmembrane viral protein, and a C-terminal His6 tag included for nickel-based affinity purification. FL-S was transiently expressed in Expi293™ (Thermo Fisher Scientific) and protein purified from culture supernatants by immobilised metal affinity followed by gel filtration in Tris-buffered saline (TBS) pH 7.4 buffer.

ELISA plates were coated with 2 µg/mL of full-length trimerised SARS-CoV-2 spike glycoprotein and stored at 4°C overnight for at least 16 h. After coating, plates were washed 6 times with PBS/0.05%Tween and blocked with casein for 1h at room temperature. Thawed samples diluted in casein were plated in triplicate and incubated for 2h at room temperature alongside two internal positive controls (controls 1 and 2) to measure plate to plate variation. Control 1 was a dilution of convalescent plasma sample and control 2 was a research reagent for anti-SARS-CoV-2 Ab (code 20/130 supplied by National Institute for Biological Standards and Control (NIBSC)). The standard pool was used in a two-fold serial dilution to produce ten standard points that were assigned arbitrary ELISA units (EUs). Goat anti-human IgG (γ-chain specific) conjugated to alkaline phosphatase was used as secondary antibody and plates were developed by adding 4-nitrophenyl phosphate in diethanolamine substrate buffer. An ELx808 microplate reader (BioTek Instruments) was used to provide optical density measurement of the plates at 405mm. Standardised EUs were determined from a single dilution of each sample against the standard curve which was plotted using the 4-Parameter logistic model (Gen5 v3.09, BioTek). Each assay plate consisted of samples and controls plated in triplicate, with ten standard points in duplicate and four blank wells.

Eligibility ELISA

Potential participants in group 2 and 4 were tested with an ELISA assay to determine likely seropositivity to SARS-CoV-2 indicating possible previous infection. The principle of the ELISA method was performed as described for the total IgG ELISA, except that samples were tested at 1:100 serum dilution in duplicate against both SARS-CoV-2 spike glycoprotein and the spike receptor-binding domain (RBD), alongside pooled pre-pandemic sera from healthy volunteers (sera taken before 2020) as a negative control and positive control derived from a pool of SARS-COV-2 convalescent plasma samples. RBD protein was produced using the same method as FL-S. The RBD construct utilises the native SARS-CoV-2 Spike signal peptide (1-14) fused directly to residues 319-541 of the Spike protein which encompasses the binding site for the human receptor ACE2. Only

samples that were positive to both spike and RBD were deemed positive and participants were not enrolled.

Marburg SARS-CoV-2 Virus neutralization (Marburg VN)

SARS-CoV-2 neutralizing activity of human sera was investigated based on a previously published protocol for MERS-CoV [2,3]. Briefly, samples were heat-inactivated for 30 min at 56°C and serially diluted in 96-well plates starting from a dilution of 1:8. Samples were incubated for 1 h at 37°C together with 100 50% tissue culture infective doses (TCID50) SARS-CoV-2 (BavPat1/2020 isolate, European Virus Archive Global # 026V-03883). Cytopathic effect (CPE) on VeroE6 cells (Vero C1008, ATCC, Cat#CRL-1586, RRID: CVCL_0574) was analyzed 4 days post-infection. Neutralization was defined as absence of CPE compared to virus controls. For each test, a positive control (neutralizing COVID-19 patient plasma) was used in duplicates as an inter-assay neutralization standard [4]

Monogram Biosciences pseudotype neutralisation assay (PseudoNA)

A lentivirus-based SARSCoV-2 pseudovirus particle was generated expressing spike protein on the surface (Accession number: MN908947.3). The PS CoV nAb assay is based on previously described methodologies using HIV-1 pseudovirions (PMID: 10722492; 12644702: 17116663).
Briefly, serum samples were heat inactivated at 56°C for one hour and diluted 1:40 in cell culture medium. Neutralizing antibody (Nab) titres were determined by creating 9 serial three-fold dilutions of test samples which were mixed with ~10^5 relative light units (RLU) of SARS-CoV2 pseudotyped virus and incubated at 37°C for one hour. Separately, irrelevant pseudotyped control virus, was also mixed with test samples. Following the 1 hour incubation HEK 293 ACE2-transfected cells were added to the well. The plates were incubated for 60-80 hours at 37°C and then assayed for luciferase expression. Neutralization titres are reported as the reciprocal of the serum dilution conferring 50% inhibition (ID_{50}) of pseudovirus infection. %Inhibition = 100% – (((RLU$_{(Vector+Sample+Diluent)}$ – RLU$_{(Background)}$)/(RLU$_{(Vector+Diluent)}$ – RLU$_{(Background)}$)) x 100%). SARS CoV-2 nAb Assay Positive and Negative Control Sera are included on each 96-well assay plate (1 positive control, 1 negative control, 6 patient specimens).

Public Health England Plaque Reduction Neutralisation Test (PHE $PRNT_{50}$).

Neutralising virus titres were measured in heat-inactivated (56°C for 30 min) serum samples. SARS-CoV-2 was diluted to a concentration of 933 pfu/ml (70 pfu/75 µl) and mixed 50:50 in 1% FCS/MEM with doubling serum dilutions from 1:20 to 1:640 in a 96-well V-bottomed plate. The plate was incubated at 37°C in a humidified box for 1 hour to allow the antibody in the serum samples to bind the virus. The virus and serum dilutions were transferred into the wells of a washed plaque assay 24-well plate, allowed to adsorb at 37°C for an hour, and overlaid with plaque assay overlay media. After 5 days incubation at 37°C in a humified box, the plates were fixed, stained and plaques counted. Median neutralising titres (ND_{50}) were determined using the Spearman- Karber formula relative to virus only control wells.

Public Health England Microneutralisation Assay (PHE MNA_{50}, MNA_{80}, MNA_{90})

The principle of the MNA is similar to the PRNT. Virus susceptible monolayers (Vero/E6 Cells) in 96 well plates were exposed to the serum/virus mixture prepared as for PRNT. Plates were incubated in a sealed humified box for 1 hour before removal of the virus inoculum and replacement with overlay (1% w/v CMC in complete media). The box was resealed and incubated for 24 hours prior to fixing for formaldehyde. Microplaques were detected using a SARS-CoV-2 antibody specific for the SARS-CoV-2 RBD Spike protein and a rabbit HRP conjugate, infected foci were detected using TrueBlue™ substrate. Stained microplaques were counted using ImmunoSpot® S6 Ultra-V Analyzer and resulting counts analysed in SoftMax Pro v7.0 software.

Mesoscale Discovery Multiplexed Immunoassay (MIA)

A multiplexed immunoassay was used to measure the antigen-specific response to ChAdOx1 nCoV-19 vaccination and/or natural SARS-CoV-2 infection (assay developed and performed by Meso Scale Discovery (MSD), Rockville, MD). A MULTI-SPOT® 96-well Plate was coated with SARS-CoV2 antigens Spike, and RBD at 200 µg/mL in PBS, washed, dried and packaged for further use (MSD® SARS-CoV-2 Plate 2). Internal quality controls and reference standard reagents were developed from pooled human serum. To measure IgG antibodies to SARS-CoV-2 antigens Spike, and RBD plates were blocked with MSD Blocker A for one hour and washed three times prior to the addition of reference standard, controls and samples. After incubation for two hours, the plates were washed three times and detection antibody was added at 2 µg/mL (MSD SULFO-TAG™ Anti-Human IgG Antibody). Plates were incubated for one hour and washed three times. MSD GOLD™ Read Buffer B was added (150 µL) and the plates were read using a MESO® SECTOR S 600 Reader. Samples at the LLOQ were set to 2.58 for Spike and 2.60 for RBD, while samples at the ULOQ were 320000 for Spike and 317073 for RBD.

