A phase IV, multi-centre, randomised controlled trial to assess immunogenicity and safety of COVID-19 and seasonal influenza vaccines given to healthy adults or those with underlying medical conditions when co-administered with a recombinant herpes zoster vaccine with adjuvant

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Table of contents

Glossary / abbreviations

ADEM	Acute disseminated encephalomyelitis
AE	Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.
AESI	Adverse Event of Special Interest
ALPS	Autoimmune lymphoproliferative syndrome
AR	Adverse reaction - is any undesirable experience that has happened to a subject while taking a drug that is suspected to be caused by the drug or drugs.
ARDS	Acute respiratory distress syndrome
aQIV	Adjuvanted influenza vaccine
BTC	Bristol Trials Centre
CI	Chief investigator
CMI	Cell-mediated immunity
e-CRF	Electronic case report form
CTA	Clinical Trials Authorisation
C19	mRNA bivalent COVID-19 vaccine
DMSC	Data monitoring and safety committee
NHS	National Health Service
NIHR	National Institute for Health Research
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
GMC	Geometric Mean Concentrations
GI	Gastrointestinal
HAI	Haemagglutination inhibition assay
HRA	Health Research Authority
HZ	Herpes zoster infection
HZV	Herpes zoster vaccine
ICF	Informed Consent Form
ICS	intracellular cytokine staining
IMP	Investigational Medicinal Product
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine system
MHRA	Medicines and healthcare products regulatory agency
µg	Microgram
MRC	Medical Research Council
PBMC	Peripheral blood mononuclear cells
PI	Principal Investigator
PIL	Patient information leaflet

pIMD	potential immune mediated disorders
PPI	Patient and public involvement
RCT	Randomised controlled trial
REC	Research ethics committee
RSI	Reference safety information
RZV	Recombinant Herpes Zoster vaccine
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SSAR	Suspected serious adverse reaction (SSAR) is any serious adverse event that is suspected to be related to the drug or drugs being taken.
SARS-CoV-2	Severe acute respiratory syndrome due to coronavirus
SSR	Solicited systemic adverse reactions
SST	Serum Separator Tube
SOP	Standard operating procedure
SMPC	Summary of Medicinal Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction - an untoward medical occurrence suspected to be related to a medicinal product that is not consistent with the applicable product information and is serious.
TMF	Trial master file
TMG	Trial management group
TSC	Trial steering committee
VRR	Vaccine response rate
UHBW	University Hospitals Bristol and Weston NHS Foundation Trust
UKCRC	UK Clinical Research Collaboration
WHO	World Health Organisation

1. Trial Synopsis

Herpes zoster (HZ) is a vaccine preventable infection with an associated mortality of up to 7%.[1] In the UK vaccination against HZ is recommended for adults on their 70th birthday.[2] Uptake of HZ vaccine (HZV) is suboptimal therefore strategies to improve uptake are needed. Routine reporting of HZV uptake suggests that uptake is greater during influenza vaccination season.[3] It is assumed that increased uptake at this time is due to opportunistic vaccination with HZV when patients attend for influenza vaccination. A recombinant herpes zoster vaccine with adjuvant (RZV) has been recommended in the UK since 2021.Up until May 2023 concomitant administration of RZV with either adjuvanted flu vaccine or COVID-19 vaccine (C-19) was not recommended due to concern about misattribution of side-effects and limited experience with COVID-19 vaccines. The policy was updated in May 2023 to allow co-administration of COVID-19 vaccines with any vaccine. This was based on recent evidence supporting the acceptable safety profile of a COVID-19 vaccine with RZV and to improve timely protection and uptake.[4]There is still a need however for safety data with co-administration of second dose of RZV as the adverse event profile differs between the doses and there is a lack of published data on the safety and immunogenicity of RZV and adjuvanted flu vaccine.

Figure 1 shows trial schema.

Table 1 Trial synopsis

Trial title	A phase IV, multi-centre, randomised controlled trial to assess immunogenicity and safety of COVID-19 and seasonal influenza vaccine given to healthy adults or those with underlying medical conditions when co-administered with a recombinant herpes zoster vaccine with adjuvant
Internal ref (or short title)	ZosterFluCov

Trial registration	ISRCTN26495549
Sponsor	University Hospitals Bristol and Weston NHS Foundation Trust Research & Innovation Department Level 3, Education Centre Upper Maudlin Street Bristol BS2 8AE
Funder	GSK
Clinical Phase	Phase IV
Trial Design	Randomised, controlled, vaccine co-administration study with blinding
Trial Participants	Adults aged 50 and above with or without stable co-morbidities
Sample Size	A total of 960 participants, consisting of two serology sub-cohorts (COVID-19, n=360; influenza, n=720); cell-mediated immunity (CMI) cohort CD4+ T cells (n=150) and exploratory immunology cohort (n=150). Participants will be randomised in a 1:1:2:2:2 ratio to one of five groups; 120 participants to groups 1 and 2, and 240 participants to groups 3-5. Only 120 participants in group 3 will progress to the second and third vaccination time points required to assess C19/RZV co-administration. • All five groups will receive two doses of RZV (except participants in group 3 who do not progress after the first vaccination timepoint and will not have any RZV doses as part of the trial) • At the first and second vaccination timepoints, participants will receive two injections (combinations of RZV, C19, aQIV or placebo)

	• At the final vaccination visit participants will receive one injection (either second RZV, if in the vaccination season aQIV or C19 or placebo)
Planned trial period	5 months per participant (following from the first study vaccination) 6 months for recruitment (following from first participant recruited) 28 months including trial set up and close down

	Objectives	Outcome Measures	Timepoint(s)
Co-primary immunogenicity outcomes	Immunogenicity, measured by S-binding total Ig, 1 month after C19 vaccine given alone compared to co-administration with RZV (first or second dose)	Anti-spike total Ig	Days 0, 28, 56 & 84 Groups 1-3
	Immunogenicity, measured by haemagglutination inhibition assay (HAI), 1 month after aQIV for 3 of the strains included in the vaccine; HAI influenza A H3N2, HAI influenza A H1N1 and HAI influenza B	HAI	Days 0, 28, 56 & 84 Groups 3-5

	Victoria given alone compared to co-administration with RZV		
	Immunogenicity of 2 doses RZV vaccine, 1 month after the second dose, given alone, compared to co-administration with C19 or aQIV with either first or second dose of RZV	Anti-gE Ig	Days 0, 56, 84, & 140 Groups 1-5
Co-primary safety outcomes	Rate of grade 3 and 4 solicited systemic adverse reactions (SSR) over 7 days after 1st and 2nd doses of RZV given alone compared to co-administration with C19	Rate of fatigue Fever Gastrointestinal (GI) symptoms† Headache Myalgia Shivering	Days 0, 56, 112 Groups 1-5

	Rate of grade 3 and 4, solicited systemic adverse reactions over 7 days after 1st and 2nd doses of RZV given alone compared to co-administration with aQIV	Rate of fatigue Fever GI symptoms† Headache Myalgia Shivering	Days 0, 56, 112 Groups 1-5
Secondary outcomes	Cell-mediated responses to 2 doses of RZV, 1 month after the second dose, given alone compared to co-administration with C19 with first or second dose of RZV	gE specific T-cells measured by intracellular cytokine staining	Days 0, 56, 84, & 140 Groups 1-5
	Exploratory evaluation of CD4+ T-cells against COVID-19 after vaccination with RZV or aQIV	T-cell Elispot	Day 0 and 28 Groups 1 -3
	N- protein immunoglobulin, before and 1 month after first vaccination in the	N-protein Ig	Day 0, 28 Groups 1-3

	(exploratory immunology cohort)		
	Grade 3 and 4 SSR after 1st RZV dose in group 1 (day 56), group 2 and 5 (day 0) compared to grade 3 and 4 SSR after 1st dose of RZV with C19 in group 3 (day 56)	Rate of fatigue Fever GI symptoms† Headache Myalgia Shivering	Day 0 and 56 Groups 1, 2, 3 and 5
	Grade 3 and 4 SSR after 2nd dose of RZV in group 1 and 3 (day 112) and group 4 (day 56) compared to grade 3 and 4 SSR after 2nd dose RZV with C19 in group 2 (day 56)	Rate of fatigue Fever GI symptoms† Headache Myalgia Shivering	Day 56 and 112 Groups 1-4
	Grade 3 and 4 SSR after 1st dose RZV in group 1 (day 56) group 2 and 5 (day 0) compared to grade 3 and 4 SSR after 1st dose of RZV with aQIV in group 4 (day 0)	Rate of fatigue Fever GI symptoms† Headache Myalgia Shivering	Days 0 and 56 Groups 1,2,4 and 5
	Grade 3 and 4 SSR after 2nd dose of RZV in group 1	Rate of fatigue Fever	Days 0, 56 and 112 Groups 1, 3 ,4 and 5

	(day 112), group 3 (day 112) and group 4 (day 56) compared to grade 3 and 4 SSR after 2nd dose RZV with aQIV in group 5	GI symptoms† Headache Myalgia Shivering	
	SSR events over 7 days after 1st and 2nd doses of RZV given alone compared to co-administration with either C19 or aQIV	Rate of fatigue Fever GI symptoms† Headache Myalgia Shivering	Days 0, 56 & 112 Groups 1-5
	SSR events over 7 days after 1st RZV dose in group 1 (day 56), group 2 and 5 (day 0) compared to SSR events over 7 days after 1st dose of RZV with C19 in group 3 (day 56)		
	SSR events over 7 days after 2nd dose of RZV in group 1 and 3 (day 112) and group 4 (day 56) compared to SSR events over 7 days after 2nd dose		

	RZV with C19 in group 2 (day 56)		
	SSR events over 7 days after 1st dose RZV in group 1 (day 56), group 2 and 5 (day 0) compared to SSR events over 7 days after 1st dose of RZV with aQIV in group 4 (day 0)		
	SSR events over 7 days after 2nd dose of RZV in group 1 (day 112), group 3 (day 112) and group 4 (day 56) compared to SSR events over 7 days after 2nd dose RZV with aQIV in group 5		
	Solicited local adverse reactions over 7 days after 1st or 2nd doses of RZV given alone compared to	Frequency and rate of injection site redness, swelling and pain	Days 0, 56 & 112 Groups 1-5

	co-administration with either C19 or aQIV		
	Days off work (for participants in employment) due to vaccine related AEs associated with different schedules under study over a period of 140 days (until study end)	Days missed	Days 0, 56 & 112 Groups 1-5
	Quality of life score over the 7 days after 1st and 2nd doses of RZV given alone compared to co-administration with either C19 or aQIV	EuroQol-5D	Days 0 and 7 days after each vaccination Groups 1-5
	AEs up to 30 days after 1st and 2nd doses of RZV given alone compared to co-administration with either Bivalent vaccine or aQIV	Frequency and rate of unsolicited AEs	Days 0, 56 & 112 Groups 1-5
	Serious adverse events and AEs of special interest Potential Immune-	Frequency and rate of serious AEs and pIMDs.	All timepoints

	Mediated Diseases (pIMDs) from after 1st vaccination until end of study		
	Describe participant and study staff attitudes to vaccine co-administration	Semi-structured interviews	Day 112 to 140

