TRIAL PROTOCOL

PROTECT-CH

Prophylactic Therapy in Care Homes Trial

Short title: PROTECT-CH

Full title: COVID-19: PROphylactic ThErapy in Care homes Trial-CH

Final v1.0, Date 13 May 2021

UTN: U1111-1265-4068

EudraCT number (CTIMPs only)	2021-000185-15
Sponsor reference number	21001
ISRCTN number	TBC
IRAS Project ID	294832
NCTU reference number	2033

FUNDED BY NIHR | National Institute for Health Research

This project is funded by the National Institute for Health Research (NIHR) HTA Programme (project reference NIHR133443). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

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Protocol Version Number:	Final Version 1.0
Protocol Version Date:	xx-xxx-2021
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TRIAL SUMMARY

Title	**PROphylactic ThErapy in Care homes Trial**
Acronym	PROTECT-CH
Short title	PROTECT-CH
Chief Investigator	Professor Philip Bath
Research Question	In residents in a UK care home setting (P), which drug or antibody interventions (I) when compared to standard care (C) are effective, safe and cost-effective (O) as prophylaxis for COVID-19?
Objectives	**Primary objective** To provide reliable estimates of the effect of trial treatments for each pairwise comparison with the standard care arm on SARS-CoV-2 infection, morbidity and mortality 60 days after randomisation (or appropriate point dependent on the intervention – where this differs to 60 days further detail will be provided in the specific investigational medicinal product (IMP) Appendix). **Secondary objectives** To assess the effects of trial treatments on mortality (all-cause and cause-specific), admission to hospital (all-cause and cause-specific), healthcare referrals for COVID-19, infection (asymptomatic, symptomatic), time to symptomatic infection and safety through serious adverse reactions. To assess the effects of trial treatments on transmission of SARS-CoV-2 infection. **Tertiary objectives** To assess the cost-effectiveness of trial treatments and explain the contextual factors which influence trial processes including adherence to intervention and outcome measurement regimens, and which might impact on subsequent implementations of pre- or post-exposure prophylaxis for COVID-19 in care homes.
Trial Configuration	Overarching platform trial designed to provide reliable evidence on the efficacy of candidate therapies for preventing SARS-CoV-2 infection and transmission in care homes.
Setting	UK Care homes (residential, nursing, mixed).
Sample size estimate per comparison of an active treatment with standard care	In order to detect an odds ratio of 0.67, a sample size of 200 care homes (around 6,400 residents) is required assuming 1:1 randomisation, two-sided significance level 5%, power 90%, 4-level ordinal primary outcome (no infection proportion 60%, infection remain in CH 15%, admission to hospital all-causes 10%, all-cause mortality 15%), intra-cluster correlation 0.11, coefficient of

	variation for care home size 0.49, average number of residents per care home in trial 32, design effect/inflation factor 5.25.
Number of participants	Each comparison of an active treatment with standard care requires 200 care homes i.e. in the region of a total of 6,400 residents.
Eligibility criteria	**Care Home criteria** ***Inclusions*** • Location: UK care homes for older people, with and without nursing. • Size: ≥20 beds in the care home in total. ***Exclusions*** • Care Quality Commission quality: Inadequate, or equivalent in devolved administrations. **Care Home criteria at treatment phase** ***Exclusions:*** • Positive PCR or lateral flow test (or equivalent) for SARS-CoV-2 in any resident and/or staff within previous 4 weeks **Resident criteria at trial entry** ***Inclusions*** • Resident in a Care Home. • Age ≥65 years • Able to give informed consent for participation or a personal legal representative has been identified who can give consent if resident lacks capacity. ***Exclusions***: • Identified by care home staff to have entered end-stage palliative care. • Resident in care home for short-term respite care. • Resident's general practitioner is unable to support their involvement in the trial. **Resident criteria at treatment phase** ***Exclusions***: • Currently taking all of the trial interventions. • Contraindication to all trial interventions - see IMP appendix. • In treatment phase of another COVID-19 prevention or treatment trial
Description of interventions	**Intervention:** To be identified by NIHR Prophylaxis Oversight Group (POG) plus standard care. Each intervention will be described within a separate IMP Appendix, each of which will be updated upon confirmation of use within the trial. **Comparator:** Standard care i.e. no additional intervention.

Randomisation and blinding	The unit of randomisation is the care home, not the (individual) resident. Allocation concealment will be ensured by enrolling care homes and residents prior to revealing the allocation. There will be no blinding apart from for outcomes sourced from routinely collected health data. Where possible IMP interventions will be open-label. Dynamic randomisation will be employed using a probabilistic minimisation algorithm to balance across important baseline characteristics including: • Care home type (residential vs nursing vs nursing and residential) • Prior COVID-19 in care home at any time (yes vs no) • Size of Care Home - Total number of residents in care home (small (≤30 residents), medium (>30, ≤50 residents), large (>50 residents)) • Care home has capacity to give oxygen and/or dexamethasone (yes vs no) Trials of pre-exposure prophylaxis (PrEP, i.e. before the care home has a case) and/or post-exposure prophylaxis (PEP, once the care home has a new case to control an outbreak) will be conducted on the platform. • For trials of PrEP the care home will be randomised once an IMP has been identified by the NIHR POG and the necessary processes have been implemented. The care home must have had no evidence of SARS-CoV-2 infection for at least 4 weeks. • For trials of PEP, care homes will only be randomised once they have an indication of a developing infection, e.g. recent positive PCR or lateral flow test (or equivalent) in a resident or member of staff (index case). The care home must have had no evidence of SARS-CoV-2 infection for at least 4 weeks prior to the index case.
Outcome measures	**Primary endpoint:** Four-level ordered categorical scale. Participants will be classified according to the highest level, that is, the most serious event they experience during the 60-day period following randomisation: 1. No SARS-CoV-2 infection. 2. SARS-CoV-2 infection but resident remains in care home. 3. Admission to hospital, all-cause. 4. Death, all-cause. SARS-CoV-2 status (positive or negative) will be diagnosed using PCR or lateral flow testing (or equivalent). **Secondary endpoints during the 60 days post-randomisation (unless otherwise stated):** Clinical

	• Healthcare referral for COVID-19, e.g. discussion outside of care home with GP (excluding routine visit), 111, 999 paramedic or Emergency Department assessment (without admission), remote hospital consultation. • Participant receives dexamethasone in the care home for COVID-19 • Participant receives oxygen in the care home for COVID-19 • Time to SARS-CoV-2 infection - positive PCR or lateral flow test (or equivalent) (i) with symptoms of COVID-19, (ii) without symptoms of COVID-19, (iii) total i.e. either with or without symptoms of COVID-19. • Time to first admission to hospital • Cause-specific hospital admission • Time to death • Days alive and not in hospital • Cause-specific mortality, including COVID-19, stroke, pulmonary embolism, myocardial infarction • Electronic frailty index at 60 days • Ordinal outcome for the most serious event experienced during the 120 days post-randomisation with the following levels: 1. No SARS-CoV-2 infection, 2. SARS-CoV-2 infection but resident remains in care home, 3. Admission to hospital, all-cause, 4. Death, all-cause. Safety • Serious Adverse Reactions (SAR, excluding primary and secondary outcomes) and Suspected Unexpected SARs (SUSARs). • Adverse events relevant to the intervention (see relevant IMP-specific Appendix) Clinical – care home level • Number of SARS-CoV-2 infections in residents in the care home (aggregate data including residents not participating in PROTECT). Economic evaluation • EQ-5D-5L utilities and EQ-VAS at 60 days • Quality Adjusted Life Years (QALY) • Healthcare resource use and costs • Incremental cost-per QALY and Net Monetary Benefit
Statistical methods	All comparative analyses will be based on contemporaneously enrolled care homes. The primary approach to between-group comparative analyses will be by intention-to-treat (i.e. according to randomised allocation regardless of adherence to trial allocation). Cluster-level and resident-level descriptive statistics will be used to illustrate balance between the groups at baseline. Primary comparative analyses will employ a multi-level ordinal logistic regression model with a random effect to account for clustering within care homes. The model will adjust for characteristics used in balancing random allocation between treatment arms and individual-level characteristics of age, sex, and vaccination status.