Ex vivo IFNγ ELISPOT to enumerate antigen-specific T cells.

ELISpot assays were performed using freshly isolated peripheral blood mononuclear cells (PBMCs) to determine responses to the SARS-CoV-2 spike vaccine antigen at days 0 (before vaccination), 7, 14, 28 and 56, and also at D35 in participants that received two doses. Assays were performed using Multiscreen IP ELISpot plates (Merck Millipore, Watford, UK) coated with 10 µg/mL human anti-IFN-γ antibody and developed using SA-ALP antibody conjugate kits (Mabtech, Stockholm, Sweden) and BCIP NBT-plus chromogenic substrate (Moss Inc., Pasadena, MA, USA). PBMC were separated from whole blood with lithium heparin by density centrifugation within four hours of venepuncture. Cells were incubated for 18–20 hours in RPMI (Sigma) containing 1000 units/mL penicillin, 1 mg/mL streptomycin and 10% heat-inactivated, sterile-filtered foetal calf serum, previously screened for low reactivity (Labtech International, East Sussex, UK) with a final concentration of 10µg/ml of pooled peptide. A total of 253 synthetic peptides (15mers overlapping by 10 amino acids) spanning the entire vaccine insert, including the tPA leader sequence were used to stimulate PBMC (Pro-Immune, Oxford UK). Peptides were pooled into 12 pools for the SARS-CoV-2 spike protein containing 18 to 24

peptides, plus a single pool of 5 peptides for the tPA leader. Peptide sequences and pooling are summarised in Supplementary Table 6. Peptides were tested in triplicate, with 2.5×10^5 PBMC added to each well of the ELISpot plate in a final volume of 100 µL. Results are expressed as spot forming cells (SFC) per million PBMCs, calculated by subtracting the mean negative control response from the mean of each peptide pool response and then summing the response for the 12 peptide pools spanning S1 and S2. Staphylococcal enterotoxin B (0.02 µg/mL) and phytohaemagglutinin-L (10 µg/ mL) were pooled and used as a positive control. Plates were counted using an AID automated ELISpot counter (AID Diagnostika GmbH, algorithm C, Strassberg, Germany) using identical settings for all plates, and counts were adjusted only to remove artefacts. A quality control process was applied where plates were excluded if responses were >80 SFC/million PBMC in the negative control (PBMC without antigen) or <800 SFC/million PBMC in the positive control wells. Responses to the negative control were low, with a median of 15 SFC/10^6 PBMCS (interquartile range (IQR) 10-22 SFC/10^6 PBMCS).

Anti-ChAdOx1 neutralization assay

Chimpanzee adenovirus ChAdOx1-specific neutralizing antibody titers were assessed using a secreted placental alkaline phosphatase (SEAP) quantitation assay as described [5]. Briefly, GripTite MSR 293 cells (Invitrogen, R795-07) were infected with the serial diluted serum in phenol red–free DMEM (Life Technologies, 31053028) and the ChAdOx1-SEAP reporter virus in a 1:1 mixture for 1 hour before replacing with phenol red–free 10% FBS DMEM for 24 hours. For each sample, SEAP concentration was assessed in 50 µl aliquots of culture supernatant, with CPSD as an indicator substrate (Tropix Phospha-Light Chemiluminescent Assay Kit, Life Technologies, T1017). Luminescence intensity was measured using a Varioskan Flash luminometer (Thermo Fisher Scientific). Serum dilution neutralization titers were measured by linear interpolation of adjacent values (to 50% inhibition) to determine the serum dilution required to reduce SEAP concentration by 50% compared to wells with virus alone.

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Study Protocol

Trial Title: A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers

Short title A phase I/II study of a candidate COVID-19 vaccine (COV001)

Study Reference:	COV001
Protocol Version:	8.0
Date:	22 JUN 2020
EudraCT number:	2020-001072-15
REC Reference:	20/SC/0145
IRAS Reference:	281259
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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

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

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1 SYNOPSIS

Title	A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers.
Trial Identifier	COV001
Trial Registration	EudraCT number: 2020-001072-15 REC Reference: 20/SC/0145 IRAS Reference: 281259
Chief Investigator	Professor Andrew Pollard
Clinical Phase	I/II
Design	Single-blinded, randomised, controlled, multi-centre
Population	Healthy adults aged 18-55 years
Planned Sample Size	Up to 1090

Group	W0	W4	W8 (-7/+14 days)
1a (n=44) Intense Follow-up	ChAdOx1 nCoV-19 $5x10^{10}$vp	-	
1b (n=44) Intense Follow-up	MenACWY	-	
2a* (n= up to 206)	ChAdOx1 nCoV-19 $5x10^{10}$vp	-	
2b* (n= up to 206)	MenACWY	-	
2c* Prime-boost (up to 20 volunteers from 2a)	ChAdOx1 nCoV-19 $5x10^{10}$vp		ChAdOx1 nCoV-19 $5x10^{10}$vp
2d* Prime-boost (up to 32 volunteers from 2a)	ChAdOx1 nCoV-19 $5x10^{10}$vp		ChAdOx1 nCoV-19 $2.5x10^{10}$vp

2e* Prime-boost (up to 10 volunteers from 2b)	MenACWY		MenACWY
3 (n=10) Prime-boost	ChAdOx1 nCoV-19 $5x10^{10}$vp	ChAdOx1 nCoV-19 $5x10^{10}$vp	
4a** (n= up to 290)	ChAdOx1 nCoV-19 $5x10^{10}$ vp	-	
4b** (n= up to 290)	MenACWY	-	

* Group 2 will consist of an overall sample size of up to 412 volunteers, of which up to 62 (52 IMP and 10 controls) will receive a booster dose at 8 weeks (-7/+14 days).

**Group 4 will consist of an overall sample size of up to 580 volunteers, of which up to

112 will be given Paracetamol at D0 visit

Visit Schedule

Group 1

	Screening	D0	D1	D3	D7	D14	D28	D56	D182	D364 (optional)
Eligibility	X									
Vaccination		X								
Safety	X	X	X	X	X		X			
Immunology	X	X			X	X	X	X	X	X

Groups 2a, 2b and 4

	Screening	D0	D28	D182	D364 (optional)
Eligibility	X				
Vaccination		X			
Safety	X	X	X		
Immunology	X	X	X	X	X

Groups 2c, 2d and 2e

	Screening	D0	D28	D56	D70	D84	D182	D364 (optional)
Eligibility	X							
Vaccination		X		X				
Safety	X	X	X					
Immunology	X	X	X	X	X	X	X	X

Group 3

	Screening	D0	D1	D3	D7	D14	D28	D31	D35	D42	D56	D182	D364 (optional)
Eligibility	X												
Vaccination		X					X						
Safety	X	X	X	X	X		X	X	X		X		
Immunology	X	X			X	X	X		X	X	X	X	X

Planned Trial Duration	6 months from enrolment with a 12 months optional visit	
	Objective	**Outcome Measure**
Primary	To assess efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19	a) Virologically confirmed (PCR positive) symptomatic cases of COVID-19
Co-Primary	To assess the safety of the candidate vaccine ChAdOx1 nCoV	a) 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	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; 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
	To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19	a) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein; b) Quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates)
Exploratory	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
	To assess safety, reactogenicity, immunogenicity and efficacy endpoints, for participants receiving prophylactic paracetamol	All safety, reactogenicity, immunogenicity and efficacy endpoints.
	To assess immunogenicity of ChAdOx1 nCoV-19 given as homologous prime-boost	Quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates) post boost

Sample analysis for the completion of exploratory endpoints may be performed under the OVC Biobank research tissue bank protocol (REC: 16/SC/0141).