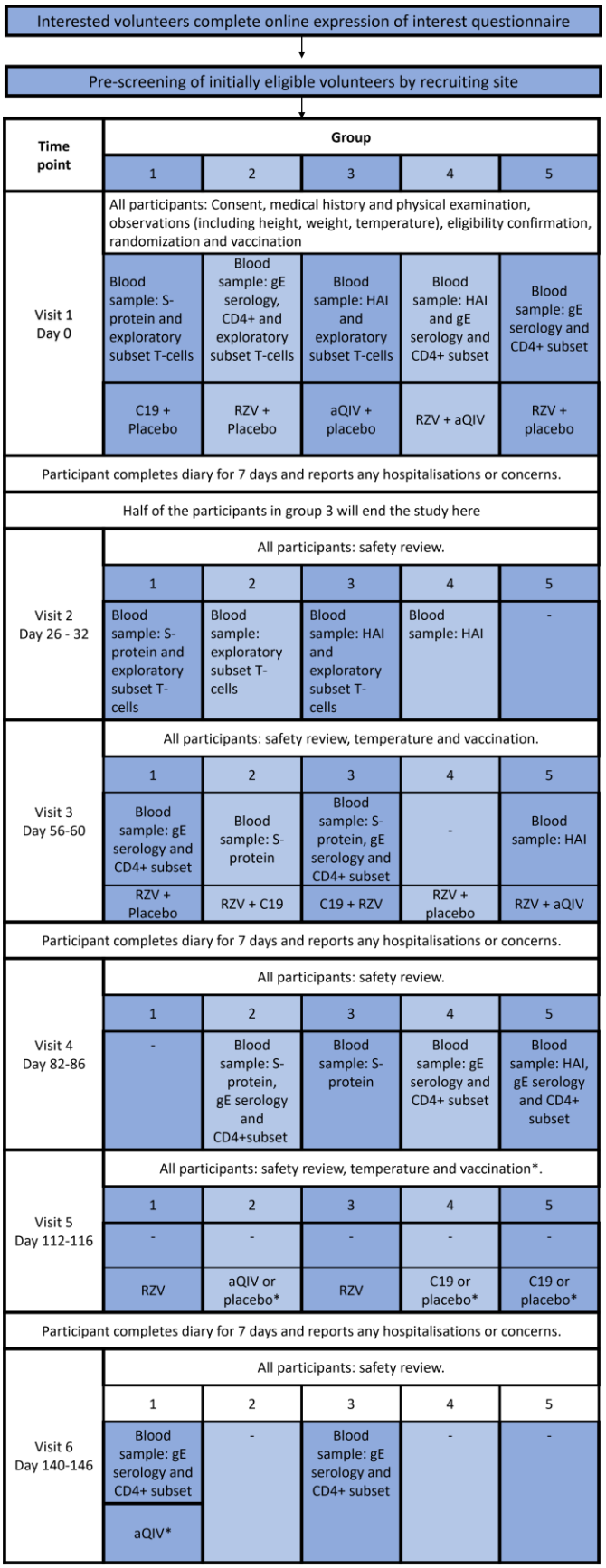
Intervention(s)	IMP	Dose	Route of administration
	Shingrix® (GSK) Recombinant subunit herpes zoster vaccine containing $AS01_B$ (RZV)	0.5ml	Intramuscular
	Comirnaty® Original/Omicron BA.4-5 (15/15 micrograms)/ dose dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified)	0.3ml	Intramuscular
	Adjuvanted Quadrivalent Influenza Vaccine (Surface Antigen, Inactivated) Sequris suspension for injection in pre-filled	0.5ml	Intramuscular

	syringe Influenza vaccine, Adjuvanted with MF59C (aQIV)		

[†]GI symptoms include nausea, vomiting, diarrhoea and/or abdominal pai

1.1 Trial schema

Figure 1 Trial schema


Interested volunteers complete online expression of interest questionnaire
Pre-screening of initially eligible volunteers by recruiting site
Time point
Group
1
2
3
4
5
Visit 1 Day 0
All participants: Consent, medical history and physical examination, observations (including height, weight, temperature), eligibility confirmation, randomization and vaccination
Blood sample: S-protein and exploratory subset T-cells
Blood sample: gE serology, CD4+ and exploratory subset T-cells
Blood sample: HAI and exploratory subset T-cells
Blood sample: HAI and gE serology and CD4+ subset
Blood sample: gE serology and CD4+ subset
C19 + Placebo
RZV + Placebo
aQIV + placebo
RZV + aQIV
RZV + placebo
Participant completes diary for 7 days and reports any hospitalisations or concerns.
Half of the participants in group 3 will end the study here
Visit 2 Day 26 - 32
All participants: safety review.
1
2
3
4
5
Blood sample: S-protein and exploratory subset T-cells
Blood sample: exploratory subset T-cells
Blood sample: HAI and exploratory subset T-cells
Blood sample: HAI
-
Visit 3 Day 56-60
All participants: safety review, temperature and vaccination.
1
2
3
4
5
Blood sample: gE serology and CD4+ subset
Blood sample: S-protein
Blood sample: S-protein, gE serology and CD4+ subset
-
Blood sample: HAI
RZV + Placebo
RZV + C19
C19 + RZV
RZV + placebo
RZV + aQIV
Participant completes diary for 7 days and reports any hospitalisations or concerns.
Visit 4 Day 82-86
All participants: safety review.
1
2
3
4
5
-
Blood sample: S-protein, gE serology and CD4+subset
Blood sample: S-protein
Blood sample: gE serology and CD4+ subset
Blood sample: HAI, gE serology and CD4+ subset
Visit 5 Day 112-116
All participants: safety review, temperature and vaccination*.
1
2
3
4
5
-
-
-
-
-
RZV
aQIV or placebo*
RZV
C19 or placebo*
C19 or placebo*
Participant completes diary for 7 days and reports any hospitalisations or concerns.
Visit 6 Day 140-146
All participants: safety review.
1
2
3
4
5
Blood sample: gE serology and CD4+ subset
-
Blood sample: gE serology and CD4+ subset
-
-
aQIV*

*these vaccinations will be given if the visit is taking place during the winter vaccination season, if not, a placebo injection will be given instead for visit 5.

2. Background & Rationale

Routine immunisation with herpes zoster vaccine (HZV) is recommended in the UK for adults on their 70th year.[2] HZV uptake is highest during influenza season. This higher uptake is thought to be due to opportunistic co-administration of HZV and influenza vaccine. HZV coverage ranges from 48.2% to 76.7% with the lowest coverage associated with the birth cohort who turned 70 in the 2020/21 season.[3] The lower coverage is due to displacement of HZV vaccination by COVID-19-related disruption to health systems and vaccine rollout. Co-administration of HZV alongside COVID-19 vaccination may help prevent such displacement in the future. Up until May 2023 concomitant administration of RZV with either adjuvanted or COVID-19 vaccine (C19) was not recommended due to concern about misattribution of side-effects and limited experience with COVID-19 vaccines. The policy was updated in May 2023 to allow co-administration of COVID-19 vaccines with any vaccine. This was based on recent evidence supporting the acceptable safety profile of a COVID-19 vaccine with RZV and to improve timely protection and uptake.[4]There is still a need however for safety data with co-administration of second dose of RZV as the adverse event profile differs between the doses and there is a lack of published data on the safety and immunogenicity of RZV and adjuvanted flu vaccine.

If, as anticipated, the COVID-19 vaccination becomes a routine vaccination, alongside influenza, then strategies to ensure uptake of other adult vaccines such as RZV, are needed. Vaccine co-administration is commonplace in the childhood immunisation programme and facilitates the uptake of vaccine. A similar strategy for adult vaccines could support vaccine uptake, however a better understanding of the impact and attitudes of multiple vaccination for both providers and those offered vaccine is needed to optimise this strategy.

In addition to the benefits that co-administration may provide for vaccine delivery, there may also be clinical benefits. Recent data suggest that both aQIV and RZV may reduce the incidence of severe COVID-19 disease. The mechanisms underlying potential cross-protection or vaccine synergy are unknown and comparative measurements of immune responses when these vaccines are given together and at separate times may help inform the design of vaccine delivery programmes and formulations.[5,6]

Here we propose to evaluate the immunogenicity and safety of RZV co-administered with an mRNA COVID-19 vaccine or an adjuvanted influenza vaccine and describe immunological mechanisms underlying potential vaccine synergy and cross-protection and describe attitudes to co-administration.

3. Aims and objectives

The ZosterFluCov trial aims to evaluate whether RZV can be co-administered with an mRNA COVID-19 (C19) vaccine or an adjuvanted influenza vaccine (aQIV) without an unacceptable increase in reactogenicity or decrease in the immunogenicity of the COVID-19, influenza or RZ vaccines.

Co-Primary Objectives

Part A: Assessment of co-administration of COVID-19 and RZV

1. Immunogenicity, measured by S-binding total Ig, 1 month after COVID-19 mRNA reinforcing dose (Bivalent) vaccine for both strains included in the vaccine given alone compared to co-administration with RZV (1st or 2nd dose).

2. Immunogenicity of 2 doses of RZV vaccine, 1 month after the second dose, given alone, compared to co-administration with C19 with either 1st or 2nd dose of RZV.
3. Rate of grade 3 and 4 solicited systemic adverse reactions over 7 days after 1st and 2nd doses of RZV given alone compared to co-administration with Bivalent vaccine.

Part B: Assessment of co-administration of adjuvanted influenza vaccine and RZV

1. Immunogenicity, measured by haemagglutination inhibition assay, 1 month after adjuvanted influenza vaccine (aQIV) for 3 of the strains included in the vaccine; HAI influenza A H3N2, HAI influenza A H1N1 and HAI influenza B Victoria given alone compared to co-administration with RZV.
2. Immunogenicity of 2 doses of RZV vaccine when given alone, 1 month after the second dose compared to co-administration with aQIV with either 1st or 2nd dose of RZV.
3. Rate of grade 3 and 4 solicited systemic adverse reactions over 7 days after 1st and 2nd doses of RZV given alone compared to co-administration with aQIV.

Key Secondary Objectives

1. Cell-mediated responses to 2 doses of RZV, 1 month after the 2nd dose, given alone compared to co-administration with C19 vaccine with 1st or 2nd dose of RZV.
2. Exploratory evaluation of CD4+T-cells against COVID-19 after vaccination with RZV or aQIV in the CMI cohort.
3. S and N- protein immunoglobulin, before and 1 month after first vaccination in the exploratory immunology cohort.

4. Solicited systemic AEs over 7 days after 1st and 2nd doses of RZV given alone compared to co-administration with either C19 vaccine or aQIV.
5. Solicited local adverse reactions over 7 days after 1st and 2nd doses of RZV given alone compared to co-administration with either C19 vaccine or aQIV.
6. Solicited systemic AEs over 7 days after 1st doses of RZV given alone compared to co-administration with either C19 vaccine or aQIV.
7. Solicited systemic AEs over 7 days after 2nd doses of RZV given alone compared to co-administration with either C19 vaccine or aQIV.
8. Grade 3 and 4 SSR after 1st RZV dose in group 1 (day 56), 2 and 5 (day 0) compared to grade 3 and 4 SSR after 1st dose of RZV with C19 vaccine in group 3 (day 56)
9. Grade 3 and 4 SSR after 2nd dose of RZV in group 1, 3 (day 112) and 4 (day 56) compared to grade 3 and 4 SSR after 2nd dose RZV with C19 vaccine in group 2 (day 56).
10. Grade 3 and 4 SSR after 1st dose RZV in group 1 (day 56), 2 and 5 (day 0) compared to grade 3 and 4 SSR after 1st dose of RZV with aQIV in group 4 (day 0).
11. Grade 3 and 4 SSR after 2nd dose of RZV in group 1, 3 (day 112) and 4 (day 56) compared to grade 3 and 4 SSR after 2nd dose RZV with aQIV in group 5.
12. Days off work (for participants in employment) due to vaccine related AEs associated with different schedules under study over a period of 140 days .
13. Quality of life score over the 7 days after 1st and 2nd doses of RZV given alone compared to co-administration with either BNT162b vaccine or aQIV.
14. Unsolicited AEs up to 30 days after 1st and 2nd doses of RZV given alone compared to co-administration with either C19 vaccine or aQIV.
15. Serious adverse events and AEs of special interest including potential immune mediated disorders (pIMD) from after first vaccination until the study end.