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Abbreviations and Definitions

Definitions

Term	Description
AE	Adverse Event
AR	Adverse Reaction
CH	Care home
CI	Chief Investigator
COVID-19	Coronavirus-induced disease-19
EQ-VAS	EQ-Visual Analogue Scale
HRQoL (EQ-5D)	Health-related quality of life instrument
ICF	Informed consent form
ISF	Investigator site file
LIS	Legal Representative Information Sheet
MAR	Medication Administration Record
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PEP	Post-exposure prophylaxis
PIS	Participant information sheet
POG	Prophylaxis Oversight Group
PrEP	Pre-exposure prophylaxis
PROBE	Prospective Randomised Open Blinded End-point
PROTECT-CH	PROphylactic ThErapy in Care homes Trial
PSS	Personal Social Services
PSC	Platform Steering Group
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2.
SCR	Summary Care Record
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. Background and Rationale

1.1. Background

In 2019 a novel coronavirus-induced disease (COVID-19) emerged in Wuhan, China. A month later the Chinese Center for Disease Control and Prevention identified a new beta- coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the aetiological agent.1 Subsequently, the disease has spread around the world infecting more than 132 million people and causing more than 2.8 million deaths (https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6). Viral infection may be asymptomatic or present, typically, with fever, fatigue, cough and anosmia. In a minority of people, COVID-19 develops into a serious or fatal disease presenting with viral pneumonitis causing respiratory failure, cerebral infarction causing stroke, pulmonary embolism, or myocardial infarction causing heart failure; these requiring hospitalisations and for some, admission to an intensive care unit for ventilation. The progression of disease from mild symptoms to hospitalisation to death typically takes 2 weeks for each transition. Risk factors for a poor outcome include increasing age, non-white ethnicity and the presence of co-morbidities such as obesity and diabetes. Beyond public health measures to prevent infection (hygiene, masks, personal protective equipment, maintaining distance), we urgently need treatments to minimise these direct and indirect impacts on residents. One treatment, dexamethasone, reduced COVID-19 deaths in hospitalised patients with severe disease and needing oxygen therapy.*[1]* No other interventions are known to alter outcome. Symptomatic disease may be prevented with some (e.g. Pfizer, Moderna and AstraZeneca/University of Oxford) but not all (CSL/University of Queensland) vaccines, and a massive world-wide effort is currently underway to offer vaccination.

The COVID-19 pandemic has had a catastrophic effect in care homes with direct effects through causing illness and death, and indirect impact from policies to reduce viral spread into care homes, e.g. by limiting family visits. Vaccination against SARS-CoV-2 has commenced in care homes but its efficacy in older people with multiple comorbidities and immunosenescence remains poorly defined. Hence, there is an urgent need for additional prophylactic interventions to protect Care Home residents.

1.2. Trial Rationale and Risk/Benefit Assessment

Vaccines are intended to and usually prevent symptomatic COVID-19 disease (and in some cases reduce disease severity), however, vaccines may be less effective in older people with immunosenescence so there is an additional need for effective prevention strategies in Care Home residents, a group who are at high risk of infection and poor outcomes.

The case fatality rate (95% CI) for care home residents with COVID-19 during the first wave of the pandemic in 2020 was 35.7% (31.9-39.7%). Importantly care home residents with no direct evidence of infection of COVID-19, were twice as likely to die if their home experienced an outbreak, than if they lived in a home with no COVID-19.[30]

Coming forward to 2021. The VIVALDI-2 study considered 10,412 residents (median age 86 years) from 310 care homes, 9,160 were vaccinated with either ChAdOx1 (6,138; 67%) or BNT162b2 (3,022; 33%) vaccines. A total of 670,628 person days and 1,335 PCR-positive infections were included. Adjusted hazard ratios (aHRs) for PCR-positive infection relative to unvaccinated residents declined from 28 days following the first vaccine dose to 0·44 (0·24, 0·81) at 28-34 days and 0·38 (0·19, 0·77) at 35-48 days. Similar effect sizes were seen for ChAdOx1 (aHR 0·32 [0·15-0·66] and BNT162b2 (aHR 0·35 [0·17, 0·71]) vaccines at 35-48 days.[29]

Vaccination diminishes the risk of COVID-19 infection for care home residents but does not remove it completely. COVID-19 infection is associated with high mortality for all residents who live in a care home where an outbreak becomes established. If prophylactic therapies can modify the transmission and severity of SARS-CoV-2 infection, then they will be of substantial benefit to residents throughout the care home. Importantly, both agents being considered at present are post-exposure prophylaxis. By the time a resident starts taking one of the study medications, they are at increased risk of dying by virtue of exposure.

1.2.1. Justification for participant population/setting

Residents of Care Homes are at both high risk of contracting SARS-CoV-2 and of developing severe disease and dying. In the UK, approximately one-third of deaths occurring during the first wave of infection (March-June 2020) took place in Care Homes. Despite the vaccination programme care home residents remain vulnerable to contracting SARS-CoV-2 due to underlying co-morbidities and possible immunosenescence.

1.2.1.1 Care Homes

UK care homes are not healthcare settings. Their primary function is to provide social care and accommodation to people who are no longer able to remain at home by virtue of consistent or unpredictable high care needs. 72% of care homes (covering 45% of beds) are care homes without nursing. These have no registered healthcare professionals as part of their core staffing. The remainder of care homes (and beds) are nursing homes – these are characteristically much larger. Care homes have a nurse present on premises 24 hours a day, but the nurse provides a supervisory role, with almost all day-to-day care provided by unregistered Care Assistants. Medical support comes from GPs. GP visits are usually triggered on an ad hoc basis in response to resident needs. The NHS England Enhanced Health in Care Homes initiative has, during 2020, stipulated the need for weekly care home multidisciplinary team meetings. These vary in constitution but are characteristically attended by NHS primary and community care staff, and not care home staff. They are conducted virtually and off premises and usually focus on residents with active issues. In many instances, community teams will discuss residents of multiple care homes in a single sitting.

The safety monitoring infrastructure proposed as part of the study treats care homes as accommodation and social care providers, and not as community hospitals. They are not designed to act as community hospitals. The study is designed to mirror the event reporting approaches that would be deployed for an equivalent community-based study conducted in residents' own homes. Our design makes the most of the round-the-clock supervision provided by care home staff and the existing relationships and referral pathways that enable them to trigger GP visits in the context of a resident becoming unwell. In addition, it provides a route to contact the study team directly to provide an additional mechanism whereby the care home team can seek medical advice in the event of a suspected adverse event.

More details about current healthcare provision in UK care homes can be found in the following publications: references 25-28

1.2.2. Justification for design

The design uses a platform structure that allows multiple treatments to be evaluated simultaneously. Randomisation will use equal probability between all active treatments in a comparison group and a single standard care arm (i.e. allocation ratio 1:1:1:1 if three experimental treatments are in the trial concurrently) and all comparative analyses will be based on

contemporaneously enrolled care homes. To ensure that the platform delivers answers on whether treatments are effective in prevention in a timely manner, the number of active treatments will be limited to three at most at any point. This is to ensure that a sufficient number of care homes can be recruited to the platform as well as limiting the duration required to determine an answer for each intervention. Trials of pre-exposure prophylaxis (PrEP, i.e. before the care home has a case) and post-exposure prophylaxis (PEP, once the care home has a new case to control an outbreak) will be conducted on the platform.