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

Formulation	ChAdOx1 nCoV-19: Liquid MenACWY: powder and solvent for solution for injection ChAdOx1 nCoV-19/MenACWY: Intramuscularly (IM) into the deltoid region of the arm
Route of Administration	IM
Dose per Administration	ChAdOx1 nCoV-19: $5x10^{10}$ vp ChAdOx1 nCoV-19: $2.5x10^{10}$ vp MenACWY: 0.5mL

2 ABBREVIATIONS

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
ChAd63	Chimpanzee adenovirus 63
CI	Confidence interval
COP	Code of Practice
CRF	Case Report Form or Clinical Research Facility
CS or CSP	Circumsporozoite protein
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
GSK	GlaxoSmithKline
HCG	Human Chorionic Gonadotrophin
HBV	Hepatitis B virus
HEK	Human embryonic kidney
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRA	Health Research Authority
HTLV	Human T-Lymphotrophic Virus
IB	Investigator Brochure
ICH	***International Conference on Harmonisation***
ICMJE	***International Committee of Medical Journal Editors***
ICS	***Intracellular Cytokine Staining***
IDT	Impfstoffwerk Dessau-Tornau Biologika GmbH
ID	Intradermal
IFNγ	Interferon gamma
IM	Intramuscular
IMP	Investigational Medicinal Product
IMP-D	Investigational Medicinal Product Dossier
IV	Intravenous
LSOC	Local safety oversight clinician
MenACWY	Quadrivalent capsular group A, C, W and Y meningococcal protein-polysaccharide conjugate vaccine
ME-TRAP	Multiple epitopes and thrombospondin related adhesion protein
MHRA	Medicines and Healthcare Products Regulatory Agency
MVA	Modified vaccinia virus Ankara
NANP	N-acetylneuraminic acid phosphatase

NHS	National Health Service
NIH	National Institutes of Health
NIHR	National Institute for Health Research
PBMC	***Peripheral blood mononuclear cell***
Pb	***Plasmodium Berghei***
PCR	Polymerase chain reaction
PI	Principal Investigator
pfu	Plaque forming unit
QP	Qualified Person
qPCR	Quantitative polymerase chain reaction
QS21	*Quillaja saponaria* saponin molecule
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 [6]. 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 [7]. 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 10th March 2020, a over 118,000 cases have been reported with more than 4200 deaths and 115 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.[8] 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 [9]. 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.[8] 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) [10].

3.2 Pre-Clinical 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.

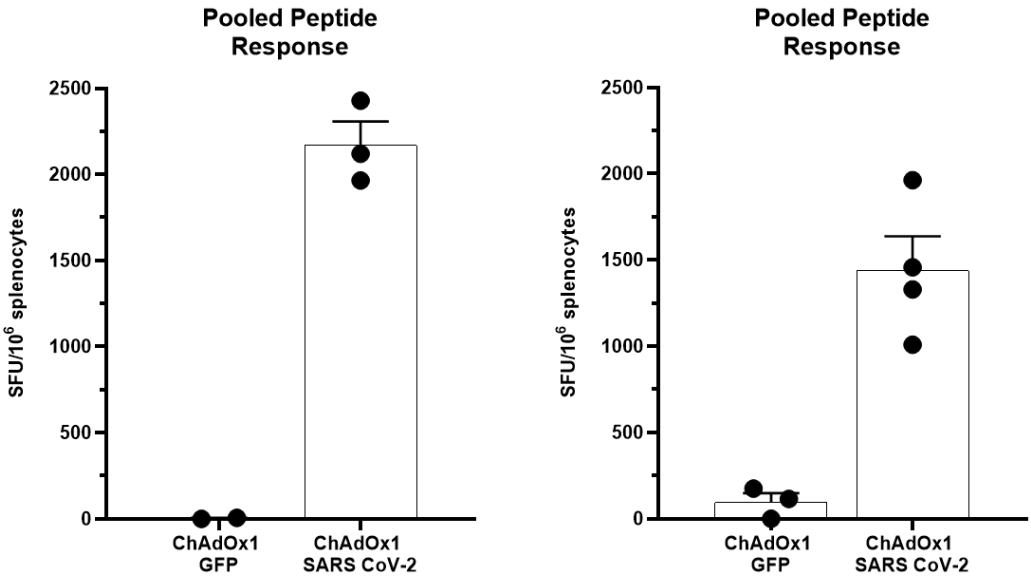

Figure 1. Summed splenic IFN-γ ELISpot responses of BALB/c (left panel) and CD-1 (right panel) mice, in response to peptides spanning the spike protein from SARS-CoV-2, nine or ten days post vaccination, with 1.7×10^{10} vp ChAdOx1 nCoV-19 or 8×10^{9} vp ChAdOx1 GFP. Mean with SEM are depicted

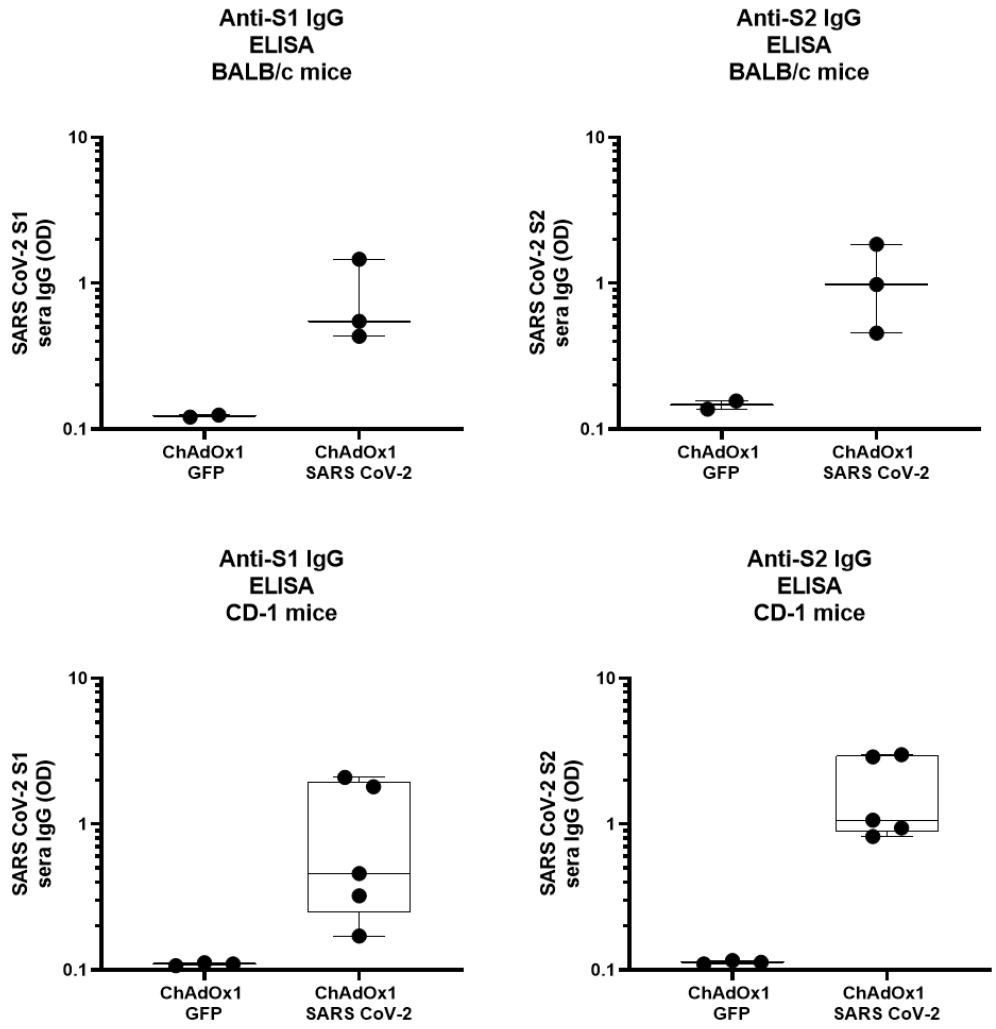

Figure 2. Box and whisker plot of the optical densities following ELISA analysis of BALB/C mouse sera (Top panel) incubated with purified protein spanning the S1 domain (left) or purified protein spanning the S2 domain (right) of the SARS-CoV-2 spike nine or ten days post vaccination, with 1.7×10^{10}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

3.2.2 Efficacy

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

3.3 Disease Enhancement

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.[11-13] To date, there has been one report of lung immunopathology following MERS-CoV challenge in mice immunised with an inactivated MERS-CoV candidate vaccine.[14] 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).[15,16]

The risks of inducing lung immunopathology in the event of COVID-19 disease following ChAdOx1 nCoV-19 vaccination are unknown. Challenge studies on ferrets and NHPs are underway and 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.