16. Describe participant and study nurse attitudes to vaccine co-administration.

4. Primary and secondary outcomes

4.1 Primary outcome

Part A: Assessment of co-administration of COVID-19 and RZV

Co-Primary Endpoints

1) Immunogenicity of C19

Anti-S protein Ig concentrations expressed as Geometric Mean Concentrations (GMCs) for both strains in C19 vaccine/RZV (first or second dose, groups 2 & 3) and C19 vaccine alone (group 1), will be used to calculate between group ratios expressed a geometric mean ratio (GMR), at 1 month after vaccination with C19 vaccine.

2) Immunogenicity of RZV

Anti-gE Ig concentrations expressed as GMCs after co-administration of C19 vaccine/RZV (first or second dose) and RZV alone, 1 month after 2nd dose of RZV, and between-group ratios expressed as GMRs.

Success criteria:

Part A of the trial will be classified as a success if both of the following meet the success criteria:

1) The combined administration of C19 vaccine and RZV (first or second dose) will be considered non-inferior to C19 vaccine alone if the lower limit of the 95% confidence interval for the (GMR) of anti-S protein Ig concentrations exceeds 0.67, the standard WHO non-inferiority margin for recommendation of new vaccines.[7], AND

2) The combined administration of C19 vaccine and RZV (first or second dose) will be considered non-inferior to RZV alone if the lower limit of the 95% confidence interval for the GMR of Anti-gE Ig concentrations exceeds 0.67.

3) Safety of RZV

The rate of grade 3 and 4 solicited systemic adverse reactions (Table 2) after C19 vaccine/RZV (first or second dose, groups 2 and 3) and RZV alone 7 days after vaccination (groups 1-5) This is a descriptive outcome.

Table 2 Solicited AEs collected on post vaccination diary cards

Systemic solicited AEs
Fatigue
Fever
GI symptoms†
Headache
Myalgia
Shivering

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain

Note: The above AEs are assumed to be related and will be classed as adverse reactions.

Part B: Assessment of co-administration of adjuvanted influenza vaccine and RZV

Co-Primary Endpoints

1) Immunogenicity of aQIV

HAI titres expressed as GMCs in aQIV/RZV (first or second dose, groups 4 & 5) and aQIV alone (group 3) will be used to calculate between group ratios, expressed as GMR at one month after aQIV vaccination.

2) Immunogenicity of RZV

Anti-gE Ig concentrations expressed as GMCs after co-administration of aQIV/RZV (first or second dose) and RZV alone, 1 month after 2nd dose of RZV, and between-group ratios expressed as GMRs.

Success criteria:

Part B of the trial will be classified as a success if both of the following meet the success criteria:

1) The combined administration of aQIV and RZV (first or second dose) will be considered non-inferior to aQIV (for 3 of the strains included in the vaccine; HAI influenza A H3N2, HAI influenza A H1N1 and HAI influenza B Victoria) alone if the lower limit of the 95% confidence interval for the GMR of HAI exceeds 0.67, the standard WHO non-inferiority margin for recommendation of new vaccines.[7], AND
2) The combined administration of aQIV and RZV (first or second dose) will be considered non-inferior to RZV alone if the lower limit of the 95% confidence interval for the GMR of Anti-gE Ig concentrations exceeds 0.67.

3) Safety of RZV

The rate of grade 3 and 4 solicited systemic adverse reactions (Table 2) after aQIV/RZV (first or second dose, groups 4 and 5) and RZV alone 7 days after vaccination (groups 1-5). This is a descriptive outcome.

4.2 Secondary outcomes

Immunological

- Vaccine response rate (VRR) to RZV as measured by anti-gE, 1 month after vaccination with 2nd dose of RZV, in all groups and between-group differences. VRR defined as a 4-fold increase in post-vaccination anti-gE compared to pre-vaccination anti-gE

concentration for participants who are seronegative at baseline then a 4-fold increase compared to a cut-off value for seropositivity.

- Exploratory evaluation of cell-mediated immunology, CD4+T-cells responses 1 month after the 2nd dose of RZV as measured by intracellular cytokine staining (ICS) compared to RZV given alone or concomitantly for either first or second dose
- S and N-protein immunoglobulin, before and 1 month after vaccination with a single dose of RZV and aQIV to assess for exploratory immunology T-cells against SARS-CoV-2 provided by RZV vaccine or aQIV

Safety

- Percentage of participants reporting grade 3 and 4 SSR after first dose of RZV alone compared to first dose co-administered with either C19 vaccine or aQIV.
- Percentage of participants reporting grade 3 and 4 SSR after second dose of RZV alone compared to second dose co-administered wither either C19 vaccine
- Percentage of participants reporting solicited local and systemic Aes, 7 days after each vaccination time point by group and between-group ratios
- Unsolicited Aes for 30 days after vaccination
- Serious adverse events throughout the study period
- Adverse events of special interest (pIMDs) throughout the study period
- Days off work (for participants in employment) during the study period reported as related to vaccination
- Quality of life score following vaccine co-administration compared to single vaccination in the 7 days after vaccination

Qualitative

Outcomes will include but not be limited to

- Participant acceptance of multiple vaccinations (2 or more) for future routine vaccinations
- Trial staff perceptions on offering multiple vaccinations (2 or more) for future routine vaccinations

5. Plan of Investigation

5.1 Trial design

The ZosterFluCov trial is a multicentre, parallel-group placebo-controlled RCT in which participants, laboratory staff analysing samples, and clinicians assessing causality will be blinded to the treatment.

5.2 Key design features to minimise bias

Selection/allocation bias will be prevented by concealed randomisation. The allocation will not be revealed until sufficient information to uniquely identify the participant has been entered into the allocation database.

Performance and detection bias will be minimised by blinding participants and clinicians assessing causality to the vaccine received. Laboratory staff analysing samples will be blinded. Laboratory staff who are processing samples only do not need to blinded. We will also define procedures for follow-up and monitor adherence to the protocol. The participant information leaflet (PIL) and the process of obtaining informed consent will describe the uncertainty about the effects of giving the two vaccines together compared to separately. Therefore, in the event

of inadvertent unblinding of a participant, he or she should not have a strong expectation that one should be better than the other.

Attrition bias will be minimised by using established methods developed in the Coordinating Centre to maximise the quality and completeness of the data (e.g., regular monitoring of data, querying of data in the trial database). Instances of non-adherence will be fully documented and reviewed at trial meetings and an action plan for maximising compliance drawn up as appropriate. Data will be analysed by intention to treat (i.e., according to the treatment allocation, irrespective of future management and events), and every effort will be made to include all randomised patients.

Reporting bias will be minimised by pre-specifying trial outcomes and following a detailed analysis plan which will be prepared in advance of any comparative analyses of the trial data.

5.3 Setting

Participating clinical trial sites that include NHS hospitals and primary care sites.

5.4 Trial population

Healthy adults aged 50 and over or those with established medical co-morbidities with stable symptoms on the day of randomisation and without prior history of shingles vaccination in the last 5 years. Prespecified maximum recruitment limits will be set for the following age groups; 69 and under and 70 and over to ensure that we have adequate representation of older adults for whom HZV is currently recommended. Recruitment of those from the global majority (Black, Asian and non-Caucasian groups) is particularly encouraged. Both men and women will be encouraged to participate.

5.4.1 Inclusion criteria

1. Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol.
2. Written informed consent obtained from the participant prior to any study-specific procedure.
3. Adults aged 50 and over at the time of randomisation.
4. Participants must have documented history (e.g. NHS app, GP record) of receiving their initial course (usually two doses) of any type of COVID-19 vaccination, irrespective of the type of COVID-19 vaccine received.
5. Female participants of childbearing potential must be willing to ensure that they or their partner use effective contraception from 1 month prior to first vaccination continuously until 3 months after final vaccination*.

** A woman of childbearing potential is defined as a pre-menopausal female who is capable of becoming pregnant. Menopause can be diagnosed in a woman aged over 50 after one year of amenorrhoea (this applies only if the woman is not using hormonal contraception). Acceptable forms of contraception for volunteers of female sex include:*

- *Established use of oral, injected or implanted hormonal methods of contraception*
- *Placement of an intrauterine device (IUD) or intrauterine system (IUS)*
- *Total hysterectomy*
- *Bilateral Tubal Occlusion*
- *Barrier methods of contraception (condom or occlusive cap with spermicide)*
- *Male sterilisation, if the vasectomised partner is the sole partner for the subject*
- *True abstinence, when this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence and withdrawal are not acceptable methods of contraception)*

5.4.2 Exclusion criteria

1. Any clinical condition that in the opinion of the investigator might pose additional risk to the participant due to participation in the study.
2. History of reaction or hypersensitivity likely to be exacerbated by any component of the study intervention including allergic reaction to any component of any of the study vaccines, known reactions related to study vaccines e.g. history of myocarditis, Guillain-Barre Syndrome.
3. Unstable medical condition on the day of enrolment as determined by clinical history and examination.
4. Bleeding disorders or continuous use of anticoagulation medicine, such as coumarins and related anticoagulants (i.e., warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban). Use of aspirin is allowed.
5. Any confirmed or suspected immunosuppressive, or immunodeficient condition, based on medical history and physical examination. People living with HIV that is well controlled can be included in the study.* Those with a new diagnosis or an AIDs defining illness in the past 12 months cannot be included.
6. Use of immunosuppressive medication, ongoing, long term or planned, defined as more than 14 days in total of immunosuppressant treatments. For corticosteroids this will mean more than 14 days of prednisolone >20mg/day or equivalent. Use of inhaled, intra-articular and topical steroids is allowed.
7. Use or planned use of long-acting immune modifying drugs in the 12-month period before randomisation (e.g. infliximab).
8. COVID-19 or influenza vaccination 90 days prior to the study vaccination
9. Previous vaccination with a live herpes zoster vaccine within the past 5 years.

10. Administration of monoclonal antibodies (including those targeting SARS CoV2), immunoglobulins and/or blood products during the 3 months before the first dose of the study vaccines, up to 1 month after the last dose or planned during the study period.
11. Planning to or concurrently participating in another interventional clinical study.
12. Pregnancy, lactation or willingness/intention to become pregnant within the study period.

**Defined as less than 50 copies/ml (convert as needed from IU/ml) on the last two occasions >3 months apart, and a CD4 over 500 when last checked.*

5.5 Randomisation

Participants will be randomised in a 1:1:2:2:2 ratio to one of five vaccine groups (Table 3). Randomisation will be performed after informed consent has been documented and eligibility confirmed by the Principal Investigator (PI) or a delegated medically qualified doctor. Randomisation will be performed using a secure internet-based randomisation system ensuring allocation concealment by a member of the local research team. Masking of group allocation will be applied to participants, clinicians making safety assessments and laboratory staff analysing samples. Staff administering vaccines, collecting blood samples, and performing subsequent study visits will be aware of what they are giving but not involved in subsequent observations or interactions with study subjects.