New treatments will be added to the platform by recruiting additional care homes or re-randomising previously enrolled care homes that have completed follow up and provided that the prophylactic effect of the previous treatment is expected to have washed-out (which will be quick for some candidate drugs, but likely up to 6 months for synthetic antibody treatments). These care homes will subsequently be randomised 1:1 between active and standard care using dynamic allocation. When a new potential treatment is to be included in the platform, it will be added immediately provided that no more than two active treatments are already in the platform. If the trial is already investigating three active treatments, then inclusion of a new treatment in the platform will be delayed until the target number of participants have been randomised in one of the current treatment comparisons.

Any platform trial design needs to be adaptable to fit the interventions being tested. This is compounded by specific issues of relevance to care home research, in particular a relative lack of research experience and capacity; a high proportion of participants who lack capacity to consent (up to 76%);[2] delivery, storage and administration of interventions; collection of outcomes by care assistants; and variable care practices and resourcing within care homes. Our platform is designed to account for these:

- Pragmatic adaptive cluster-randomised parallel group platform design. This allows multiple agents to be compared simultaneously, and with new agents added once existing ones have been tested and shown to be beneficial or futile. Treatments may also be tested in combination, if appropriate.
- Cluster randomisation. Cluster designs are particularly relevant to care home trials since they reduce the risk of bias due to contamination,[3] facilitate recruitment and drug management and delivery, and ease identification of serious adverse events. Further, they likely reflect the manner that prophylactic agents will be used in care homes, i.e. for all residents able/willing to take treatment.
- Randomisation of care homes without current infection, and care homes with new outbreaks, as appropriate to the treatment being evaluated, i.e. a mix of pre- and post-exposure prophylaxis.
- The comparator is expected to be standard care. This approach has pros and cons, but we will use a PROBE design in PROTECT-CH (as in the RECOVERY, PRINCIPLE, ATOMIC2, and AVID-CC trials); placebo will be considered on a case-by-case basis depending on the IMP.
- Interventions may vary in what primary outcome is most appropriate, so the platform can accommodate different primary outcomes for different interventions (all outcomes will be recorded in all participants). For the purpose of this platform, we have chosen an ordinal outcome following the WHO recommendation to use ordinal outcomes in COVID-19 trials.[4, 5]

1.2.3. Choice of treatment

To be identified by the NIHR Prophylaxis Oversight Group (POG).

1.2.4. Timing of outcome measures

The key timings for each comparison are:

- End of treatment: 42 days
- Primary outcome based on routine national data: 60 days
- Clinical outcomes based on data from care homes: 60 days
- End of follow-up based on routine national data: 120 days
- End of trial: Once last resident has reached 120 days and data cleaned and analysed.

The explanation for separating the assessment of the primary outcome from end of treatment is that outcomes following acute COVID infection can be delayed. The median (IQR) time from symptom onset to death based upon ONS data is 14 (0-28) days.[6] Hence, assessing the primary outcome at 60 days following randomisation maximises the likelihood that we'll capture most adverse events associated with the infection, this based on a median outbreak duration of 28 days.

There is evidence that some older people with COVID deteriorate as a consequence of deconditioning and loss of physical function following acute infection. These adverse effects are related to physical deconditioning, rather than the direct effect of the virus, but they could be ameliorated by preventative therapies that reduce the likelihood, duration or severity of COVID infection. We have therefore included a 120 day follow-up point using routinely collected NHS data to gather information on how study treatments modify longer-term adverse outcomes as a consequence of COVID-19, e.g. long-COVID.

1.2.5. Sub-studies (if appropriate)

There are currently no planned sub-studies.

2. Aims, Objectives and Outcome Measures

2.1. Aims and Objectives

To set in place a research and governance infrastructure for the efficient delivery of a suite of randomised comparisons to prevent COVID-19 infection and reduce severity/transmission and death in residents in care homes.

2.2. Outcome Measures

Primary endpoint

A four-level ordinal outcome will be used to capture the ability of the drug candidate(s) to prevent/reduce morbidity and mortality from COVID-19 in care home residents, and to reduce transmission in care home settings during the 60 days post-randomisation (or at a relevant time point dependent on intervention – see relevant IMP-specific Appendix for further details). Participants will be classified according to the highest level, that is, the most serious event they experience during the 60-day period (or relevant time point) following randomisation:

1. No SARS-CoV-2 infection.
2. SARS-CoV-2 infection but resident remains in care home.
3. Admission to hospital, all-cause.
4. Death, all-cause. [1, 7, 8] [1, 7, 8]

SARS-CoV-2 status (positive or negative) will be diagnosed using PCR or lateral flow testing (or equivalent) in accordance with the care home's routine testing schedule.

Secondary endpoints (during the 60 days post-randomisation unless stated otherwise)

Clinical

- Healthcare referral for COVID-19, e.g. discussion outside of care home with GP (excluding routine visit), 111, 999 paramedic or Emergency Department assessment, remote hospital consultation.
- Participant receives dexamethasone in the care home for COVID-19
- Participant receives oxygen in the care home for COVID-19
- Time to SARS-CoV-2 infection - positive PCR or lateral flow test (or equivalent)
  - (i) with symptoms of COVID-19
  - (ii) without symptoms of COVID-19,
  - (iii) total i.e. either with or without symptoms of COVID-19.
- Time to first admission to hospital.
- Cause-specific hospital admission
- Time to death
- Days alive and not in hospital
- Cause-specific mortality, including COVID-19, stroke, pulmonary embolism, myocardial infarction.
- Electronic frailty index at 60 days.
- Ordinal outcome for the most serious event experienced during the 120 days post-randomisation with the following levels: 1. No SARS-CoV-2 infection, 2. SARS-CoV-2 infection but resident remains in care home, 3. Admission to hospital, all-cause, 4. Death, all-cause.

Safety

- Serious Adverse Reactions (SAR, excluding primary and secondary outcomes), Suspected Unexpected SARs (SUSARs).
- Adverse events relevant to the intervention (see relevant IMP-specific Appendix)

Clinical – care home level

- Number of SARS-CoV-2 infections in residents in the care home (aggregate data including residents not participating in PROTECT)

Economic evaluation

- EQ-5D-5L utilities and EQ-VAS at 60+/-2 days
- Quality Adjusted Life Years
- Healthcare resource use and costs
- Incremental cost-per QALY and Net Monetary Benefit

3. Trial Design and Setting

3.1. Trial Design

Multi-centre, open-label, parallel-group, superiority, adaptive platform cluster-randomised controlled trial, allowing up to three interventions to be compared simultaneously with standard care. Interventions may be tested in combination in a factorial design, if appropriate.

Two trial designs may be assessed:

- In pre-exposure prophylaxis (PrEP), care homes will be randomised to IMP versus control once residents have consented to the trial.
- In post-exposure prophylaxis (PEP), care homes will only be randomised to IMP versus control once they have an indication of a developing infection, e.g. recent positive PCR or lateral flow test (or equivalent) in a resident or member of staff (index case).

The choice of whether an IMP should be tested as a PrEP or PEP will depend on multiple factors, including the IMP and its route of administration and cost.

3.2. Trial Setting

UK residential and nursing care homes registered for old age and/or dementia. Care homes will be identified from the commercial (including chains and individual homes), charity and council sectors using multiple ascertainment methods including care home registers, social media and email lists, and media promotion of the trial. With more than 18,000 UK care homes (and 430,000 residents), it is likely that there will be more than enough that are willing to join the trial.

The Nottingham Clinical Trials Unit who are coordinating the trial will identify suitable care homes to take part in the trial. Each care home will have a clinical Principal Investigator (PI) assigned either from their Clinical Research Network (England) or equivalent in the devolved nations (Northern Ireland, Scotland, Wales), or identified by a member of the PROTECT-CH research team. Each Principal investigator will be responsible for the research activity and participants within multiple care homes for their assigned region(s) however each regional PI may delegate duties to other PIs (essentially creating a "central team/pool" of PIs) to ensure adequate cover of clinical PI responsibilities at all times during the course of the trial.