3.4 Previous clinical experience

This will be the first-in-human study employing ChAdOx1 nCoV-19. However, 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 1. 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 [17]
					$5x10^9$ 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 [18]
		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 [19]
					$2.5x10^{10}$ vp	12	
		ChAdOx1 85A MVA85A (week 8)	18-50	IM	$2.5x10^{10}$ vp	12	
		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	ChAdOx1 85A	18-49	IM	$5x10^9$ vp	6	Clinicaltrials.gov: NCT03681860
					$2.5 x10^{10}$	6	

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

Table 2. 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 DOI: https://doi.org/10.1016/S1473-3099(20)30160-2 Folegatti et.al. 2020, Lancet Infect.Dis.[2]
					$2.5x10^{10}$ vp	9	
					$5x10^{10}$ vp	9	
					$2.5x10^{10}$ 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	-	

3.5 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 is now at 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 [20]. 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.

Data generated in this study will be used to support further larger phase II/III efficacy studies, which will include target groups at higher risk of severe disease.

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, and it has been previously recommended following Meningococcal B vaccine administration without negatively impacting its immunogenicity profile (reference: Bexsero SmPC). A prophylactic paracetamol dose arm has been introduced in order to assess safety, reactogenicity, immunogenicity and efficacy of the co-administration of paracetamol and ChAdOx1 nCoV-19 as an exploratory objective.

Whilst a single-dose regimen is the preferred option in the context of a pandemic, a two-dose schedule is likely to boost seroconversion rates and increase neutralising antibody levels, although correlates of protection for COVID-19 are still unknown. Groups 2c, d, and e have been added in order to gather additional evidence on immunogenicity of ChAdOx1 nCoV-19 given as part of the two-dose schedule.

4 OBJECTIVES AND ENDPOINTS

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure
Primary Objective To assess efficacy of ChAdOx1 nCoV-19 against COVID-19	a) Virologically confirmed (PCR positive) symptomatic cases of COVID-19	Throughout the study
Co-primary Objective To assess the safety of the candidate vaccine ChAdOx1 nCoV	a) occurrence of serious adverse events (SAEs) throughout the study duration	Throughout the study
Secondary Objectives To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV	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; f) Occurrence of SAE of special interest: disease enhancement episodes	Day 0-7 Self-reported symptoms recorded using electronic diaries Day 0-7 Self-reported symptoms recorded using electronic diaries Day 0-28 Self-reported symptoms recorded using electronic diaries Blood samples drawn at enrolment (before vaccination), day 3, 7 and 28 Throughout the study
To assess efficacy of ChAdOx1 nCoV-19 against 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	Throughout the study Throughout the study Throughout the study

	d) Seroconversion against non-Spike antigens	Blood samples drawn at D0, D28 and D182 (D364 optional)
To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19	a) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein; b) Quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates)	See schedule of attendances
Exploratory Objectives 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	See schedule of attendances
To assess safety, reactogenicity, immunogenicity and efficacy endpoints, for participants receiving prophylactic paracetamol	All safety, reactogenicity, immunogenicity and efficacy endpoints.	Throughout the study
To assess immunogenicity of ChAdOx1 nCoV-19 given as homologous prime-boost	Quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates) post boost	Blood samples drawn at D0, D28, D56, D70, D84, D182 and D364

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 I/II, single-blinded, -controlled, individually randomised study in healthy adults aged 18-55 years recruited in the UK. ChAdOx1 nCoV-19 or active control (licensed MenACWY) will be administered via an intramuscular injection into the deltoid. The study will assess efficacy, safety and immunogenicity of ChAdOx1 nCoV-19. Additional steps may be taken to keep clinical investigators assessing the primary efficacy endpoint blinded to group allocation with an aim to minimise unblinding of participants, where this is possible and practical to do so.

There will be 4 study groups with up to 540 volunteers in each of the single dose vaccine arms (ChAdOx1 nCoV-19 or licensed MenACWY) in groups 1, 2 & 4 combined and 10 participants in group 3 with an overall sample size of up to 1090 (Table 3). Randomisation will take place at an intervention to control ratio of 1:1. Only participants enrolled in groups 1, 2 and 4 will be randomised. Participants in group 3 will not be randomised or blinded. Up to 112 participants in group 4 will be requested to take prophylactic paracetamol 1000mg every 6 hours for 24 hours from the time of vaccination to reduce the chance of fever post immunisation.

Staggered enrolment will apply to the first volunteers receiving the IMP as described in section 7.4.2.2. Participants will be first recruited in groups 1 and 3. Once groups 1 and 3 are fully recruited, subsequent volunteers will be enrolled in groups 2 and 4.

Safety will be assessed in real time and interim reviews are scheduled after 1, 4, and up to 54 participants received the IMP. Randomisation blocks will ensure there is at least 1 control for each participant receiving the IMP, so these safety reviews will take place after 2, 8, and up to 98 participants are enrolled in the study overall (groups 1 and 3).

Up to 62 participants enrolled in group 2 (a and b) will be invited to receive a booster vaccine. Participants in groups 2c and 2d will be randomised to receive either a standard booster dose ($5x10^{10}$vp), or a lower booster dose ($2.5x10^{10}$vp) at approximately 8 weeks post prime. Up to 10 volunteers from 2b will be receive a second dose of MenACWY at the same interval

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.

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.

5.1 Study groups

Group	Number of Volunteers	Dose	Route
1a	44	ChAdOx1 nCoV-19 $5x10^{10}$ vp	IM
1b	44	MenACWY	IM
2a*	Up to 206	ChAdOx1 nCoV-19 $5x10^{10}$ vp	IM
2b*	Up to 206	MenACWY	IM
2c*	Up to 20 volunteers from 2a	Homologous Prime-Boost $5x10^{10}$ vp, 8 weeks apart (-7/+14 days)	IM
2d*	Up to 32 volunteers from 2a	Homologous Prime-Boost $5x10^{10}$ vp (prime) and $2.5x10^{10}$ vp (boost) 8 weeks apart (-7/+14 days)	IM
2e*	Up to 10 volunteers from 2b	Homologous Prime-Boost MenACWY 8 weeks apart (-7/+14 days)	IM
3	10	Homologous Prime-Boost $5x10^{10}$ vp	IM
4a **	Up to 290	ChAdOx1 nCoV-19 $5x10^{10}$ vp	IM
4b**	Up to 290	MenACWY	IM

* Group 2 will consist of an overall sample size of up to 412 volunteers, of which up to 62 (52 IMP and 10 controls) will receive a booster dose at 8 weeks (-7/+14 days).

**Group 4 will consist of an overall sample size of up to 580 volunteers, of which up to 112 will be given Paracetamol at D0 visit

5.2 Trial volunteers

Healthy adult volunteers aged 18-55 will be recruited into the study. Volunteers will be considered enrolled immediately following administration of first vaccination.