Table 3 Vaccine groups

Groups	**D0**	**D56**	**D112**
1 **	C19/P	RZV/P	RZV
2	RZV/P	RZV/C19	aQIV or P*
3	aQIV/P	C19/RZV	RZV
4	RZV/aQIV	RZV/P	C19 or P*
5	RZV/P	RZV/aQIV	C19 or P*

P: placebo

**if in winter vaccination season aQIV/ C19 will be given*
***Group 1 will receive aQIV at visit 6 if in winter vaccination season (day 140)*

The allocation will be computer-generated, and randomisation will be stratified by age (50 to 64 years, 65 to 70 years, 71 to 74 years, and 75 years and over) and centre to ensure distribution of age groups between the vaccine groups, by an independent BTC statistician, not involved in the trial, before recruitment begins.

All injections will be administered intramuscularly. When a vaccine is given alongside placebo, the vaccine will be administered in the non-dominant arm. When vaccines are co-administered RZV will be administered into the non-dominant arm and C19 vaccine or aQIV in the dominant arm.

5.6 Blinding

Participants, laboratory staff analysing samples and clinicians assessing causality of AEs will not be informed of the treatment allocation. Staff involved in delivery of the trial treatment and collecting blood samples will be aware of which vaccines/injections a participant is receiving.

Vaccines will be prepared out of sight of the participant and the blind will be maintained by either i) asking participants to look away, ii) masking the syringe with tape and iii) using syringes that as similar as possible. The success of blinding will be assessed using the Bang Blinding Index.

5.7 Unblinding

Requests to unblind on clinical grounds are not anticipated. However, if unblinding is requested on safety grounds (e.g., a participant may be unblinded if they experience anaphylaxis), this will be facilitated by contacting the coordinating centre (during normal office hours) or UHBW

pharmacy (outside normal office hours). Any such request will be fully documented including who requested the unblinding and the reason for unblinding. Unblinding will only be permitted if it is required for clinical management. Details of the trial treatment received will be sent to the attending physician.

If a suspected unexpected serious adverse reaction (SUSAR) is reported, the Sponsor will receive an unblinded report from the BTC for further reporting purposes as required by the MHRA. The CI, local PI and blinded clinicians will not be unblinded unless it is indicated on safety grounds.

Unblinding rates will be monitored throughout the trial by the trial team and by the independent Data Monitoring and Safety Committee (DMSC) established to oversee participant safety in the trial (see Section 13 for further details).

Participants will be made aware before entering the trial that they will not be told which treatment they will receive until after the trial has completed.

5.8 Research procedures: participants

Participants will be required to do, or undergo, the following tasks or investigations specifically for the trial which are also outlined in schedule of events (Table 4).

Table 4 Schedule of events

Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
Timing (days)	D0	D28	D56	D84	D112	D140
Window periods (days)	-	D26-32	D56-60	D82-86	D112-116	D140-146
Eligibility	x					
Urine sample*	x		x		x	

Randomisation	x					
Vaccinations	x		x		X	X**
Bloods (serum) (COVID-19 subset)	x	x	x	x		
Bloods (serum) (Influenza subset)	x	x	x	x		
Bloods (serum) Anti-gE Ig	x		x	x		x
Blood (whole) RZV Cell-mediated immunology (CMI)	x		x	x		x
Blood (whole) exploratory immunity	x	x				
+Diary Card training	x					
Diary Card review	→					
Safety Review	→					
Quality of life survey	X		X***		X***	
Missed workdays			x		x	

** Urinary pregnancy testing for female participants of child-bearing potential only** Group 1 will receive the flu vaccine at visit 6 if in the winter vaccination season.*

****Quality of life survey completed 7 days after vaccination*

Volunteers interested in participating will be asked to complete an 'expression of interest/initial screening' questionnaire available via a public website. See section 12.3 for details of how the public will be made aware of the trial.

The 'expression of interest/initial screening' questionnaire will assess whether the volunteer meets the key inclusion criteria for participation (e.g. age, received their initial course (usually two doses) of COVID-19 vaccinations). If these criteria are met, they will be asked to indicate their electronic consent to proceed to more detailed screening, and for the research team to contact their GP for further clarification of medical history (if required) and confirmation of vaccination record.

5.8.1 Detailed pre-screening

This second stage includes the following elements:

- Reporting their medical history
- Review of medical history (if required, depending on responses, may be completed remotely)

Volunteers without a past medical history or drug history requiring review will proceed to a full eligibility check (section 5.8.2) once their vaccination status has been confirmed.

Volunteers will be contacted by delegated members of the research team who will obtain medical information and check medical records if needs be to confirm provisional eligibility. The volunteer will be asked to contact the trial team if there are significant changes to their health status between pre-screening and their first trial visit (if this takes place on different days).

5.8.2 Visit 1: Recruitment and administration of trial vaccine

Once confirmed as potentially eligible volunteers will be asked to:

- Confirm they understand the contents of the ZosterFluCov trial PIL (this will be available via the pre-screening website)
- Discuss the trial with a member of the research team

Provide informed consent to participate, to the PI or an appropriately trained and delegated member of the study team, if willing to do so

If consent is given the participant will undergo the following:

- Medical history review
- History directed physical examination as required
- Eligibility confirmation by PI or medically qualified doctor
- Measurement of temperature, height and weight
- Complete Quality of Life questionnaire

Following consent and collection of baseline data, the participant will be randomised. The participant will then provide a blood sample for assessment of RZV, COVID-19 and influenza vaccine immunogenicity (immunogenicity and exploratory/CMI subsets*). Then, the trial vaccines will be administered. The participant will remain at the trial site for observation for at least 15 minutes following the vaccination, in case of immediate AEs.

In group 3 only 129 participants will progress to the second and third vaccination time points required to assess C19/RZV co-administration.

5.8.3 Between visit 1 and visit 2

In the period following the first visit and the second visit approximately 4 weeks later participants will be required to:

- Complete an electronic diary card for the first 7 days. This diary card will be used to capture:
    - AEs, including their timing and severity
- Report any hospitalisation as soon as is practically possible using the emergency 24-hour telephone number provided
- Report any other urgent medical concerns using the trial centre emergency procedures

- Report any unsolicited adverse events on the electronic diary card between day 8 and day 30 after vaccination
- Complete Quality of Life questionnaire 7 days after vaccination

Diary cards will be reviewed by the local research team daily for 7 days after visit 1 and as required thereafter, and participants may be telephoned by the local research team if any entries are missed and the PI or delegated clinician if there are any concerns about reported symptoms. Participants will be provided with a ruler and thermometer to aid their reporting of AEs. Participants who do not have access to an internet connected device, will have the option to complete a paper diary. Participants will be encouraged to report any symptoms to the local research team and will be contacted by the local research team between day 4-7 to review their diary entries.

5.8.4 Visit 2: Safety review and blood sampling

At this visit, approximately 4 weeks after visit 1, participants will undergo the following:

- Safety review to assess for any serious adverse events
- Review and reconciliation of diary card data submitted
- Assessment for local and systemic adverse reactions and events and medical history since visit 1
- Provide blood sample for assessment of COVID-19, influenza vaccine immunogenicity
- Provide blood sample for exploratory immunology analysis*
- Participants in group 3 who will not be invited to continue the study will be informed and permission sought to follow up to resolution any clinically significant adverse events after the end of trial participation

5.8.5 Between visit 2 and visit 3

In the period between the second visit and the third visit approximately 4 weeks later participants will be required to:.

- Report any hospitalisation as soon as is practically possible using the emergency 24-hour telephone number provided
- Report any other urgent medical concerns using the trial centre emergency procedures
- Report any unsolicited adverse events on the electronic diary card

5.8.6 Visit 3 Safety review, blood sampling and administration of trial vaccine

- Safety review to assess for any serious adverse events
- Confirm fitness to continue in study
- Provide blood sample for assessment of RZV, COVID-19, influenza vaccine immunogenicity
- Provide blood sample for assessment of RZV immunogenicity and cell-mediated immunity against RZV in CMI subset*
- Measurement of temperature
- Receive trial vaccines as per randomisation allocation

5.8.7 Between visit 3 and visit 4

- Complete an electronic diary card for the first 7 days. This diary card will be used to capture:

    - AEs, including their timing and severity
- Report any hospitalisation as soon as is practically possible using the emergency 24-hour telephone number provided
- Report any other urgent medical concerns using the trial centre emergency procedures
- Report any unsolicited adverse events on the electronic diary card between day 8 and day 30 after vaccination
- Complete Quality of Life questionnaire 7 days after vaccination

5.8.8 Visit 4

At this visit, approximately 4 weeks after visit 3, participants will undergo the following:

- Safety review to assess for any serious adverse events
- Review and reconciliation of diary card data submitted
- Assessment for local and systemic adverse reactions and events and medical history since visit 3
- Provide blood sample for assessment of RZV, COVID-19 and influenza vaccine immunogenicity
- Provide blood sample for assessment of cell-mediated immunity against RZV in CMI subset*

5.8.9 Between visit 4 and visit 5

In the period between the fourth visit and the fifth visit approximately 4 weeks later participants will be required to:.

- Report any hospitalisation as soon as is practically possible using the emergency 24-hour telephone number provided

- Report any other urgent medical concerns using the trial centre emergency procedures
- Report any unsolicited adverse events on the electronic diary card

5.8.10 Visit 5 Safety review, blood sampling and administration of trial vaccine

- Safety review to assess for any serious adverse events
- Review and reconciliation of diary card data submitted
- Assessment for local and systemic adverse reactions and events and medical history since visit 1
- Physical examination (if clinically indicated)
- Measurement of temperature
- Administration of trial vaccines as per randomisation
- Semi-structured interview (optional)* (See section 8 for further details)

5.8.11 Between visit 5 and visit 6

- Complete an electronic diary card for the first 7 days. This diary card will be used to capture:
    - AEs, including their timing and severity
- Report any hospitalisation as soon as is practically possible using the emergency 24-hour telephone number provided
- Report any other urgent medical concerns using the trial centre emergency procedures
- Report any unsolicited adverse events on the electronic diary card between day 8 and day 30 after vaccination
- Complete Quality of Life questionnaire 7 days after vaccination

5.8.12 Visit 6

At this visit, approximately 4 weeks after visit 5, participants will undergo the following:

- Provide blood sample for assessment of RZV vaccine immunogenicity
- Provide blood sample for assessment of cell-mediated immunity against RZV in CMI subset
- Participants randomised to group 1 will receive the flu vaccine if the visit is taking place during the winter vaccination season
- Confirm consent to follow up any clinically significant adverse events after end of participation in the study
- Semi-structured interview (optional) (See section 8 for further details)

5.8.13 Safety concerns

If participants experience adverse events (laboratory or clinical), which the PI or delegated clinician, determine necessary for further close observation, the participant may be admitted to an NHS hospital for observation and further medical management under the care of the Consultant on call.

5.8.14 Missed visits

If a participant cannot attend a visit for any reason, where possible, this should be re-arranged to an in-person visit within the time window. If this is not possible, in exceptional circumstances a visit may be conducted outside of the window, but this must be discussed with BTC and CI first who will assess the impact on patient safety and data integrity of allowing a visit outside of the specified window. A telephone visit may be conducted instead to ascertain as much relevant information as possible if the participant is unable to attend a visit in person and a visit out of window is not possible or not agreed by BTC.

6. Trial intervention

6.1 Trial interventions

Study participants will be randomly allocated a combination of the IMP below or alongside a placebo. All three vaccines used in this study will be considered IMP (Table 5).