During the process of setting-up care homes, GP practices associated with the care of residents within each home will be identified and will be contacted to seek their agreement to take part in the trial. GPs will be required to provide an initial assessment of a participant's eligibility for the treatments being tested so their involvement in the trial is crucial for residents within a care home to take part. Where a GP practice is unable/unwilling to support the trial, any residents under the care of the GP practice will not be able to take part in the trial. GP practices will be required to sign a contract agreeing to their responsibilities in the trial.

Care home staff will be required to complete trial training via a series of web-based training modules (including essential elements of GCP) before carrying out any research activities within their care home. Research Nurses will be delegated duties by the Principal Investigator to support research activity within care homes. Care Home staff will identify residents, assess their capacity to consent, assist with giving out of trial information within the care home and liaise with the Research Nurses to arrange appointments for the Research Nurse team to discuss the trial and obtain informed consent. In addition, care home staff will seek permission from personal legal representatives for collection of their contact details to enable the research team to contact them regarding participation in the trial.

4. Eligibility

4.1. Care Home Eligibility Criteria

Care home inclusion criteria

- Location: UK care homes for older people, with and without nursing
- Size: ≥20 beds in the care home in total.

Care home exclusion criteria
- Care Quality Commission quality: Inadequate, or equivalent in devolved administrations.

Care home criteria at treatment phase
- ***Exclusions:***
- Positive PCR or lateral flow test* (or equivalent) for SARS-CoV-2 in any resident and/or staff within previous 4 weeks. (This does not include the index case for a PEP intervention.)

4.2. Participant Eligibility Criteria

Resident criteria at trial entry
Inclusions
- Resident in a Care Home.
- Age≥65 years
- Able to give informed consent for participation or a personal legal representative has been identified who can give consent, if resident lacks capacity.

Exclusions:
- Identified by care home staff to have entered end-stage palliative care.
- Resident in care home for short-term respite care.
- Resident's general practitioner is unable to support their involvement in the trial.

Resident criteria at treatment phase
Exclusions:
- Currently taking all* of the trial interventions.
- Contraindication to all* trial interventions - see IMP appendix.
- In treatment phase of another COVID-19 prevention or treatment trial

* A resident will be eligible if they can take at least one intervention at the point of randomisation. Residents allocated to an intervention which they are already taking (or another drug in the same class), or to which they have a contraindication, must not be given the trial IMP. Residents in all trial arms will be excluded from all comparisons involving IMPs that were contraindicated or being taken at the time of randomisation, except for a limited number of supplementary analyses based on all residents or all residents who consented to participation.

Following trial consent, two stages of eligibility will be performed:
1. By the resident's General Practitioner (GP) based on their knowledge of the resident and the trial treatment inclusion and exclusion criteria. The eligibility checks will be performed by the GP after initial consent and confirmation will be recorded within the trial database. The GP will also upload the summary care record (SCR) to a secure storage vault. If additional treatments are added to the platform after the initial eligibility has been completed further contact will be made with the GP to ascertain eligibility for the additional treatments.
2. By the Principal Investigators (PIs) or delegate based on the GP's confirmation of eligibility for each potential treatment, review of the summary care record (SCR) sent by the GP at

stage 1, and review of the medication administration record (MAR) sent by the care home immediately prior to randomisation.

5. Consent

Written consent will be collected electronically using the REDCap consent feature or via paper forms if necessary. Consent will be sought from the resident themselves or their nominated personal legal representative and will specifically request consent for the following:

1. For the trial team to obtain routine information about them from national databases.
2. For the trial team to ask the resident's General Practitioner to i) confirm eligibility (stage 1 as above) and ii) upload their SCR to a secure storage vault.
3. For the resident to join the randomised treatment phase of the trial and so take medication if randomised, and have information collected into the trial's electronic case report form.

Informed consent will comprise either:

- Consent by the resident following a discussion about the trial with a Research Nurse. We expect approximately 24% of residents to have capacity.
- Proxy consent by the personal legal representative for residents who lack capacity following a discussion about the trial with a Research Nurse. We expect approximately 76% of residents to lack capacity. Remote discussion and consent with the personal legal representative by video-call is currently accepted practice if the personal legal representative cannot attend the care home. The Research Nurse who explains the trial to the personal legal representative will verify this proxy consent.

Where it is unclear whether the resident has capacity to consent for themselves, a Three Question Test will be used by the care home staff (e.g. the resident is given a statement; the trial is trying to reduce COVID-19 with a medicine that reduces the chance of infection; the resident is only deemed to have capacity if all three bits of information are correctly fed back to the Staff member).[8-10] The resident must be able to Understand, Retain, Weigh the information in order to Decide and then communicate their decision (Mental Capacity Act).

For residents with capacity

Written informed consent for each participant will be obtained prior to performing any trial related procedure; this will be collected electronically using REDCAP or on paper in cases where this cannot be done electronically. Care Home staff will identify residents for participation, assess their capacity to consent, assist with giving out of trial information within the care home and liaise with Research Nurses to arrange appointments for the Research Nurse team to discuss the trial with them and obtain informed consent. The potential participant will be given the opportunity to ask questions throughout the process.

Residents will be provided with written information about the trial. This will be available in several different languages and may include a variety of media formats which can also be used to ensure full comprehension of the trial as part of the initial consent process. Information sheets can be read to the residents and where practical to do so, information about the trial and what taking part will involve may also be given using a video. It is assumed that care homes who have residents where English is not their first language will have adequate translation services in place in order to communicate with their residents .

An informed consent discussion will take place with a member of the PROTECT-CH research team (Research Nurse or Principal Investigator). It is expected that this will be via telephone or video call.

A member of the PROTECT-CH research team delegated the responsibility to take consent (e.g. Principal Investigator or Research Nurse) will ensure that they adequately explain the aim, trial treatment(s), anticipated benefits and potential hazards of taking part in the trial to the resident. They will also stress that participation is voluntary and so the resident is free to decline participation and may withdraw from the trial at any time. The potential participant will be given time to consider the trial information and to discuss their participation with others (i.e. family members if they wish). The resident shall give explicit consent for the regulatory authorities, members of the research team and representatives of the Sponsor to be given direct access to the resident's medical records. Where a paper consent form is used and the resident is unable to make a mark or sign for themselves a witness may do this on their behalf.

The Research Nurse will countersign and date the consent form electronically. Where a paper consent form has been completed, this will be sent to the PROTECT-CH trial team at the NCTU who will upload the form to the trial database. The Research Nurse will be sent a notification to countersign the form electronically. A copy of the fully signed ICF will be made available to the care home, who will print a copy to give to the participant.

A copy of the completed ICF will be filed in the care home records, and where a paper informed consent form is used the original will be retained within the local care home trial site file and a copy uploaded to the trial database.

Once consent has been obtained the resident's GP will receive a notification requesting them to log in to the trial database and complete an initial eligibility assessment. A copy of the participant's informed consent form will be made available to the GP within the trial database. The GP will also be required to upload a copy of the SCR to a secure electronic storage vault. The SCR will be reviewed by the Principal Investigator or delegated investigator prior to randomisation to confirm that the resident is eligible to take part in the treatment phase of the trial.

The resident's decision to participate in the trial or not should be recorded in their care home records. Ideally this will include date of discussion, the name of the trial, summary of discussion, version number of the Participant Information Sheet (PIS) given to participant and a copy of the ICF signed and date consent received (if completed on paper).

Contact details of the research team will be provided to participants/personal legal representatives should they have any questions about their ongoing participation in the trial. Any new information that may be relevant to their continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, they will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the care home notes. Should an additional treatment be added to the platform, information will be provided to the resident and they will be re-consented and eligibility re-confirmed. The participant's right to withdraw from the trial will remain.