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 Duration of study

The total duration of the study will be 6 months from the day of enrolment for all volunteers with an optional 12 months follow-up.

5.5 Potential Risks for volunteers

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

Venepuncture

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 six month period will be 177.5-621.5mL (blood volumes may vary slightly for volunteers at different investigator sites due to use of different volume vacutainers, following local Trust SOPs). 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.

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 2-3 days. Presyncopal and syncopal episodes may occur at the time of vaccination which rapidly resolve. For subset of participants in group 4, use of prophylactic paracetamol for 24 hours will be advised to alleviate potential fevers and flu-like symptoms. As with any other vaccine, 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).

Control participants will receive one 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. Challenge studies on ferrets and NHPs are underway and results will be reviewed as they emerge. 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.

5.6 Known Potential Benefits

Volunteers enrolled into the control groups will receive 1 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. The only benefits for participants would be information about their general health status.

6 RECRUITMENT AND WITHDRAWAL OF TRIAL VOLUNTEERS

6.1 Identification of Trial Volunteers

Healthy adults in the UK 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 web-site).
- 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 other 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 between 18-55 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 other trial sites databases: We may contact individuals from databases of groups within the CCVTM (including the Oxford Vaccine Centre database) and other trial sites of previous trial participants who have expressed an interest in receiving information about all future studies for which they may be eligible.

6.2 Informed consent

All volunteers will sign and date the informed consent form before any study specific procedures are performed. The information sheet will be made available to the volunteer at least 24 hours prior to the screening visit. At the screening visit, a video presentation of the aims of the study and all tests to be may be carried out may be screened to an audience, or made available for them to access it remotely. Individually each volunteer will have the opportunity to question an appropriately trained and delegated researcher before signing the consent. At the screening visit, the volunteer will be fully informed of all aspects of the trial, the potential risks and their obligations. 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. 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, GP and other medical records from local systems, by contacting the GP practice, or volunteers bringing their medical care summaries from the GP to the study clinicians. However, volunteers may be enrolled based on medical information obtained during screening only, 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 anonymised. 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 volunteer will be registered on the TOPS database (The Over volunteering Prevention System; www.tops.org.uk).

The aims of the study and all tests to be carried out will be explained. The volunteer will be given the opportunity to ask about details of the trial, and will then have time to consider whether or not to participate. If they do decide to participate, they, and the investigator will sign and date the consent form. However, in the current crisis, there may be occasions when it is necessary for the consent form to be signed by an appropriately trained and delegated research nurse instead of the investigator. The participant would always have the opportunity to discuss the study with a medically qualified investigator if they wish. The volunteer will then be provided with a copy of the consent form to take away and keep, with the original

being stored in the case report form (CRF). Reconsent will be taken by appropriately trained and delegated members of the team.

6.3 Inclusion and exclusion criteria

This study will be conducted in healthy adults, 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:

- Healthy adults aged 18-55 years.
- Able and willing (in the Investigator's opinion) to comply with all study requirements (participants must not rely on public transport or taxis).
- 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 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.

6.3.2 Exclusion Criteria

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

- Prior receipt of any vaccines (licensed or investigational) ≤30 days before enrolment
- Planned receipt of any vaccine other than the study intervention within 30 days before and after each study vaccination .
- Prior receipt of an investigational or licensed vaccine likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines).
- 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, including HIV infection; 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) .
- Any autoimmune conditions, except mild psoriasis, well-controlled autoimmune thyroid disease, vitiligo or stable coeliac disease not requiring immunosuppressive or immunomodulatory therapy.

- History of allergic disease or reactions likely to be exacerbated by any component of the ChAdOx1 nCoV-19 or MenACWY vaccines.
- Any history of angioedema .
- Any history of anaphylaxis .
- Pregnancy, lactation or willingness/intention to become pregnant during the study.
- History of 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 (e.g. ongoing severe depression, history of admission to an in-patient psychiatric facility, recent suicidal ideation, history of suicide attempt, bipolar disorder, personality disorder, alcohol and drug dependency, severe eating disorder, psychosis, use of mood stabilisers or antipsychotic medication).
- Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
- Any other serious chronic illness requiring hospital specialist supervision.
- Chronic respiratory diseases, including mild asthma (resolved childhood asthma is allowed)
- Chronic cardiovascular disease (including hypertension), gastrointestinal disease, liver disease (except Gilberts Syndrome), renal disease, endocrine disorder (including diabetes) and neurological illness (excluding migraine)
- Seriously overweight (BMI≥40 Kg/m^2) or underweight (BMI≤18 Kg/m^2)
- Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units every week.
- Suspected or known injecting drug abuse in the 5 years preceding enrolment.
- Any clinically significant abnormal finding on screening biochemistry, haematology blood tests or urinalysis.
- 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.
- History of laboratory confirmed COVID-19.

- New onset of fever or a cough or shortness of breath or anosmia/ageusia since February 2020. Should a reliable test become available, this exclusion criteria will be replaced with seropositivity for SARS-CoV-2 before enrolment.
- Those who have been at high risk of exposure before enrolment, including but not limited to: close contacts of confirmed COVID-19 cases, anyone who had to self-isolate as a result of a symptomatic household member, frontline healthcare professionals working in A&E, ICU and other higher risk areas. Should a reliable test become available, this exclusion criteria will be replaced with seropositivity for SARS-CoV-2 before enrolment.
- Living in the same household as any vulnerable groups at risk of severe COVID-19 disease (as per PHE guidance)

Additional exclusion criteria (subset of participants receiving Paracetamol in group 4 only)

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

6.3.3 Re-vaccination exclusion criteria

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 be withdrawn from the study and followed up by the clinical team or their GP until resolution or stabilisation of the event:

- Anaphylactic reaction following administration of vaccine
- Pregnancy

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 (i.e until their last follow-up visit).

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 abdominal 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 (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception

6.3.5 Prevention of 'Over Volunteering'

Volunteers will be excluded from the study if they are concurrently involved in another trial where an IMP has been administered within 30 days prior to enrolment, or will be administered during the trial period. In order to ensure this, volunteers will be asked to provide their National Insurance or Passport number (if they are not entitled to a NI number) and will be registered on a national database of participants in clinical trials (www.tops.org.uk). They will not be enrolled if found to be actively registered on another trial until further information on IMP and bleeding schedule is obtained.

6.3.6 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. The DSMB or DSMB chair may recommend withdrawal of volunteers.

Any volunteer who is withdrawn from the study may be replaced, if that is possible within the specified time frame.

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 TRIAL PROCEDURES

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

7.1 Schedule of Attendance

All volunteers in groups 1 will have the same schedule of clinic attendances and procedures as indicated in the schedules of attendance (Table 6). Group 2 will have clinic attendances and procedures as indicated in the schedules of attendances below (Table 7). Group 3 will have clinic attendances and procedures as indicated in the schedules of attendances below (Table 8). Group 4 will have clinic attendances and procedures as indicated in the schedules of attendances below (Table 9). Subjects will receive either the ChAdOx1 nCoV-19 vaccine or MenACWY control, and undergo follow-up for a total of 6 months with an optional visit at 1 year post enrolment. The total volume of blood donated during the study will be 177.5 – 621.5mL depending on which group they are allocated to. Additional visits or procedures may be performed at the discretion of the investigators, e.g., further medical history and physical examination, urine microscopy in the event of positive urinalysis or additional blood tests if clinically relevant.

7.2 Observations

Pulse, blood pressure and temperature will be measured at the time-points indicated in the schedule of procedures and may also be measured as part of a physical examination if indicated at other time-points.