IMP:

- Recombinant subunit Herpes Zoster vaccine with $AS01_B$ adjuvant (RZV) (Shingrix, GSK)
- Bivalent Covid-19 vaccine (Comirnaty Pfizer BioNTech)
- Adjuvanted Quadrivalent Influenza Vaccine (aQIV) (Seqirus)

Placebo:

Sodium chloride 0.9% injection

Any commercially available Sodium Chloride Injection BP 0.9% w/v can be used.

Manufacturer's storage conditions and expiry dates should be observed.

Table 5 IMP

	Shingrix, GSK	**Comirnaty original/omicron BA.4-5**	**Adjuvanted quadrivalent influenza Vaccine, Seqirus**

Description	Herpes Zoster vaccine (RZV) a recombinant vaccine that contains VZV specific antigen (gE) with an adjuvant system, AS01B. RZV is designed to induce antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against VZV. AS01B induces transient activation of innate immune system through specific molecular pathways. This facilitates the recruitment and activation of antigen presenting cells carrying gE-derived antigens in the draining lymph node. This in turn leads to the generation of gE-specific CD4+ T cells and antibodies. The adjuvant effect of AS01B is the result of interactions	. Comirnaty original/omicron BA.4-5 is a lipid nanoparticle-formulated, single-stranded, 5'-capped mRNA, encoding the viral spike (S) protein of SARS-CoV-2 (Original) and 5'-capped mRNA encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).	Adjuvanted quadrivalent influenza Vaccine (aQIV) is an inactivated subunit vaccine. The vaccine antigens consist of inactivated surface antigens from the WHO recommended influenza virus, HA and neuraminidase for the given season, as this study will run over 2 influenza seasons. The vaccine contains an adjuvant MF59C which is a squalene-based adjuvant.

	between MPL and QS-21 formulated liposomes.		

Dosing* schedule	The dose of RZV is 0.5ml. The vaccine should be administered intramuscularly, preferably in the deltoid muscle. Shingrix is presented as 2 vials, one containing the antigen powder and the other adjuvant in suspension. Shingrix must be reconstituted prior to administration. Two doses need to be administered, at the interval of 2-6 months between the doses.	The dose of Comirnaty original/omicron BA.4-5 vaccine is 15ug original and 15 µg omicron contained in 0.3ml of diluted vaccine. The vaccine should be administered intramusculary into the deltoid. Each pack of the Comirnaty original/omicron BA.4-5 vaccine contains 195 vials with 6 doses per vial. The vaccine should be stored out of the light prior to use.	The dose of aQIV contains 15µg of each strain in a 0.5ml dose. The vaccine is administered by intramuscular injection with the preferred site being the deltoid muscle of the upper arm. The vaccines come in pre-filled syringes with or without needles. The vaccine should be allowed to reach room temperature before use.

Regulatory status	Marketing authorisation from the MHRA from 1st January 2021	Marketing authorisation from the MHRA from 21st December 2020, renewed on 9th November 2022.	Marketing authorisation from the MHRA from 7th September 2021.
Preparation and labelling	There will not be investigational medicinal product (IMP) labelling for this trial. Products will be used as supplied by the manufacturer (as for national supply) and blinding will be performed as per section 5.6.		
Drug storage and supply**	Stored at 2-8°C and in the original package to protect from light. Once reconstituted the vaccine should be used immediately, if not used immediately it should be stored at 2-8°C for no longer than 6 hours.	Stored at -90°C - 60°C. Once thawed, the vaccine may be stored for 10 weeks at 2-8°C	Stored at 2-8°C.

** Dose modifications are not expected to occur.*

*** Vaccines and placebo will be stored in accordance with manufacturers' recommendations, in accordance with GCP pharmacy department standard operating procedures (SOPs).*

6.2 Accountability of the trial treatments

All movements of the trial vaccines will be documented in accordance with existing local pharmacy department SOPs. Vaccine accountability, storage, shipment and handling will be in accordance with local relevant SOPs.

6.3 Reference Safety Information

See safety section11.

6.4 Contraindications to vaccination after the first visit

The following AEs, identified on or before the day of vaccination, constitute absolute contraindications to further administration of a trial vaccine to the participant in question. If any of these events occur on or before the day of the second trial vaccination (visit 2), the participant will not be eligible to receive the IMP/placebo at visit 2 and will be followed up by the clinical team or their GP as required:

- Anaphylactic reaction following administration of vaccine
- Any AE that in the opinion of the local PI or delegated clinician may affect the safety of the participant or the interpretation of the trial results

6.5 Concomitant medications

Concomitant medications taken at enrolment will be recorded, as will new medications taken during trial participation.

6.6 Post-trial Treatment

No specific post-trial treatment considerations.

6.7 Other Treatments

There are no additional treatments other than those specific in this protocol.

6.8 Other Interventions

There are no additional interventions other than those specified in this protocol.

6.9 Treatment adherence

All vaccinations will be administered by the clinical care or research team. The trial medication will be at no time in the possession of the participant. Problems with adherence (e.g., failure to follow randomisation allocation) are not expected to be an issue. The research team will document whether the allocated treatment was given, if there were any deviations from the allocated intervention and the reason.

Withdrawals from treatment are expected to be low. All participants will receive their first double vaccination but may not receive subsequent vaccinations if they choose not to or because of a related adverse event that prevents further trial vaccinations. All withdrawals and reasons for withdrawal will be documented.

6.10 Duration of treatment period

The duration of the treatment commences when the participant receives their first vaccines as per randomisation and concludes one month after visit 5. For each participant this will be a total of approximately 5 months.

7. Data collection

Each participant will be assigned a unique trial number. Administrative data recorded on paper relating to the participant will be stored securely. Staff with authorisation to make changes to the trial records on the trial database, will be listed on the site delegation log.

Baseline data will be collected after written informed consent. Volunteers will be contacted by an authorised member of the local research or direct care team (as specified in the delegation log) who will provide the opportunity to understand the nature, significance, implications and risks of the trial so that they may make an informed decision if they should take part. If the patient decides to take part the member of the local research or direct care team will obtain informed consent.

Data collection will include the following elements:

a) A log of all volunteers who express interest in joining the trial and pass the pre-screening eligibility checks.
b) Volunteers assessed against the full eligibility criteria and, if ineligible, reasons for ineligibility.
c) Consent information collected prior to randomisation for all participants.
d) Baseline information (e.g., medical history and assessments) collected for all participating patients.
e) Data collected from participant diaries completed throughout their participation in the trial.
f) Data collected at trial visits.
g) Data derived from analyses of blood samples.

Impact of life measures

This will be assessed using the EQ-5D health survey which participants will be asked to fill in electronically through the platform used for trial management. If participants do not have access to an internet connected device, they will have the option to complete a paper EQ-5D questionnaire.

Diary cards will capture missed time from work by employed participants and caregivers.

8. Integrated Qualitative Research

8.1 Qualitative interviews

The ZosterFluCov trial will use a qualitative inductive approach, conducting semi-structured interviews with trial participants and study staff members to explore their experiences and perceptions of vaccine co-administration.

Interview guides will be used for the semi-structed interviews. The interview guides are tailored for the specific populations, with questions provided in a manner such that they are clear,

unambiguous and comprehensible to the broad audience. The questions will be in an open-ended format, to seek to facilitate conversation and engagement with the interview participant.

The interviews will explore the perceptions and experiences of participants and study staff members around vaccine co-administration, and their concerns and information needs. Paraphrasing and additional questions will be used to seek clarification during the interviews. All sessions will be digitally recorded with permission and transcribed using an UoB approved transcription service that has signed the necessary confidentiality agreements. Study staff members will also be asked to complete a short (2 minute) face sheet that will collect general demographic and work-related information. This information will be used to generally describe the study population and their level of experience in any published work. In any publication, information will be provided in such a way that participants cannot be identified.

8.2 Sample

For the qualitative semi-structured interviews, we envisage that we will recruit up to 20 study participants, and up to 20 study staff members involved with the trial. Interviews will continue until we feel confident that we have rich data to support analysis (information power[8]).
Purposive sampling will be used to generate rich data and include maximum variation in terms of age, ethnicity, and gender (trial participants), and of role (study staff).
Participants and study staff who agree to participate in the qualitative interviews will be compensated a £10 voucher for their time.

8.3 Identifying and consenting participants for qualitative interviews

Participants

Participants being invited to take part in this trial will be informed about the (optional) interviews through the study information sheet. If they are happy to be contacted about an interview, they will indicate this on the study consent forms. Those who agree to be contacted and who are selected to be invited for an interview will be contacted by the qualitative researcher who will provide the qualitative interview PIL (either electronically or via the post), explain more about the interview and answer any questions. If the participant then agrees to take part in the interview, the researcher will arrange a convenient time and preferred method to conduct the interview. Consent will be obtained from a researcher with valid Good Clinical Practice (GCP) training. Verbal consent will be obtained at the start of the interview and will be audio-recorded. The researcher will read out the statements at the top of the interview guide and participants will verbally state they agree/understand as appropriate. Volunteers can participate in interviews even if they later stop taking part in the study.

Study staff

Interviews will be held with study staff who have administered the study vaccines. The qualitative researcher will provide study staff with the healthcare professional interview information sheet. If a study staff member is interested in taking part in the interview, the qualitative researcher will explain more about the interview, answer any questions and if they agree to take part, arrange a convenient time to conduct the interview. Consent for the interview will be obtained by the qualitative researcher using the same process outlined for participants (as above). Members of the qualitative research team will be responsible for obtaining consent and maintaining suitable records.

8.4 Data Collection

Using purposive sampling (outlined above) potential participants will be approached after they have completed trial visit 4 (or equivalent for those who have stopped taking part in trial

activities). This will enable interviewees to reflect over their experience and talk about how their feelings and experiences may have changed over time. Interviews will take place remotely using telephone or online video conferencing software (MS Teams). Interviews will be audio- or video-recorded with participant permission (video-recordings will be converted into audio files immediately).

8.5 Qualitative analysis

The six-step thematic analysis qualitative framework developed by Braun and Clarke will be used to guide data analysis. The first few transcripts will be reviewed for early themes and concepts, from which the preliminary coding scheme will be constructed, and then code all transcripts, revising the scheme iteratively to reflect emergent themes from interview responses. QSR International's NVivo 10 qualitative data analysis software will be used to code all transcripts, categorise the data and facilitate comparison of participant views. A second investigator will then independently code at least 20% randomly selected interviews to ensure coding consistency. The two investigators will convene to share their categories; any discrepancies found will be resolved through discussion and negotiated consensus. Data analyses and interpretation will be iterative, and all investigators will participate in this process, to identify and agree upon emergent themes, and discuss their face validity.

8.6 Data management, protection and participant confidentiality in relation to the qualitative research data

Interviews will be audio- or video-recorded with participant permission (video-recordings will be converted into audio files immediately). Audio-recordings will be transcribed verbatim and any identifiable information will be removed. Audio files will be transferred as soon as possible after

the interview to secure UoB storage and video files destroyed. Audio-recordings of interviews will be transcribed by a UoB approved transcription service that has signed the necessary confidentiality agreements. Audio-recordings and transcripts will be labelled with an appropriate screening number or appropriate (unique) study I.D number and stored securely, adhering to the University of Bristol's data storage policies. Transcripts will be edited to ensure anonymity of respondents. Excerpts of audio-recordings concerning verbal consent will be retained for auditing purposes in line with trial archiving policies. Anonymised quotations may be used for training, teaching, research and publication purposes for this and future studies. Anonymised transcripts may be made available by controlled access to other researchers who secure the necessary approvals for purposes not related to this study, subject to individual recorded informed consent from participants. The remaining content will be deleted at the end of the study.