For residents who lack capacity

The above process will be followed except that a personal legal representative identified by the care home as responsible for decisions about the resident's care will be asked to give consent on behalf of the resident. Care home staff will seek permission from personal legal representatives for

collection and storage of their contact details to enable the research team to contact them regarding a resident's participation in the trial. Minimal identifying details about the resident will also be collected with their permission to facilitate the consenting process. If a personal legal representative cannot be identified the resident will not be recruited into the trial. A personal Legal Representative Information Sheet (LIS) will be provided to facilitate this process. The legal representative will be given time to read the LIS and to discuss participation with others (i.e. family members, GP or other healthcare professionals outside of the site research team, if they wish). The personal legal representative will give explicit consent for the regulatory authorities, members of the research team and representatives of the Sponsor to be given direct access to the participant's medical records.

Direct contact by the research team/nurse with the personal legal representative will not be made more than twice regarding initial trial participation.

Consent of new residents

Any residents entering a care home prior to randomisation will still be considered for trial participation for PEP but not PrEP interventions. NCTU will maintain regular contact with all participating care homes from the point of initial care home set-up to confirm the continued residence of currently consented participants and any change in number of residents not yet approached about the trial. Any new residents will be approached about trial participation in the same manner as described above.

6. Enrolment and Randomisation

6.1. Enrolment/Registration

We will enrol residents prior to care home randomisation. For equity, we will approach and aim to recruit all residents, but anticipate that we will only enrol a proportion of these because of difficulties in obtaining consent (access to relatives within a limited time, residents/relatives declining participation). We will then allocate care homes dynamically to standard care plus active treatment vs. standard care.

6.2. Randomisation

The unit of randomisation is the care home (cluster). The allocation for a particular care home will only be revealed following the screening of residents for eligibility, gaining informed consent and collection of baseline data. The randomisation programme will allocate care homes 1:1 to each available treatment arm or standard care arm.

Care homes will be randomised via a secure password-protected website created and maintained by Nottingham Clinical Trials Unit. The dynamic randomisation will use a probabilistic minimisation algorithm to ensure balance across:

- Care home type (residential vs nursing vs nursing and residential)
- Prior COVID-19 in care home at any time (yes vs no)
- Size of Care Home - Total number of residents in care home (small ($\leq$30 residents), medium (>30, $\leq$50 residents), large (>50 residents))
- Care home has capacity to give oxygen and/or dexamethasone (yes vs no)

The NCTU will confirm that all checks required for "green light" of a care home for randomisation have been completed. Randomisation will then be carried out by the PI (or delegated investigator) using a remote, internet-based randomisation system to obtain the treatment allocation for each care home after confirmation of care home participation, and consent and eligibility checks for the residents.

For trials of PrEP the care home will be randomised once an IMP has been identified by the NIHR POG and the necessary processes have been implemented.

For trials of PEP the care home will be randomised once an IMP has been identified by the NIHR POG and the necessary processes have been implemented and a resident or member of staff in the care home has tested positive for SARS-CoV-2 (PCR or lateral flow test, or equivalent).

6.3. Blinding and concealment

Care home residents and staff will not be blinded to treatment allocation. Dynamic randomisation of care homes using a minimisation algorithm and release of allocation only following enrolment, resident consent and baseline data collection, will ensure allocation concealment.

7. Trial treatment / intervention

7.1. Treatment

For information on modes of administration, dosing regimens, duration of treatment of the trial IMPs see IMP appendices.

Trial IMPs will be sourced directly from the manufacturer(s) and stored at a central pharmacy. Each IMP manufacturer will provide the required regulatory documentation e.g. Investigational Medicinal Product Dossier, Investigator's Brochure as detailed in the relevant IMP appendix.

Following resident/personal legal representative consent and eligibility checks by the resident's GP and the PI (or delegated investigator) will prescribe the allocated IMP for each consented and eligible resident in care homes randomised to an IMP arm of the trial. The central pharmacy will receive the prescriptions and dispense the required IMP labelled with the individual resident's details. IMP will then be shipped from the central pharmacy by an accredited distributer to a responsible person at the care home. The resident's GP will be informed that the care home has been randomised and their patient has entered the treatment phase of the trial. They will be provided with information on the resident's allocated IMP.

8. Trial procedures and assessments.

8.1. Summary of assessments

Figure 1 – Summary of assessments

	Pre-randomisation	Baseline (randomisation*)	Post-randomisation			
TIMEPOINT (days)	**<Day 0**	**Day 0**	**t1**	**EoT (t+42)**	**60 ****	**120 Ω**
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Care Home Randomisation		X*				
INTERVENTIONS:						
IMP + standard care			←	→		
Standard Care			←	—	—	→
ASSESSMENTS:						
Demographics, medical history	X					
Outcome Events (care-home reported)			←	—	→	
Primary ordinal outcome components†					X	X
SAE/SAR/SUSAR			←	→		
QoL (EQ-5D-5L, EQ-VAS)	X				X	
Resource use					X	

t1: Day 1 of trial treatment, EoT: end of trial treatment, EQ-5D-5L: Euro-Quality of Life-5 dimension-5 level; EQ-VAS: Euro-Quality of Life-visual analogue scale; SAR: serious adverse reaction, SUSAR: Suspected unexpected S

* For PrEP: care home will be randomised once an IMP has been identified by the NIHR POG and care homes are given the green light for randomisation. For PEP: care homes will be randomised once they have an indication of a developing infection e.g. recent positive PCR or lateral flow test (or equivalent) in a resident or member of staff (index case).

** Primary ordinal outcome components and resource use cover the period from Day 0 to Day 60 and will be requested to complete data entry within 7 days of the day 60 timepoint by care home staff. Quality of life questionnaires will be completed at Day 60+/-2 and in accordance with the trial data management plan.

† Primary (ordinal) outcome: no infection / infection (asymptomatic or symptomatic) but remains in home / admission to hospital all-causes / all-cause mortality. Ascertainment of the primary outcome measure will be performed centrally using UK death, hospitalisation and COVID-19 registers. Central and care home derived data will then be cross-checked.

Ω follow-up beyond 60 days to 120 days based on routinely collected health data only.

8.2. Schedule of Assessments

Pre-Randomisation

- Eligibility screen
- Informed consent
- Demographics and medical history
- Quality of Life: EQ-5D-5L; EQ-VAS
- Number of residents in care home

For PEP only - At point of outbreak (care home level)

- Source of infection of SARS-CoV-2(resident, staff), date and type of test (lateral flow, PCR or equivalent).

Day 0 (randomisation)

- Number of residents in care home.

Days 1-EoT

- Administration of intervention if randomised to trial treatment (according to duration specified in IMP appendix).
- Safety: targeted adverse events and serious adverse events (including SARs)

Days 1–60

- Components of primary outcome.

Day 60(+/-2)

- QoL: EQ-5D-5L; EQ-VAS
- Healthcare resource use

Day 60 Care home level

- Number of residents in care home (whether in trial or not) who became SARS-CoV-2 positive
- Number of residents in care home.

Days 1-120 (based on routinely collected health data only after 60 days)

- Outcome: no infection; SARS-CoV-2 infection and stayed in care home; admission to hospital; died (most serious event experienced during the 120 days post-randomisation)

8.3. Trial Procedures

Care home staff involved in the trial will be trained in the aspects of Good Clinical Practice relevant to their role in the trial and in trial-specific procedures including delivering trial assessments (e.g. EQ-5D, EQ-VAS), recording participant information, and assisting participants to take the IMP (where relevant).

8.3.1. Sub studies

There are no planned sub-studies.