7.3 Blood tests, Nose/Throat Swab and urinalysis

Blood will be drawn for the following laboratory tests and processed at 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 (specific consent will be gained prior to testing blood for these blood-borne viruses)
- **Immunology;** Human Leukocyte Antigen (HLA) typing (groups 1 and 3 only)

A nose/throat swab will be conducted for COVID-19 PCR

- **COVID-19** PCR processing (nose/throat swabs)

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:

- **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. 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. SARS-CoV-2 serology to be conducted at screening on participants at high risk of COVID-19 exposure (healthcare workers will be prioritised), subject to test availability and lab capacity.

- **Urinalysis;** Urine will be tested for protein, blood and glucose at screening. For female volunteers only, urine will be tested for beta-human chorionic gonadotrophin (β-HCG) at screening and immediately prior to vaccination.

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 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 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).

7.4 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 (Tables6-9). Each visit is assigned a time-point and a window period, within which the visit will be conducted.

7.4.1 Screening visit

Participants will be required to complete an online questionnaire as an initial confirmation of eligibility. 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. 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, as described in section 6.2. If consent is obtained, the procedures indicated in the schedule of attendances will be undertaken including a medical history, physical examination, blood tests and height and

weight. 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 COV001).

We will aim to contact the subject's general practitioner with the written permission of the subject after screening to corroborate medical history when possible and practical to do so. GPs will be notified that the subject has volunteered for the study. During the screening, the volunteers will be asked to provide their National Insurance or passport number so that this can be entered on to a national database which helps prevent volunteers from participating in more than one clinical trial simultaneously or over-volunteering for clinical trials (www.tops.org.uk).

Abnormal clinical findings from the urinalysis or blood tests at screening will be assessed by a medically qualified study member. Abnormal blood tests following screening will be assessed according to 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.

7.4.2 Day 0: Enrolment and vaccination visit

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. Pulse, blood pressure and temperature will be observed and if necessary, a medical history and physical examination may be undertaken to determine need to withdraw the participant. Participants with symptoms meeting the case definition for COVID-19 or likely recent exposure to COVID-19 will be excluded. Vaccinations will be administered as described below.

7.4.2.1 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, in case of immediate adverse events. Observations will be taken 60 minutes after vaccination (+/- 30 minutes) and the sterile dressing removed and injection site inspected.

In all groups, volunteers will be given an oral thermometer, tape measure and diary card (paper or electronic), with instructions on use, along with 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. Diary cards will collect information on the timing and severity of the following solicited AEs:

Table 4. ***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

7.4.2.2 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 elsewhere, and discussed with the DSMB and/or MHRA as necessary. For safety reasons, the first volunteer to receive the IMP will be vaccinated ahead of any other participants and the profile of adverse events will be reviewed after 24 hours (+24h) post vaccination. Provided there are no safety concerns, as assessed by a medically qualified investigator and/or chair of DSMB, another 3 volunteers will be vaccinated with the IMP after at least 48 hours (±24h) has elapsed following first vaccination and at least 1 hour apart from each other. The profile of AEs will be assessed by a medically qualified investigator in real time and after 24 hours (+24h) of the first 4 participants receiving the IMP, further vaccinations will proceed provided there are no safety concerns. Relevant investigators and chair of DSMB will be asked to provide a decision on whether further vaccinations can go ahead after the first 4 participants received the IMP. A full DSMB may also be consulted should safety concerns arise at this point.

A review will be conducted based on accumulated safety data of the first up to 54 participants receiving the IMP. Enrolment of the remaining participants will only proceed if the CI, and/or other designated relevant investigators and the chair of DSMB assess the data as indicating that it is safe to do so. At this point, any new immunopathology data from pre-clinical challenge studies in ferrets and non-human primates will be assessed by the CI and/or other designated relevant investigators and the DSMB prior to enrolment of the remaining participants.

A second review will be conducted based on accumulated safety data once the trial is fully recruited. The table below provides an estimate of the sequence of recruitment

Table 5. Expected recruitment schedule

By Day	0	3	5	6 onwards
Single Dose IMP arms (up to)	1	3	40	496
Control arms (up to)	1	3	40	496
Prime-Boost Group (up to)			10	
Total per Day (up to)	2	6	90	Approximately 120 per day until trial fully recruited
Cumulative IMP	1	4	54	Up to 540
Cumulative Total	2	8	98	Up to 1090
Safety Review	Real time Review of pre-clinical data	Real time	Real time Review of first 54 participants receiving IMP before enrolling the remainder	Review of Immunopathology data (pre-clinical studies) Review of accumulated safety data once trial fully recruited

7.4.3 Subsequent visits:

Follow-up visits will take place as per the schedule of attendances described in tables 6-9 with their respective windows. Volunteers 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.

7.4.4 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 using smartphone or computer app if clinically appropriate in order to obtain core study data where possible.

Table 6 Schedule of attendances for participants in group 1

Attendance Number	1[S]	2	3	4	5	6	7	8	9	10	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 Follow-up
Timeline** (days)	≤ 90	0	1	3	7	14	28	56	182	364 (Optional)	As required	7 days post COVID-19 Testing	As required
Time window (days)				±1	±2	±3	±7	±7	±14	±30	N/A	±2	N/A
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	
Telephone/Video call			X										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)	
Biochemistry, Haematology (mL)	5	5		5	5		5				5	5	
Exploratory immunology (mL)	(5)*	50			50	50	50	50	50	50	up to 50	up to 50	
PAXgenes (mL)		2.5									2.5	2.5	
Nose/Throat Swab											X	X	
Urinalysis	X												

Attendance Number	1[S]	2	3	4	5	6	7	8	9	10	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 Follow-up
Urinary bHCG (women only)	X	X											
HLA typing (mL)		4											
HBsAg, HCV Ab, HIV serology (mL)	5												
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 ^ = Vital signs includes pulse, blood pressure and temperature; ** 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. % 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. *SARS-CoV-2 serology to be conducted at screening on participants at high risk of COVID-19 exposure (healthcare workers will be prioritised), subject to test availability and lab capacity. An extra 5mls should be added to cumulative blood volumes if extra COVID-19 serology is required at screening.

Table 7 Schedule of attendances for participants in group 2a and 2b

Attendance Number	1[S]	2	3	4	5	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 follow-up
Timeline** (days)	≤ 90	0	28	182	364 (Optional)	As required	7 days post COVID-19 Testing	As required
Time window (days)			±7	±14	±30	N/A	±2	N/A
Informed Consent	X							
Review contraindications, inclusion and exclusion criteria	X	X						
Vaccination		X						
Vital signs^	X	X	X	X	X	X	X	
Telephone/Video call								As required
Ascertainment of adverse events		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)	
Biochemistry, Haematology (mL)	5	5	5			5	5	
Exploratory immunology (mL)	(5)*	50	50	50	50	up to 50	up to 50	
PAXgenes (mL)		2.5				2.5	2.5	
Nose/Throat Swab						X	X	
Urinalysis	X							
Urinary bHCG (women only)	X	X						
HBsAg, HCV Ab, HIV serology (mL)	5							
Blood volume per visit	15	57.5	55	50	50	up to 57.5	up to 57.5	

Attendance Number	1[S]	2	3	4	5	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 follow-up
Cumulative blood volume[%]	15	72.5	127.5	177.5	227.5	285	342.5	

S = screening visit; (X) = if considered necessary ^ = Vital signs includes pulse, blood pressure and temperature; ** 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.% 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. *SARS-CoV-2 serology to be conducted at screening on participants at high risk of COVID-19 exposure (healthcare workers will be prioritised), subject to test availability and lab capacity. An extra 5mls should be added to cumulative blood volumes if extra COVID-19 serology is required at screening.