9. Sample collection

9.1 Blood samples

Serology

One 10 ml plain tube (usually red topped) or Serum Separator Tube (SST, usually Gold topped) vacutainer of blood will be taken at each visit.

Cell-mediated and exploratory immunology subset

40ml blood and 30ml at subsequent time points will be taken into a lithium heparin tube (usually green top)

Blood will be drawn prior to each vaccination and one month after final vaccination visits for assessment of humoral responses. Humoral responses will be measured using S-binding Ig for C19, HAI for influenza and anti-glycoprotein E (gE) for RZV.
S-binding Ig and HAI will be performed by Porton Down, UKHSA, UK and anti-gE by GSK.

PBMC will be used to assess cell-mediated immunity in each group to VZV gE specific CD4+T-cells, through intracellular cytokine staining will be quantified and exploratory analysis to assess the extent of cross protection afforded by RZV against COVID19 will also be performed. Exploratory immunology will be performed by University of Bristol laboratories.

9.2 Urine sample

Urinary pregnancy testing for female participants of child-bearing potential only, urine will be tested for beta-human chorionic gonadotrophin (β-HCG) at visit every vaccination visit This will be a point of care test and no sample will be stored.

9.3 Samples remaining after all testing for this trial is completed

Participants will be informed that there may be leftover samples of their blood (after all testing for this trial is completed). Participants will be able to decide if they permit future use of any leftover samples.

With the participants' informed consent, any leftover serum or peripheral blood mononuclear cells will be kept for future analysis of COVID-19 and other coronavirus-related diseases or vaccine-related responses and other future research (exploratory immunology), including genotypic testing of genetic polymorphisms potentially relevant to vaccine immunogenicity.

If a participant elects not to permit this, all that participants' leftover samples will be discarded at the end of the trial.

Samples that are to be stored for future research will be transferred to a licenced Research Tissue Bank.

10. Definition of end of trial

The definition of the end of the trial is the date when all participants have completed visit 6, or are lost to follow-up, all samples have been analysed, the database has been locked and all data queries have been resolved.

The end of the trial for an individual patient is defined as completion of visit 6 or loss to follow-up.

11. Safety data collection and reporting

Participants will be asked to complete an electronic diary of solicited local (pain, redness, and swelling at injection site) and systemic (fatigue, fever GI symptoms (nausea, vomiting, diarrhoea and/or abdominal pain) headache, myalgia, shivering) AEs for 7 days after each vaccination. Participants will be asked to record unsolicited AEs, up to 30 days after vaccination. Participants would be counselled with regard to expected side effects during the consent process and in the diary training. Leaflets about side effects would also be provided for participants.

Serious adverse events and adverse events of special interest (pIMDs) should be collected until the study end.

Safety monitoring

Safety monitoring would be continuous throughout the whole study and performed in real-time for the first 7 days after vaccination in the following ways:

- Participants would be required to complete electronic diary cards that would be reviewed in real time by trial physicians and the trial coordination team. All events will be reviewed, and reports of any grade 3 or above will trigger an alert to the relevant teams.
- Participants who do not complete the diary to would be contacted by email/text message/telephone within 48 hours in order to minimise recall bias
- Participants should have 24/7 access to an emergency 24-hour telephone number

- Participants who do no have access to the electronic diaries, can complete a paper diary. The participant would be encouraged to report any symptoms to the local research team and would be contacted for review by the local research team between day 4-7. All events will be reviewed, the relevant teams would be notified of any reports of grade 3 or above.

Additional measures

- Primary care physicians will be notified promptly if their patients were involved in the study therefore if participants presented to their primary care doctor this information would be on hand
- Participants would be given a handheld card identifying them as a study participant that they could share with healthcare professionals in the event they sought medical attention outside of their primary physician.

11.1 Overview

Serious adverse events (SAEs) will be recorded and reported in accordance with GCP guidelines and Bristol Trials Centre Standard Operating Procedures (see Figure 2).

11.2 Definitions

Adverse event (AE) is any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.

Adverse reaction (AR) is any undesirable experience that has happened to a subject while taking a drug that is suspected to be caused by the drug or drugs.

Serious adverse event (SAE) is any event which results in death, is life threatening, requires hospitalisation or prolongs hospitalisation, results in persistent or significant disability or incapacity, results in abnormal pregnancy outcomes or a congenital anomaly/birth defect in the offspring of a study participant, or any other event which may jeopardise the participant or require intervention to prevent one of the other outcomes listed above

Suspected serious adverse reaction (SSAR) is any serious adverse event that is suspected to be related to the drug or drugs being taken.

Suspected unexpected serious adverse reaction (SUSAR) is an untoward medical occurrence suspected to be related to the drug or drugs being taken that is not consistent with the applicable product information and is serious.

All AEs must be reviewed, and causality must be assessed by the PI or delegated individual not involved in the administration of the trial vaccines (to maintain blinding).

Severity grading for adverse events

The severity of adverse events will be assessed according to scales based on FDA toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, listed in Table 6 and Table 7 below.

Table 6 Severity grading for local adverse events

Adverse Event	Grade	Intensity
Pain at injection site	0	No pain
	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
Redness at injection site*	0	<2.5 cm
	1	2.5- 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis or exfoliative dermatitis
Swelling at injection site	0	<2.5cm
	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 7 Severity grading for systemic adverse events

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

If an event meets any of the 'serious' criteria listed below it is classified as an SAE:

a) Results in death

b) Life threatening

c) Requires hospitalisation (unless hospitalisation is pre-planned)

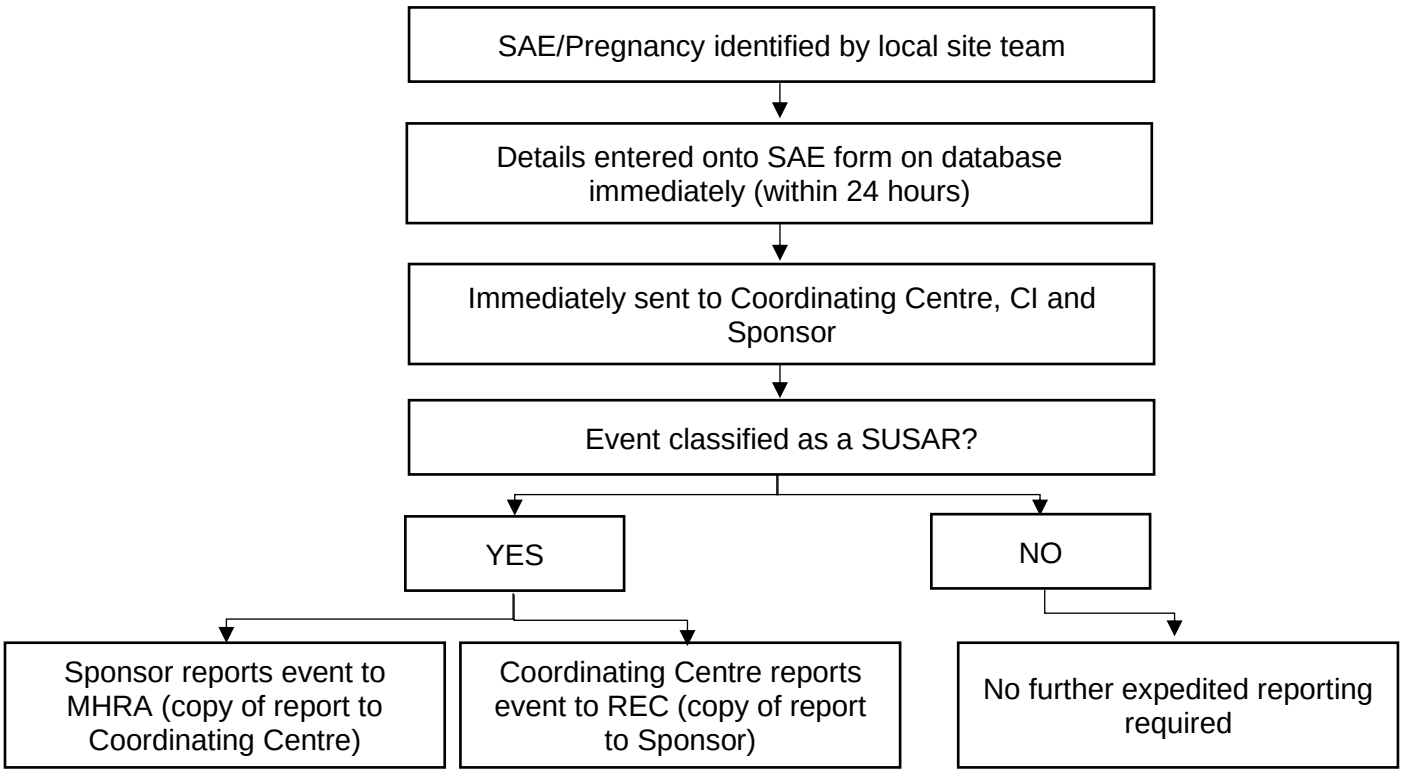
d) Prolongation of existing hospitalisation

e) Results in persistent or significant disability or incapacity

f) Abnormal pregnancy outcomes, Congenital anomaly / birth defect

g) Any other event which may jeopardise the participant or require intervention to prevent one of the other outcomes listed above

Figure 2 SAE* reporting process



**This will include pIMDs and AESIs that meet the definition of SAE*

11.3 Period for recording adverse events

Data on serious adverse events, will be collected for the period the participant is taking part in the trial, i.e., from visit 1 to visit 6.

11.4 Process for reporting serious adverse events

Centres should expedite reporting of SAEs to the coordinating centre and the Sponsor within 24 hours of becoming aware, using an SAE report form. If the event is classified as a SUSAR, the Sponsor will report the SUSAR to the MHRA and copy all reports to the coordinating centre; coordinating centre will report the SUSAR to the REC. These reports will be sent within 8 days for fatal or life-threatening events and 15 days for all other SUSARs.

11.5 Expected adverse events associated with trial interventions

Expected events are those listed in the Reference Safety Information (RSI), which for this trial is the summary of product characteristics (SmPC) for the vaccines (see Appendix). The RSI for each IMP is:

- RZV: Section 4.8 of the SmPC, dated 07/06/2022
- C19 vaccine: Section 4.8 of the SmPC, dated 05/2023
- aQIV: Section 4.8 of the SmPC, dated 06/2023

All other events that are not consistent in nature or severity with the SmPC should be considered unexpected. Fatal events will always be considered unexpected.

11.6 Expected adverse events associated with trial procedures

Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. These will be documented as adverse events if they occur.

11.7 Events that will not be reported as serious adverse events (SAEs)

The following events will not be reported as SAEs:

- hospitalisation for a pre-existing condition, including planned elective procedures
- attendances at an emergency department unless they meet the SAE definition as described in Section 11.2.

11.8 Adverse events of special interest

The following adverse events are considered adverse events of special interest (Table 8) and potential immune-mediated disorders (Table 9).