8.4. Discontinuation of trial intervention/trial status

At the discretion of the participant (or clinician/GP/personal legal representative), aspects of trial participation may be discontinued/adjusted for example:

- Discontinue IMP but continue follow-up in accordance with the trial schedule and continue to provide trial data and allow routinely collected health data to be obtained for use in the analysis.
- Discontinue IMP and trial data provision but allow routinely collected health data to be provided for inclusion in the trial analysis.
- Discontinue from participation in trial interview if optional consent was given (See section 12.4).
- Participants may also choose to withdraw (or be withdrawn by clinician or personal legal representative) from trial intervention and all subsequent data collection.‡

Participants will be withdrawn from treatment at the wishes of the resident or personal legal representative, or at the discretion of the care home manager, principal investigator, general practitioner or chief investigator if continuation in the trial is deemed to be against the participant's best interest.
Treatment will be stopped if:

- Participant is hospitalised for COVID-19. (Treatment may be restarted if the participant returns to the care home within the treatment period.)**
- Participant experiences unacceptable drug reaction as specified in the IMPD appendices.

Participants who have been withdrawn from the trial treatment and are experiencing ongoing toxicity will be followed up until the adverse reaction concludes. In the event of a Participant being withdrawn from the trial treatment, they will continue to receive the most appropriate standard of care treatment available under the guidance of their general practitioner or other treating clinician.

‡NB data collected prior to withdrawal will not be deleted and will be included in analyses. Routinely collected health data will still be obtained for use in the analysis unless the participant (or personal legal representative) explicitly states otherwise.

**IMP should not be sent with the resident if they are admitted to hospital, i.e. the IMP should not be administered in hospital. If the resident returns to the care home before the end of the treatment period, then it should be restarted and continued up to the original planned stop date.

9. Adverse Event Reporting

It is expected that participants in the trial will have a range of underlying co-morbidities and so infection with SARS-CoV-2 may lead to serious and significantly life-threatening conditions, which are outcomes for this trial. Safety reporting in the trial will therefore focus only on those events that could be related to the trial medication, are serious in nature (according to the SAE definition below) and are unexpected (either the event itself or in severity) according to the reference safety information (RSI) for the IMP. Further information regarding the RSI can be found in the appendix for each IMP. Once an intervention has been identified by the NIHR Prophylaxis Oversight Group, the risk profile of the IMP will determine any further safety reporting requirements beyond those described below. These will be detailed within the IMP appendix.

The known or anticipated side effects of the IMPs are listed in the IMP appendices. Side effects will be apparent to residents with capacity and to care home staff. In particular, care home staff know their residents and their medical problems intimately and so can see deterioration very early; indeed side effects are likely to be identified earlier and potentially more frequently than they would be in people living in their own home. We will train care home staff to look for side effects through training at the site initiation visit and in videos available for download via the trial website. If side effects are apparent, care home staff may inform the resident's GP. All side effects will be entered into the trial database on a weekly basis by care home staff. Serious adverse events, hospitalisation and death will all be reported in real time via the trial database for review by the relevant principal investigator, for independent review by the medical adjudicator and Data Monitoring Committee, and for forwarding to the competent authority within the standard reporting periods relevant to SAEs, SARs and SUSARs.

A serious adverse event that is not expected against the RSI and considered to be related or suspected to be related to the IMP is classed as a Suspected Unexpected Serious Adverse Reaction (SUSAR) and requires expedited reporting as per the clinical trials regulations.

9.1. Adverse events

Adverse events are common in this population due to the range of underlying comorbidities, therefore events that are deemed expected for this population (see section 9.2.1) will not be reported. Care home staff will report pre-specified adverse events (based on treatments under investigation for any given comparison group within the platform – further details are specified within the relevant IMP appendices) for all residents directly via the eCRF

9.2. Serious adverse events

Care home staff directly involved in the care of participants will report all events that meet the definition of an SAE, other than those events excluded from reporting (listed in section 9.2.1). An SAE is defined as an AE that meets any of the below criteria:

1. results in death;
2. is life-threatening;
3. requires hospitalisation or prolongation of existing hospitalisation;
4. results in persistent or significant disability or incapacity; and
5. consists of a congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

9.2.1. Events that do not require reporting

The following events are frequent in care homes and will not be reported as AEs or SAEs:

- Agitation
- Allergic reaction (not related to trial medication)
- Anorexia, loss of appetite
- Bowel obstruction
- Bruising, ecchymoses
- Confusion
- COVID-19 (part of the primary outcome)
- Delirium
- Dehydration
- Diarrhoea, with/without norovirus/Clostridium difficile
- Fall with injury, with/without fracture
- Heart failure, volume overload
- Hypoglycaemia
- Hypotension
- Incontinence (urinary, bowel)
- Medication (non-trial) error
- Nursing care, missed
- Pressure ulcer
- Respiratory distress/failure (non-COVID-19)
- Respiratory infection (non-COVID-19)
- Sepsis, bacteraemia
- Skin tear, abrasion, breakdown
- Suicide, attempted suicide, self-harm
- Surgical/procedural site infection
- Urinary tract infection, with/without catheter
- Venous thromboembolism
- Vomiting, with/without norovirus
- Any event listed in the IMP appendices

Similarly, diagnoses present at baseline (including any worsening of that condition) and known co-morbidities will not be reported. Known side effects for the intervention(s) will be listed in the relevant IMP appendix.

If any of the above lead to hospitalisation or death, then they will comprise part of the primary outcome.

9.3. Reporting period

As a minimum, SAEs will be documented and reported in accordance with the procedures described above from the date of first administration of IMP until the end of the IMP treatment period. Any collection of SAEs beyond the treatment period will be specific to the intervention under investigation and the rationale for this will be described within the specific IMP appendix of the protocol. SUSARs must still be reported in an expedited manner irrespective of how long after administration the reaction occurred.

9.4. Reporting procedure

9.4.1. Adverse events

Specified adverse events will be reported directly into the eCRF for all participants, including those randomised to receive standard care. The data monitoring committee will review reported adverse events across all arms of the trial on a regular basis to monitor for any safety signals. Care home staff will be trained to report any adverse events that meet the criteria for a SAE and which are not excluded from requiring reporting via the SAE reporting process outlined in section 9.4.2.

9.4.2. Serious adverse events

SAEs will be entered into a trial SAE form within the eCRF by a member of care home staff or GP directly responsible for the care of the participant. The person completing the report will include sufficient details of the event to facilitate the assessment of relatedness by a member of the national team of medically qualified Principal Investigators. Should a participant's general practitioner become aware of an SAE during the reporting period, they may report the event via the same process. A Principal Investigator will review the information in the SAE report and will liaise with the reporting care home or GP to obtain further information where necessary.

On receipt of an SAE, seriousness and causality will be determined independently by the PI. An SAE judged by the PI to have a reasonable causal relationship with the trial treatment will be regarded as a SAR. The PI will also assess all SARs for expectedness against the Reference Safety Information for the IMP. If the serious event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected SAR (SUSAR). Expedited reporting for SUSARs will be carried out as detailed in section 9.5.2.

9.4.3. Provision of follow-up information

Only SARs will be followed-up to resolution.

9.5. Expedited reporting

9.5.1. Reference safety information (RSI)

RSI is a list of medical events that defines which events are expected for the IMP within a given trial and thus determining which SARs require expedited reporting.

For the purpose of this trial, the Reference Safety Information is referred to in the IMP appendices.

9.5.2. Suspected Unexpected Serious Adverse Reactions (SUSARs)

The PI will report events categorised as a SUSAR immediately to the Sponsor.

For fatal or life-threatening SUSARs, the Sponsor will ensure expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) within 7 days. Any additional relevant information will be provided within an additional 8 days of the report.

For non-fatal or non-life-threatening SUSARs, the Sponsor will ensure expedited reporting as soon as possible but no later than 15 days.

9.5.3. Adverse events

The Sponsor, MHRA and REC will be notified immediately if a significant safety issue is identified by the DMC during the course of the trial.

9.5.4. Investigators

Details of all SUSARs and any other safety issue which arises during the trial will be reported to Principal Investigators, GPs and care homes.