Table 8 Schedule of attendances for participants in group 2c, 2d and 2e

Attendance Number	1[S]	2	3	4	5	6	7	8	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 follow-up
Timeline** (days)	≤ 90	0	28	56	70	84	182	364 (Optional)	As required	7 days post COVID-19 Testing	As required
Time window (days)			±7	-7/+14	±7	±7	±14	±30	N/A	±2	N/A
Informed Consent	X										
Review contraindications, inclusion and exclusion criteria	X	X									
Vaccination		X		X							
Vital signs^	X	X	X				X	X	X	X	
Telephone/Video call											As required
Ascertainment of adverse events		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	(X)	(X)				(X)	(X)	(X)	(X)	
Biochemistry, Haematology (mL)	5	5	5	5	5	5			5	5	
Exploratory immunology (mL)	(5)*	50	50	Up to 50	Up to 50	Up to 50	Up to 50	Up to 50	up to 50	up to 50	
PAXgenes (mL)		2.5							2.5	2.5	
Nose/Throat Swab									X	X	
Urinalysis	X										

Attendance Number	1[S]	2	3	4	5	6	7	8	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 follow-up
Urinary bHCG (women only)	X	X		X							
HBsAg, HCV Ab, HIV serology (mL)	5										
Blood volume per visit	15	57.5	55	55	55	55	50	50	up to 57.5	up to 57.5	
Cumulative blood volume[%]	15	72.5	127.5	182.5	237.5	292.5	342.5	392.5	450	507.5	

S = screening visit; (X) = if considered necessary ^ = Vital signs includes pulse, blood pressure and temperature; ** 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.% 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. *SARS-CoV-2 serology to be conducted at screening on participants at high risk of COVID-19 exposure (healthcare workers will be prioritised), subject to test availability and lab capacity. An extra 5mls should be added to cumulative blood volumes if extra COVID-19 serology is required at screening.

Table 9 Schedule of attendances for participants in group 3

Attendance Number	1[S]	2(V1)	3	4	5	6	7 (V2)	8	9	10	11	12	13	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 Follow-up
Timeline** (days)	≤ 90	0	1	3	7	14	28	31	35	42	56	182	364 (optional)	As required	7 days post COVID-19 Testing	As required
Time window (days)			+1	±1	±3	±3	±7	±1	±2	±3	±3	±14	±30	N/A	±2	N/A
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	
Telephone/Video call			X													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	(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	
Exploratory immunology[£] (mL)	(5)*	50			50	50	50		50	50	50	50	50	up to 50	up to 50	
PAXgenes (mL)		2.5												2.5	2.5	
Nasal/Throat Swab														X	X	

Attendance Number	1[S]	2(V1)	3	4	5	6	7 (V2)	8	9	10	11	12	13	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 Follow-up
Urinalysis	X															
Urinary bHCG (women only)	X	X					X									
HLA typing (mL)		4														
HBsAg, HCV Ab, HIV serology (mL)	5															
Blood volume per visit	15	61.5		5	55	50	55	5	55	50	55	50	50	up to 57.5	up to 57.5	
Cumulative blood volume[%]	15	76.5		81.5	136.5	186.5	241.5	246.5	301.5	351.5	406.5	456.5	506.5	564	621.5	

S = screening visit; (X) = if considered necessary ^ = Vital signs includes pulse, blood pressure and temperature; ** 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.% 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. *SARS-CoV-2 serology to be conducted at screening on participants at high risk of COVID-19 exposure (healthcare workers will be prioritised), subject to test availability and lab capacity. An extra 5mls should be added to cumulative blood volumes if extra COVID-19 serology is required at screening.

Table 10 schedule of attendances for participants in group 4

Attendance Number	1[S]	2	3	4	5	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 Follow-up
Timeline** (days)	≤ 90	0	28	182	364 (Optional)	As required	7 days post COVID-19 Testing	As required
Time window (days)			±7	±14	±30	N/A	±2	N/A
Informed Consent	X							
Review contraindications, inclusion and exclusion criteria	X	X						
Vaccination		X						
Prophylactic Paracetamol for 24h[p]		X						
Vital signs^	X	X	X	X	X	X	X	
Telephone/Video call								As required
Ascertainment of adverse events		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)	
Biochemistry, Haematology (mL)	5	5	5			5	5	
Exploratory immunology (mL)	(5)*	10	10	10	10	up to 50	up to 50	
PAXgenes (mL)		2.5				2.5	2.5	
Nose/Throat Swab						X	X	
Urinalysis	X							
Urinary bHCG (women only)	X	X						

Attendance Number	1[S]	2	3	4	5	COVID-19 Testing	COVD-19 Testing + 7 days	COVID-19 Follow-up
HBsAg, HCV Ab, HIV serology (mL)	5							
Blood volume per visit	15	17.5	15	10	10	up to 57.5	up to 57.5	
Cumulative blood volume[%]	15	32.5	47.5	57.5	67.5	125	182.5	

S = screening visit; (X) = if considered necessary ^ = Vital signs includes pulse, blood pressure and temperature; ** 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.% 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. *SARS-CoV-2 serology to be conducted at screening on participants at high risk of COVID-19 exposure (healthcare workers will be prioritised), subject to test availability and lab capacity. An extra 5mls should be added to cumulative blood volumes if extra COVID-19 serology is required at screening.P = prophylactic paracetamol over the first 24h post immunisation in a subset of participants in group 4 only.

7.4.5 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 new onset of fever or cough or shortness of breath or anosmia/ageusia and if they are admitted to hospital for any reason. At the COVID-19 testing visit, a nose/throat swab, blood samples for safety (FBC, Biochemistry, CRP, 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 7 days (±2 days) post COVID-19 testing for clinical review and further testing. Clinical data, a second nose/throat swab, and additional blood samples for safety and immunology purposes will be taken. Participants will be asked to record information on an electronic diary COVID-19 related symptoms for safety monitoring until symptom resolution.

7.4.6 Household Weekly Questionnaire

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.

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.

7.4.7 Medical notes review

With the participants 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.

7.4.8 Randomisation, blinding and code-breaking

Participants will be randomised to investigational vaccine or MenACWY in a 1:1 allocation, using block randomisation. Block sizes will reflect the numbers to be recruited at each stage of the study. The first block will be a block of 2 participants, followed by a block of 6, then blocks of 4 as required to meet the totals for randomisation for each day.

Participants enrolled in groups 1, 2 and 4 will be blinded to the arm they have been allocated to, whether investigational vaccine or control. 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.

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.

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.

Participants enrolled in group 3 will not be randomised or blinded

8 INVESTIGATIONAL PRODUCT AND TRIAL INTERVENTIONS

8.1 Manufacturing and presentation

8.1.1 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 the Clinical BioManufacturing Facility (CBF), University of Oxford or Advent Srl, Italy. At the CBF the vaccine will be certified and labelled for the trial by a Qualified Person (QP) before transfer to the clinical site.

8.3 Storage

The vaccine is stored at nominal -80^{o}C in a secure freezer, 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 within 1 hour of removal from storage. The vaccine will be administered intramuscularly into the deltoid of the non-dominant arm (preferably). All volunteers will be observed in the unit for 1 hour (±30 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 (Folegatti et al. Lancet Infect Dis, 2020, in press). 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.

As this is a first-in-human assessment of the SARS-CoV-2 S antigenic insert, a staggered enrolment will apply for the first volunteers enrolled in the study. The same procedure will apply, should other batches of ChAdOx1 nCoV-19 become available. Safety of ChAdOx1 nCoV-19 will be monitored in real time. and should unacceptable adverse events or safety concerns arise, doses will be decreased via an amendment.

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 intervention 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 control vaccine will be conducted in accordance with the relevant SOPs.

8.10 Paracetamol (non-IMP)

Paracetamol will be provided to a subset of participants in group 4 to be taken at vaccination day for 24hours.