Table 8 Adverse events of special interest

Immunologic	Anaphylaxis	
Neurological	Isolated anosmia/ageusia* Guillain-Barre Syndrome Acute disseminated encephalomyelitis (ADEM) Aseptic meningitis	Meningoencephalitis Peripheral facial nerve palsy Generalised convulsion Myelitis

Haematological	Thrombosis** Stroke Thrombocytopaenia (G3 or above) Eosinophilia	Coagulation disorder (includes coagulopathy, thrombosis, thromboembolism, internal/external bleed and stroke)
Cardiac	Acute cardiovascular injury (includes myocarditis, pericarditis, arrhythmias, heart failure, infarction)	
Dermatological	Chilblain-like lesions Single organ cutaneous vasculitis	Erythema multiforme Alopecia
Gastrointestinal	Acute liver injury	Appendicitis
Respiratory	ARDS	
Renal	Acute kidney injury	

**In the absence of COVID-19*

*** Excluding superficial thrombophlebitis (including line-associated)*

Table 9 List of potential immune-mediated diseases (pIMDs)

Medical Concept	**Additional Notes**
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia

Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”, “idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”.
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	Including but not limited to: • Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic pulmonary fibrosis	Including but not limited to:

	• Idiopathic interstitial pneumonia (frequently used related terms include “Interstitial lung disease”, “Pulmonary fibrosis”, “Immune-mediated pneumonitis”) • Pleuroparenchymal fibroelastosis (PPFE)
Pulmonary alveolar proteinosis (PAP)	• Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”
Endocrine disorders	
Addison’s disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis

Autoimmune diseases of the testis and ovary	• Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis

	• Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn's disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis

	• Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty’s syndrome
Sjögren’s syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis

	• Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	• Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (Systemic Sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory demyelinating variants	Includes the following: • Acute necrotising myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis

Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (e.g. Optic neuritis) • Idiopathic nerve palsies/paresis (e.g. Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple Sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy

Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis

	• Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localised Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	

Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis

	• Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include : “systemic capillary leak syndrome (SCLS)” or “Clarkson's Syndrome”
Goodpasture syndrome	• Frequently used related terms include : “pulmonary renal syndrome” and “anti-Glomerular Basement Membrane disease (anti-GBM disease)”
Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include “vaccine-mediated enhanced disease (VMED)”, “enhanced respiratory disease (ERD)”, “vaccine-induced enhancement of infection”, “disease enhancement”, “immune enhancement”, and “antibody-dependent enhancement (ADE)
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	

Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

12. Trial methods

12.1 Source data

Outcome data will be collected using a purpose-designed database. Where the trial database is the site of original recording this will be considered source data. Data will be captured at each trial visit (see Table 4 for schedule of data collection). Volunteers and participants will enter data directly into the screening and trial databases. These will be the source data for these responses.

Where the database is not the original recording the source data will include, but is not limited to medical history, medication records, vital signs, physical examination records, urine assessments, blood results, and details of vaccinations.

12.2 Planned recruitment rate

Anticipated rate of enrolment:

We will recruit 960 participants at approximately 15 sites over a 6 month period. For the first 50 participants recruited to Groups 4 and 5 there will be real time safety monitoring. Once the first 50 participants in Groups 4 and 5 reach visit 3, then a safety review will take place and will include data up to 30 days after the second vaccination point. Recruitment to the study will continue during the safety review but will pause if there are any safety concerns.

12.3 Participant recruitment

The public will be made aware of the trial via:

- Press announcements
- On a website
- Social media
- Notification via the National Vaccines Studies Register
- Notification via vaccination centres
- Contact from their direct care team (e.g. the GP practice responsible for their vaccinations)
- Be Part of Research Volunteer Service
    - The purpose of the Be Part of Research Volunteer Service (BPORVS) is to allow members of the public to become volunteers by creating an account, specifying the areas of research that they are interested in and give consent to be contacted by the Be Part of Research team. Those who consent will receive information about BPORVS, in particular to alert them to specific BPORVS registered studies that they may be interested in, based on their volunteered details and study specific eligibility criteria, using an online self-registration service. The register is

open to those that live in the UK, are over 18 and have an email address. At the time of registration, volunteers are made aware that they are not signing up to take part in a specific health study when they join this register and that they will only be signposted to studies that have NIHR funding or are listed on the NIHR CRN Portfolio. If the volunteer is interested in the study there will be a link in the email to take them to the study team (e.g. website, pre-screener) where they will move into the study teams screening process and consenting process if they take part in the study. The Be Part of Research Volunteer Service is funded by the Department of Health and Social Care and delivered by the National Institute for Health and Care Research (NIHR) in conjunction with Public Health Agency, Research & Development, Northern Ireland, NHS Scotland and Health and Care Research Wales. Further information on the Be Part of Research Volunteer Service is available here: https://bepartofresearch.nihr.ac.uk/volunteer-service/researcher

- Charities via social media, websites and newsletters as well as sending study information to individuals who have expressed as interest of being informed of research opportunities relevant to them.

Volunteers interested in joining the trial will be directed to a 2-stage online screening process using a purpose-designed website hosted by the University of Bristol and approved by the Research Ethics Committee (REC). The REC-approved participant information leaflet (PIL) will be available via this website to download. A REC-approved video presentation of the PIL may be made available for volunteers to access remotely.

Study sites will access the details of volunteers in their local area and will follow the process outlined in Section 5.8. Direct care teams can contact potential volunteers directly without prior registration on the website, as described in section 5.8.

Prior to consent volunteers will have an opportunity to discuss the trial with a member of the research team, who will answer any questions and take written informed consent if the volunteer decides to participate. The volunteer will be given an explanation of the exact nature of the trial, what it involves for the participant, implications and constraints of the protocol, known side effects and any risks involved in taking part, and that anonymised samples taken during the trial may be shared for future research. The consent form will include permission to inform their GP of their participation and optional consent to allow indefinite storage of any leftover samples for use in other ethically approved research. A copy of the signed informed consent form will be given to the participant.

The voluntary nature of participation and that the participant can stop active participation at any time will be emphasised. It will also be explained that participants will not be exempt from following the contemporaneous government COVID-19 guidance to minimise viral transmission.

12.4 Discontinuation of vaccinations or active trial participation of participants

Each participant has the right to stop active participation at any time for any reason and is not obliged to give their reasons for doing so. Data and samples collected prior to the change in status will be retained and reported.

A clinician may decline trial vaccinations for a participant at any time if they feel it is in the participant's best interests (e.g., due to ineligibility, either arising during the trial or

retrospectively having been overlooked at screening, significant protocol deviation, participant non-compliance with trial requirements, adverse event which requires discontinuation of the trial involvement or results in inability to continue to comply with trial procedures, administrative reason).

Reasons for all discontinuations will be captured in the trial database and reported.

The DMSC may recommend cessation of treatment for participants.

12.5 Frequency and duration of follow up

Participants are followed up for 5 months from enrolment and randomisation. Pregnant women will be followed-up to delivery.

12.6 Likely rate of loss to follow-up

With a short period of participation of 6 months loss to follow-up is expected to be minimal (less than 5%).

12.7 Expenses

Volunteers will be compensated for their time, the inconvenience of having blood tests and procedures, and their travel expenses. The total amount compensated will depend on the exact number of visits, and whether any repeat or additional visits are necessary. For all trial visits participants will be compensated up to £45 per visit (total compensation for completing trial would be £90 for a subset of participants in groups in group 3 and up to £270 for all other participants.

13. Statistics

13.1 Sample size calculation

Sample size calculations have been performed to test all primary immunogenicity objectives in both part A and part B of the trial. All sample size calculations were performed using the SSI module in Stata.[9]

Part A: Assessment of co-administration of COVID-19 vaccine and RZV

We hypothesise that (1) immunogenicity (anti-S protein Ig concentrations, both Original and Omicron strains) of concomitant administration of C19 and RZV (first or second dose) will be non-inferior to C19 alone, and (2) immunogenicity (anti-gE Ig concentrations) of concomitant administration of RZV (first or second dose) and C19 will be non-inferior to RZV alone.

The power calculations to test hypotheses in part A are provided in Table 10.

Table 10 Sample size estimates for part A

Outcome	Sample size excluding 10% inflation for dropout	SD (log10 scale)	Assumed true GMR	Non-inferiority margin (log10 scale)	Power for each outcome	Conjunctive power for part A
Anti-S Ig	95	0.35	1	0.174	92.9%	80.1%
Anti-gE Ig	95	0.35	1	0.174	92.9%	

A sample size of 106 per group will provide 80% power to test all part A hypotheses using a 2.5% one-sided significance level and allowing for 10% dropout.

Part B: Assessment of co-administration of adjuvanted influenza vaccine and RZV

We hypothesise that (1) immunogenicity (for 3 of the strains included in the vaccine; HAI influenza A H3N2, HAI influenza A H1N1 and HAI influenza B Victoria) of concomitant administration of aQIV and RZV (first or second dose) will be non-inferior to aQIV alone, and (2) immunogenicity (anti-gE Ig concentrations) of concomitant administration of RZV (first or second dose) and aQIV will be non-inferior to RZV alone.

The power calculations to test hypotheses in part B are presented in Table 11.

Table 11 Sample size estimates for part B

Outcome	Sample size excluding 10% inflation for dropout	SD (log10 scale)	Assumed true GMR	Non-inferiority margin (log10 scale)	Power for each outcome	Conjunctive power for correlated outcomes (HAI)*	Conjunctive power for part B
HAI influenza A H3N2	216	0.45	1	0.174	98.0%	80.7%	80.6%
HAI influenza A H1N1	216	0.54	1	0.174	91.8%		
HAI influenza B Victoria	216	0.57	1	0.174	88.7%		
Anti-gE Ig	216	0.35	1	0.174	99.93%	-	

* Estimated using correlation matrix from ComFluCOV HAI data; conjunctive power for HAI outcomes was calculated using R.

A sample size of 240 per group will provide 80% power to test all part B hypotheses using a 2.5% one-sided significance level and allowing for 10% dropout.

Final sample size justification

A sample size of 960 (120 into groups 1 and 2, 240 into groups 3-5, after inflating to fit a 1:1:2:2:2 allocation ratio) will allow us to adequately assess all primary immunogenicity objectives.

13.2 Safety review

This study will have a planned safety review after the recruitment of the first 50 participants in Groups 4 and 5. During this review safety reporting information will be reviewed by the DMSC. The safety review will include data up to 30 days after the second vaccination point (visit 3). The DMSC will determine whether the trial should continue. No formal statistical analysis will be performed at this review.

13.3 Stopping rules

The trial can be put on hold upon advice of the DMSC, Chief Investigator, Study Sponsor, regulatory authority, REC, for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the participants or the reliability of the data.

13.4 Plan of analysis – primary and secondary outcomes

Analyses will be performed on an intention-to-treat basis and will be directed by a pre-specified statistical analysis plan (SAP). Results will be reported in accordance with CONSORT reporting guidelines. [10, 11]

Co-primary and secondary immunogenicity outcomes will be analysed using a mixed regression model, with treatment group, age group (50-64, 65-70, 71-74 and 75+ years) and baseline values fitted as fixed effects and centre fitted as a random effect, where possible.

The analysis of the co-primary and secondary safety outcomes will be descriptive only. The number and percentage of participants in each group experiencing each safety outcome will be reported.

Days off work will be analysed using Poisson regression. Quality of life scores (EQ-5D) will be analysed using a mixed regression model, with treatment group, time point (day/visit at which the questionnaire was completed), age group and baseline EQ-5D score fitted as fixed effects and centre fitted as a random effect, where possible. An interaction between treatment group and time point (day/visit) will be included to enable the treatment effects of interest to be estimated.

Two subgroup analyses are planned. The first will be comparing anti-S Ig by COVID-19 vaccine in previous 6 months (yes/no); and the second will be comparing HAI by influenza vaccine in previous 6 months (yes/no). A third subgroup analysis will be considered if a significant number of participants in groups 2 and 3 have a COVID-19 infection between visit 1 and visit 3, comparing anti-S Ig between those who have had a COVID-19 infection between visits 1 and 3 and those who haven't.