9.6. Data Monitoring Committee (DMC)

The independent DMC will act in accordance with the DMC charter. The DMC will review safety data captured through the reporting of adverse reactions at regular intervals throughout the trial, in addition to reported SAEs in order to monitor for any safety signals.

9.7. Adjudication of SAEs

A team of blinded independent adjudicators will carry out a consistency review on reported events to ensure accurate and complete reporting. Adjudicators will communicate directly with PIs where any inconsistencies are identified.

10. Data Handling and Record Keeping

10.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the participant, source data will be accessible and maintained.

Data will be collected either directly from the participant or care home staff and uploaded onto a secure database. Source documents shall be filed at the care home and may include but are not limited to, current medical records, laboratory results and records. An eCRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the relevant regulatory authorities permitted to have access.

10.2. CRF Completion

Data reported on each electronic Case Report Form will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete eCRFs will be trained to adhere to relevant aspects of GCP associated with data entry.

10.3. Data Management

Arrangements for data handling will be specified in the DMP. This will include the agreed validation specification which will validate data for consistency and integrity as it is entered. Additional manual

and electronic reviews may also be conducted, and data queries / clarifications may arise from such reviews.

Data will be held on secure servers. These servers are located within The University of Nottingham data centres, which are managed and monitored 24/7. Security is both physical (secure limited access) and electronic (behind firewalls, access via user accounts (username and password) on encrypted connections,
restricted access – e.g. care home users only have access to their care home's data, and by user type/role). All access and data transactions will be logged in a full audit trail.

Data collected using the eCRF will be transferred from the University of Nottingham to the Trusted Research Environment (TRE) at the University of Dundee's Health Informatics Centre, where it will be linked with participant data from routine sources (GP data, SARS-CoV-2 testing data, hospital data, mortality statistics). Linked data in the TRE will be processed by data manager(s) at the University of Nottingham, via secure remote access, in preparation for analyses. MAR sheets from care homes and Summary Care Records (SCRs) from GPs will be uploaded to the PROTECT-CH secure vault. The PROTECT-CH vault is a secure encrypted data store, separate to the trial database. The secure vault will be accessed by the Principal Investigators (PIs) to check participant eligibility.

10.4. Archiving

In compliance with the ICH:GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator and care home manager will maintain all records and documents regarding the conduct of the trial. These will be retained for at least 7 years or for longer if required. Participants' medical files should be retained in accordance with applicable legislation and in accordance with the maximum period permitted by the hospital, institution or private practice. Research data sets for analyses will be retained indefinitely.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes. No documents shall be destroyed until the minimum retention period has passed and the Sponsor has agreed to the destruction.

10.5. Site Set-up and Initiation

All participating care home managers and Principal Investigators will be asked to sign trial agreements. All members of care home staff facilitating the trial will also be required to sign a trial delegation log. Prior to commencing recruitment all sites will undergo a process of initiation and will have completed essential GCP and trial training. The NCTU must be informed immediately of any change in the care home research team.

11. Quality Control and Quality Assurance

11.1. Monitoring

11.1.1. On-site Monitoring

It is not anticipated that there will be any on site monitoring unless triggered by central monitoring checks and it is feasible to conduct these.

11.1.2. Central Monitoring

The NCTU will be in regular contact with the care homes to check on progress and address any queries that they may have. The trial team will check incoming consent forms, Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Care homes will be asked for missing data or clarification of inconsistencies or discrepancies.

11.1.3. Protocol violations

Treatment compliance will be recorded within the REDCap database. Protocol non-compliance outside those recorded in the eCRF will be recorded and reported on a violation form within the database. All instances of non-compliance reported on the violation form will be reviewed by NCTU and where believed to constitute a protocol violation or a potential serious breach will be further investigated. Violations and serious breaches will be investigated as per the appropriate NCTU SOPs and escalated where necessary to the Sponsor and REC/MHRA.

The following will be considered protocol violations and will lead to retraining of the relevant care home:

- Treatment without consent
- Treatment but ineligible
- Non-reporting of primary outcome measures
- Non-reporting of serious adverse events

11.2. Audit and Inspection

The Principal Investigators and care home managers will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator and care home managers will comply with these visits and any required follow up.

12. End of Trial Definition

The key timings for each comparison are:

- End of treatment: 42 days
- Primary outcome based on routine national data: 60 days
- Clinical outcomes based on data from care homes: 60 days
- End of follow-up based on routine national data: 120 days
- End of trial: Once last resident has reached 120 days and data cleaned and analysed.

The end of the scheduled treatment phase is defined as the date of the last follow-up visit of the last participant. The end of individual comparisons within the platform will be the date of the final data extraction from NHS Digital. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, the NCTU will inform the MHRA and REC within 15 days of the end of trial. The NCTU will provide them with a summary of the clinical trial report within 12 months of the end of trial.

13. Statistical Considerations

13.1. Power Calculations / sample size calculation

A total of 530 residents per group are required to detect an odds ratio of 0.67 for a 4-level ordinal primary outcome (no infection proportion 60%, infection remain in CH 15%, admission to hospital all causes 10%, all-cause mortality 15%), assuming a two-sided significance level of 5% and 90% statistical power, with no adjustment for clustering.[12]

Care homes of varying size will be included, and the number of residents recruited per care home will likely be in the range 20–60. Assuming an intra-cluster correlation of 0.11, a coefficient of variation for care home size of 0.49 (Lothian population analysis in 189 care homes [13]) and an average of 32 residents per care home in the trial (assuming that the average number of beds per care home is 40 [Competition and Markets Authority. Care Homes Market Study. London: 2017] and that not all residents will take part in the trial), this gives rise to a design effect or inflation factor of 5.25.[14]

Therefore, to compare a single active treatment versus standard care, we will need in the region of 174 care homes i.e. in excess of 5,500 residents. Allowing for the uncertainty surrounding the parameters listed above (e.g. levels of mortality and transmission rates are expected to be different in the second wave due to improved preparedness, better treatments and the potential impact of the expected vaccination programme, therefore it is possible that the observed proportions in the Standard Care group may differ), we propose a sample size of 200 care homes and a total number of residents in the region of 6,400 per comparison, with sample size re-estimation during the trial (once 60-day outcome data are available for at least 75% of residents randomised to standard care).

Therefore, comparing three active (unrelated) treatments versus standard care (in a 1:1:1:1 allocation ratio) would require 400 care homes in total, corresponding to around 13,000 residents.

13.2. Analysis of Outcome Measures

Statistical analyses

The analysis and reporting of the trial will be in accordance with CONSORT guidelines for adaptive and cluster designs [14, 15] with the primary comparative analyses being conducted according to randomised allocation with due emphasis on confidence intervals for between-arm comparisons. All comparative analyses will be based on contemporaneously randomised care homes. A full statistical analysis plan will be developed and agreed with the Platform Steering Committee (PSC) prior to the first release of treatment allocations for final pairwise comparison. The primary approach to between-group comparative analyses will be by intention-to-treat (i.e. according to randomised allocation regardless of adherence to trial allocation). Cluster-level and resident-level descriptive statistics will be used to illustrate balance between the groups at baseline.

Primary comparative analyses will employ a multi-level ordinal logistic regression model including all residents eligible for the intervention of interest prior to care home randomisation. The model will adjust for the minimisation factors, plus the individual-level covariates age, sex and vaccination status. A random effect to adjust for clustering within care homes will be used. The treatment comparison will be presented as an adjusted common odds ratio for a shift in the direction of a better outcome on the ordinal scale together with 95% confidence intervals.[16-19]

Secondary outcomes will be analysed using appropriate regression models dependent on data type (binary, categorical, continuous, time to event etc.), adjusted similarly and accounting for clustering within care homes.