8.11 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 or there is planned receipt of any other vaccine within 30 days of each vaccination, any investigational product within 30 days prior to enrolment or if receipt is planned during the study period, or if there is any use of immunosuppressant medication within 6 months prior to enrolment or if receipt is planned at any time during the study period (except topical steroids and short course of low dose steroids < 14 day).

8.12 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 control 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 and nausea.

9.4 Adverse Events of Special Interest (AESI)

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.

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 $x10^9$/L will be reported as SAEs.

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 11). 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 11. *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. 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 11-13 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 12. 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 13. ***Severity grading criteria for physical observations.*** **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 14. Severity grading criteria for local and systemic AEs.

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.

9.9 Reporting Procedures for SUSARS

All SUSARs (including SUSARs related to the non-IMP where there is a possibility of an interaction between the non-IMP and IMP) 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. 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 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.

Interim safety reviews are planned after the first volunteer in the intervention arm and after the first 4 participants have been given a dose of the IMP.

Data from pre-clinical studies will be assessed by the CI, relevant investigators and the DSMB a soon as they are available and before up to 100 volunteers receive a dose of the IMP.

Safety data available from the first up to 54 volunteers receiving a dose of the IMP will be reviewed by the CI, relevant investigators and the chair of DSMB before proceeding with vaccination in the remaining volunteers.

The DSMB will review safety data accumulated when the study is fully recruited.

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.

9.13 Data Safety Monitoring Board

A Data Safety Monitoring Board will be appointed to

a) periodically review and evaluate the accumulated study data for participant safety, study conduct, progress, and efficacy.

b) make recommendations concerning the continuation, modification, or termination of the trial.

There will be a minimum of three appropriately qualified committee members of whom one will be the designated chair. The DSMB will operate in accordance with the trial specific charter, which will be established before recruitment starts.

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 has the power to place the study on hold if deemed necessary following a study intervention-related SAE.

9.14 Safety Group Holding Rules

Safety holding rules have been developed considering the fact that this is a first-in-human study. Safety holding rules apply to participants receiving ChAdOx1 nCoV-19 only.

Solicited AEs are those listed as foreseeable ARs in section 9.3 of the protocol, occurring within the first 7 days after vaccination (day of vaccination and six subsequent days). 'Unsolicited adverse events' are adverse events other than the foreseeable ARs occurring within the first 7 days, or any AEs occurring after the first 7 days after vaccination

9.14.1 Group holding rules

For safety reasons, the first volunteer to receive a new vaccine will be vaccinated alone and the trial Investigators will wait 48 hours (±24 hours) before vaccinating subsequent volunteers. Three further volunteers may be vaccinated 48 hours (±24 hours) after the first and then at least another 48 hours (±24 hours) gap will be left before vaccinating the rest of the volunteers. Group holding rules mentioned below will apply to all study Groups

- **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 a holding rule is activated, then further vaccinations in any group 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.

9.14.2 Individual stopping rules (will apply to prime-boost group 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

A fully detailed statistical analysis plan will be developed and signed by the chief investigator prior to any data analysis being conducted. In brief, the analysis will incorporate the following;

10.1.1 Primary efficacy

The primary efficacy analysis endpoints include: PCR positive COVID-19 symptomatic cases.

Only events that occur more than 14 days after vaccination will be included in efficacy evaluations to allow time for the vaccine recipients to mount a protective immune response and to provide a more accurate estimation of VE. 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.

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

10.1.2 Primary Safety

All SAEs will be presented for each group using descriptive analyses.

10.1.3 Secondary efficacy

The secondary efficacy analysis endpoints include;

- Hospital admissions with PCR positive COVID-19
- Intensive Care Unit admissions with PCR positive COVID-19
- Death due to PCR positive COVID-19 infection
- Seroconversion to non-Spike SARS-CoV-2 antigens

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

10.1.4 Safety & Reactogenicity

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

10.1.5 Immunogenicity

Highly skewed ELISA 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.

Comparisons between groups will be made using a Mann Whitney U test.

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.

10.1.6 Interim analysis of the primary outcome

One formal interim analysis is planned which will be conducted when 15 cases have occurred within the efficacy evaluation window (from day 14 onwards).

The interim analysis of efficacy for the primary outcome will apply the Pocock alpha spending function method for group sequential tests and will consider a p value less than 0.0294 as significant. A p value less than 0.0294 will occur if not more than 3 cases are observed in the vaccine arm.

A significant p value at the interim analysis will not be considered a reason to stop the trial, but instead will be interpreted as early evidence of efficacy.

10.1.7 Full power analysis of the primary outcome

The primary analysis of the primary outcome will be conducted when at least 30 cases have occurred within the efficacy evaluation window. Following the Pocock alpha spending function method, the analysis will consider a p value less than 0.0294 as significant.

10.1.8 Final Analysis

A final analysis will be conducted at the end of the study if further cases have accrued by this time. This will be considered a secondary analysis.

10.2 Power of interim and full analyses

With 30 cases of COVID-19, the study will have 80% power to detect a VE of 70%, assuming an event rate of 23 cases in the control arm and 7 cases in the vaccine arm. This power calculation assumes 2 sequential tests are made using the Pocock spending function. The power of the interim analysis will be 48%. These calculations use an overall two-sided 5% alpha.

10.3 Combined analyses

The Phase I/II study (COV001) and the phase 2/3 study (COV002) are expected to be running concurrently during a period of high disease incidence in the UK. Efficacy data from both studies will be combined in a prospective meta-analysis to enable more precise estimation of efficacy and safety parameters.

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

All available data will be included in the analysis

10.5 Inclusion in Analysis

All vaccinated participants will be included in the analysis of safety and will be analysed according to vaccine received.

The primary analysis of the primary and secondary efficacy outcomes will include participants who are seronegative to the spike protein at baseline. Sensitivity analyses for both primary and secondary outcomes will be conducted including all vaccinated participants regardless of seropositivity status.

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 each review time-points 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.

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 personal. 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.

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.

All trial records will be stored for a minimum of 5 years after the end of the trial at a secure archiving facility . 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.

Source data verification requirements will be defined in the trial risk assessment and monitoring plan.

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. Participants' bank details will be stored for 7 years in line with the site financial policy.

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 Monitoring

Regular monitoring will be performed according to GCP by the monitor. Following written SOPs and an approved, risk based monitoring plan, 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.

12.3 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.

12.4 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 and participant ID logs. 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 are diagnosed with COVID-19 during the course of the study then the study team will pass on their details to the local health protection team, if required, in line with the relevant notifiable disease legislation. 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.

15 FINANCING AND INSURANCE

15.1 Financing

The study is funded through UK Government

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 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 **£190-625** 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 6-8, 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

Should the volunteer decide to withdraw from the trial before it is completed, payment will be pro rata

16 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.

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

Ownership of IP generated by employees of the University vests 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.

APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes
N/A	1.0	13 Mar 2020	Pedro Folegatti, Daniel Jenkin, Sarah Gilbert, Andrew Pollard, Adrian Hill, Merryn Voysey
N/A	2.0	18 Mar 2020	Pedro Folegatti
SA01	3.0	23 Mar 2020	Pedro Folegatti
SA02	4.0	20 Apr 2020	Pedro Folegatti, Merryn Voysey, Emma Plested
SA03	5.0	21 Apr 2020	Pedro Folegatti
SA05	6.0	06 May 2020	Pedro Folegatti, Merryn Voysey
SA06	7.0	19 May 2020	Pedro Folegatti
SA08	8.0	22 Jun 2020	Pedro Folegatti

Appendix. Toxicity grading scale for Lab AEs

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	>1.5-3.0xULN 157-312	>3.0xULN >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	-

Normal lab ranges may vary between sites and should be adapted accordingly

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