Full details of the proposed models will be specified in the SAP. Model validity will be checked using standard methods; alternative models or transformations will be explored if model fit is inadequate. Findings will be reported as effect sizes and 95% confidence intervals.

13.5 Frequency of analyses

The analysis of the primary safety outcome will take place when all recruited participants have submitted 7-day diary information, that this has been reviewed at visit 6, the data relating to the 7-day outcomes are checked and complete and that element of the database can be locked.

Analyses of other outcomes will take place when the trial is complete, and the database is locked.

14. Trial management

University Hospitals Bristol and Weston NHS Foundation Trust will act as Sponsor. The BTC will act as the coordinating centre for the trial. Responsibility for running the ZosterFluCov trial will be established via a collaboration agreement with the University of Bristol. Agreements between the Sponsor and participating centres will be required, as well as standard site initiation documents, before recruitment commences. Appropriate contractual arrangements will also be put in place with other third parties.

The trial will be conducted in accordance with GCP guidelines, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, the Data Protection Act and the UK Policy Framework for Health and Social Care Research. The trial will be registered on an open access clinical trial database (ISRCTN).

Clinical trial documents will be archived and held by the Sponsor for 15 years after trial closure in accordance with the standard operating procedures of the Sponsor and in compliance with the principles of GCP.

The trial will be managed by the Chief Investigator (CI), with mentoring and support from senior members of the research team who will provide experience of implementing large scale clinical trials, and the Trial Managers, with full support from the wider BTC, which is a UK Clinical Research Collaboration registered clinical trial unit (UKCRC Reg. No 70). The BTC has an

established track record of designing, conducting, managing and reporting multi-centre clinical trials.

The CI and coordinating centre team will work with the co-applicants to prepare the final protocol and submit the REC, MHRA and associated Health Research Authority (HRA) applications. The coordinating centre will prepare the trial documents, provide the randomisation service and design and implement the data management system.

The CI, coordinating team and Sponsor will endeavour to ensure that the trial runs according to the agreed timetable, recruitment targets are met, the Case Report Forms (CRFs) are completed accurately, the trial complies with relevant ethical and other regulatory standards, and that all aspects of the trial are performed to the highest quality. The CI and coordinating centre team will also train investigators at participating centres, check that each centre is ready to start ("green light") and monitor their progress during the trial. The Trial Managers will be the contact point to provide support and guidance to the participating centres throughout the trial.

14.1 Day-to-day management

The ZosterFluCov trial will be managed by a Trial Management Group (TMG), which will meet face-to-face or virtually regularly. The TMG will be chaired by the CI and others will be invited as appropriate (see CI & Research Team Contact Details).

14.2 Monitoring of sites

14.2.1 Initiation training

Before the trial commences, training session(s) will be organised by the coordinating centre. These sessions will ensure that personnel at each site involved fully understand the protocol, e-CRFs, interventions, the operational requirements of the trial and the assessments to be conducted within the trial.

14.2.2 Site monitoring

The trial coordinating centre will carry out regular monitoring and audit of compliance of centres with GCP and data collection procedures. Monitoring of data collection will be via the trial database (checks for data completeness and routine data query review), which will be carried out on a regular basis. The TMG will review accumulating data on, including but not limited to, screening, eligibility, recruitment, data completeness, adherence to trial visits and procedures, adverse events and protocol deviations in the form of central monitoring reports.

14.3 Trial Steering Committee and Data Monitoring and Safety Committee

The remit of the independent Trial Steering Committee (TSC) will include, but not be limited to, recommending trial pauses due to safety concerns on the advice of the DMSC.

The independent DMSC established will review data from this trial in line with the DMSC charter and will make recommendations concerning the conduct, continuation, or modification of the trial for safety reasons.

The DMSC will be provided with safety reports at an agreed frequency prior to the start of the study. During the safety review for the first 50 participants in Groups 4 and 5, the DMSC would

perform interim safety review. Recommendations based on the safety analysis would be made by the DMSC. Stopping conditions would be:

- Clear harm, as determined by the committee
- New external evidence

Safety review with potential pause would also be triggered by a SUSAR at any point in the study.

15. Ethical considerations

15.1 Review by an NHS Research Ethics Committee

The research will be performed subject to a favourable opinion from an NHS REC and HRA approval. Ethics review of the protocol for the trial and other trial related essential documents (e.g., PIL and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

15.2 Risks and anticipated benefits

15.2.1 Potential benefits

The potential benefits will be protection against COVID-19, Herpes zoster and influenza.

15.2.2 Potential risks

Phlebotomy

Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. The total volume of blood drawn over a 6-week period will be approximately 250mL (blood volumes may vary slightly for participants at different investigator sites due to use of different volume vacutainers, following local Trust procedures). This should not compromise these otherwise healthy volunteers, as these volumes are within the limits of 470mL every 3 – 4 months for blood donations to the National Blood Transfusion Service.

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 (Public Health England 2020b).

Specific risk from vaccines

Please refer to Section 11 for full details.

15.3 Informing potential trial participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL.

15.4 Obtaining informed consent from participants

All participants will be required to give written informed consent. This process, including the information about the trial given to patients in advance of recruitment, is described above in section 11.3.

The PI or members of the team delegated by the PI will be responsible for obtaining informed consent. The consent process will be described in detail in the trial documents. Research personnel authorised to obtain consent will be recorded on the Delegation of Responsibilities Log. All individuals obtaining informed consent will have received GCP training.

15.5 Co-enrolment

Subject to agreement with the CI, a participant may be co-enrolled to a non-interventional study as well as to the ZosterFluCov trial. A participant must not be co-enrolled to another interventional study while they are actively participating (up to visit 6) in the ZosterFluCov trial.

16. Research governance

This trial will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004 and subsequent amendments
- Good Clinical Practice (GCP) guidelines
- UK Policy Framework for Health and Social Care Research

16.1 Sponsor approval

Any amendments to the trial documents must be approved by the sponsor prior to submission to the HRA, REC and MHRA as applicable.

16.2 NHS confirmation of capacity and capability

Confirmation of capacity and capability is required from each participating site prior to their participation in the trial.

Any amendments to the trial documents approved by the REC, HRA and MHRA (if applicable) will be submitted to participating sites for information and implementation, as required.

16.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and trial documents and with completion of the e-CRFs. Investigators will be required to allow access to trial documentation or source data on request for monitoring and audits performed by the Sponsor or the coordinating centre or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any approved amendments to the trial documents that they receive and ensure that the changes are complied with.

16.4 Monitoring by sponsor

The trial will be monitored and audited in accordance with University Hospitals Bristol and Weston's NHS Trust Monitoring and Oversight of Research Activity SOP, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for

Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All trial related documents will be made available on request for monitoring and audit by the sponsor (or the coordinating centre if they have been delegated to monitor), the relevant REC and for inspection by the MHRA or other licensing bodies. A monitoring plan will be prepared by the Sponsor and BTC.

16.5 Indemnity

This is an NHS-sponsored research trial. For NHS sponsored research if there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

16.6 Clinical Trial Authorisation

Herpes zoster, COVID and influenza vaccines are classed as investigational medicinal products and a Clinical Trial Authorisation (CTA) from the MHRA must be in place before starting the trial.

16.7 Serious breaches

The Medicines for Human Use (Clinical Trials) Regulations require "serious breaches" to be notified 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 affect 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 serious breach is suspected, the Sponsor must be contacted within 24 hours. The serious breach will be reviewed by the Sponsor in collaboration with the CI and, if appropriate, the Sponsor will report it to the REC, MHRA and the relevant NHS host organisation within seven calendar days of become aware of the serious breach.

17. Data protection and participant confidentiality

17.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and UK General Data Protection Regulation (GDPR) 2016.

17.2 Data handling, storage and sharing

17.2.1 Data handling

The ZosterFluCov trial team will provide the Sponsor with a Data Management Plan prior to the trial opening to recruitment.

Data will be entered into a purpose-designed database hosted on the University of Bristol network. Information capable of identifying participants will be held in the pre-screening

questionnaire, with participant consent. The pre-screening questionnaire will be held on a secure University of Bristol server. ZosterfluCOV trial staff at the coordinating centre will have access to the pre-screening questionnaire and will share this information securely with participating sites who will contact potential participants, for the purposes of the study. Information capable of identifying participants will not be held in the study database. Database access will be password-controlled and restricted to ZosterFluCov trial staff at the participating site and the co-ordinating centre. The processing of personal data of participants will be minimised by making use of a unique participant trial number on trial documents and the study database, with the exception of signed consent forms, pre-screening questionnaire and the screening log.

The database and randomisation system will be designed to protect participant information in line with data protection legislation. Trial staff will ensure that the participant's confidentiality is maintained through secure handling and storage of participant information at participating sites and in accordance with ethics approval. All documents will be stored securely and only accessible by trial staff and authorised personnel. Data will be collected and retained in accordance with data protection legislation.

Access to the database will be via a secure password-protected web-interface. Study data extracted from the database for statistical analyses will contain the participant's unique trial number only. Data validation and cleaning will be carried out throughout the trial.

Each recruiting centre will have access to trial materials, which will cover database use, data validation and data cleaning. The coordinating centre will maintain and update the trial materials as required.

17.2.2 Data storage

All trial documentation will be retained in a secure location during the conduct of the trial and for 15 years after the end of the trial, when all participant identifiable paper records will be destroyed by confidential means. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial and clearly stating the 'do not destroy before' date. Where electronic records are in use, local site policy will be followed. In compliance with the Medical Research Council (MRC) Policy on Data Sharing, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique participant number, will be held indefinitely.

17.2.3 Data sharing

Anonymised trial data will only be made available for sharing after publication of the main results of the trial. Thereafter, individual participant data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g., a protocol for a Cochrane systematic review. If participants' consent for storage of samples for future research, a copy of the participant's consent form will be shared with the licenced Research Tissue Bank. If participants' consent, local sites will store their contact details so they can be contacted about future studies that may be relevant.

18. Dissemination of findings

The Investigators will be involved in drafting and reviewing manuscripts, abstracts, press releases and any other publications arising from the trial. Social networking media will be used to disseminate and publicise the trial results via the trial website and Twitter streams. Patient and Public Involvement groups will be consulted to identify how to best publicise the trial findings.

Expected outputs include publication of the trial results, informing the UK government, the National Institute for Health Research (NIHR), clinicians and the public on the safety of giving the Herpes Zoster and COVID-19 or influenza vaccines together. It is anticipated that the results of the trial will inform national and international guidelines.

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19. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
SA1	V2.0	26/01/2023	V3.0	06/07/2023	• Update to study background • COVID-19 vaccine updated • Be Part of Research vaccine registry added • Changes to eligibility criteria • Updates to vaccination schedule so that all participants receive C19 and flu vaccine • Update to secondary outcomes and	

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					qualitative interviews added • Update to blood sample time-points	
SA2					• Use of charities has been added as a recruitment method	
NSA04	V4.0	18/09/2023	V5.0	08/11/2023	• Typographical errors corrected • Baseline blood sample to be collected after randomisation, instead of before	
SA3					• Removing the testing of the HAI influenza B Yamagata strain from the influenza immunogenicity outcome in Part B, and updating the sample size calculation to account for this	

20. Appendix 1

Please see the following pages for the SmPCs relating to the below vaccines:

- Adjuvanted quadrivalent influenza Vaccine (aQIV)
- Comirnaty Original/Omicron BA.4-5
- Shingrix