13.3. Economic evaluation

[21-23] [24] [25]A cost-utility analysis will be conducted from an NHS and Personal Social Services (PSS) perspective, based on within-trial data collection from routine sources, or eCRF where not possible. Resource use data will be gathered on primary care (including GP and nurse contacts) and secondary healthcare usage (including A&E attendance, hospital admission and critical care hospital stay) and 111(119)/999 services. Unit costs will be applied based on national sources to increase generalisability (https://www.england.nhs.uk/national-cost-collection/ ; https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/).

Health related quality of life questionnaires (EQ-5D-5L) will be completed at baseline and follow-up both by self-report, where a resident has capacity to complete the questionnaire, and by proxy, with response patterns explored and reporting subgroups (self-report vs proxy) examined in sensitivity analysis [18-20]. The UK crosswalk tariff [21] will be used to derive utility scores from responses and combined with survival data using the area under the curve approach to compute quality adjusted life years (QALYs).

Group mean costs (including prophylaxis acquisition and administration costs), utilities and QALYs will be analysed in line with other outcomes, using linear mixed effects models to take account of clustering and key baseline prognostic factors, with QALYs adjusted for baseline EQ-5D utility scores [22] and presented with associated 95% confidence intervals. Cost-effectiveness will be expressed as Incremental Cost Effectiveness Ratios and Incremental Net Monetary Benefit at various cost-effectiveness thresholds, accompanied by cost-effectiveness acceptability curves, produced using non-parametric bootstrapping techniques that take account of clustering. If between arm differences in costs and QALYs are observed at 60 days post randomisation, parametric modelling will be conducted to perform simple extrapolations of costs and QALYs to incorporate a lifetime horizon. A Health Economic Analysis Plan (HEAP) will be produced to present planned analyses in more detail.

13.4. Process evaluation

Alongside the trial we will undertake a concurrent process evaluation in order to:

- provide contextualised insight into the delivery of the intervention(s);
- consider acceptability of the intervention to staff, residents, and their families; and,
- reflect upon and inform trial processes.

All care homes will be invited to indicate a willingness (or otherwise) to participate in this concurrent process evaluation at recruitment. We will purposively select 10-20 settings to participate taking account of: size of care home, home ownership, the presence of nursing staff, proportions of residents living with dementia, and prior experience of COVID-19 (deaths/hospitalisations). These may be refined or added to as we test our programme theories and develop insight about contextual factors which influence delivery of the intervention and/or research processes. In each setting we will seek to include care home management, care home staff, and care home residents (and their families). Where appropriate we will include external care home management and health care providers who are involved in delivery of the prophylactic intervention.

Care home records and trial data will be reviewed to assess fidelity with the planned delivery of the prophylactic intervention. We will record the number of staff delivering the intervention, the number of residents who received it.

Interviews with care home and healthcare professionals will consider: their experience of delivering the intervention(s); their views on the appropriateness of the intervention(s) in care homes; their views on research in this setting; and, their views on the PROTECT-CH research processes. Interviews with residents (and their families where possible) will consider: their experience of the intervention(s); their view on the appropriateness of the intervention(s); and, their views on the appropriateness of researching this topic. Individuals will be contacted who have expressed an interest in taking part in an interview via the Trial Consent and interviews will take place with prior verbal consent.

All interviews will be undertaken remotely, either via telephone or video conferencing software such as Microsoft Teams, and recorded using an appropriate digital mechanism. Interview data will be transcribed in full, anonymised and handled using the NVivo software package.

The focus of analysis in realist evaluation is the iterative development of the initial programme theories. This is done through the conceptual lens of Context-Mechanism-Outcome configurations, which map evidenced experiences of delivering the prophylactic intervention(s) and/or the research processes. In this process evaluation we will consider context and outcome as 'measurable', with the mechanism ascribed the causal power to explain why/how specific outcomes emerged in a particular context.

We will develop a generalizable programme theory which will explain how trial processes influenced outcomes and which will also support implementation of the intervention if the trial is positive.

13.5. Planned Interim Analysis

There will be no planned interim statistical analysis (unless a safety concern is raised by the DMC e.g. based on external evidence) in view of the short-anticipated treatment phases.

13.6. Planned Primary Analyses

The primary analysis for each intervention will be performed once all residents in the active treatment and corresponding standard care arms have reached 60 days (or appropriate time point as detailed in the IMP appendix) of follow-up and have outcome data available from both the care home (via the trial database) and the central data repository.

13.7. Planned Subgroup Analyses

Subgroup analyses will be conducted for the ordinal primary outcome and for all-cause mortality for the following factors for each separate pairwise comparison:

(i) type of care home (residential vs residential/nursing vs nursing);

(ii) previous COVID-19 cases in the care home (yes vs no)

(iii) care home size: small (≤30 residents) vs medium (>30, ≤50 residents) vs large (>50 residents)

(iv) Care home has capacity to give oxygen and/or dexamethasone (yes vs no)

(v) age group (<80 vs 80–89 vs ≥90 years old)

(vi) sex (female vs male)

(vii) vaccination status (none vs partial vs full)

14. Trial Organisational Structure

14.1. Sponsor

Ms Angela Shone for The University of Nottingham.

14.2. Trials Unit

Nottingham Clinical Trials Unit (NCTU) at The University of Nottingham.

14.3. Platform Management Group

The Platform Management Group (PMG) will comprise the Chief Investigator, Deputy Chief Investigator, NCTU Director, Senior Trial Manager(s), Statistician and Data Manager, or their deputies.

The role of the PMG is to ensure high quality trial conduct, to manage and administer the comparisons under investigation (site liaison, manufacturer liaison, staffing, finances) to time and within budget, to monitor all aspects of the conduct and progress of the evaluations, ensure that the master protocol is adhered to and take appropriate action to safeguard participants and the quality of the platform itself. They will meet weekly-monthly as necessary.

14.4. Platform Steering Committee

The role of the Platform Steering Committee (PSC) is to maintain oversight of the trial. The PSC will include members who are independent of the Investigators, their employing organisations, funders and Sponsor. Its terms of reference will be agreed within a PSC charter which will outline its roles and responsibilities. As funder, NIHR may send an observer to monitor proceedings. Meetings of the PSC will take place at least once a year when there are randomised comparisons open to recruitment.

The PSC will monitor and supervise the progress of the trial towards its interim and overall objectives. The PSC will consider and act upon, as appropriate, the recommendations of the Data Monitoring Committee (DMC) or equivalent. The Sponsor and PSC ultimately carry the responsibility for deciding whether a trial needs to be modified or stopped on grounds of safety or efficacy and informing the funding body on the progress of the trial.

14.5. Data Monitoring Committee

Interim analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further

participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Platform Steering Committee (PSC) who will convey the findings to the Sponsor.

14.6. Finance

This trial is funded by the National Institute of Health Research, NIHR133443.

14.7. Role of Principal Investigators (PIs)

A UK-wide pool of Principal Investigators will assess eligibility, prescribe IMP, and oversee safety reporting:

- PIs will be contracted within the trial, be provided log-in access to the trial database and receive recompense for time spent on the trial.
- PIs will confirm stage 2 eligibility through review of: i) the GP's stage 1 eligibility data; ii) the resident's summary care record as provided by the GP at stage 1 eligibility; iii) the resident's medication administration record (MAR) as sent by the care home immediately prior to randomisation.
- Once the eligibility of all residents at that care home has been confirmed, the PI will randomise the care home to IMP or standard care using the trial database system.
- If the care home is randomised to IMP, the PI will confirm that no resident has a specific exclusion to that IMP in which case that resident will not be included in the treatment phase of the trial.
- The PI will then prescribe the IMP. Prescriptions will be sent to the central pharmacy for processing and IMP. A trial-specific medication administration record (MAR) will be provided to the care home.
- PIs will review SAEs and assess relatedness.
- If the PI is informed by a care home about a potential SAE, they will ensure that the care home submits this using the trial database reporting system.
- PIs will work regionally with their care homes but nationally for prescribing.

14.8. Role of General Practitioners (GPs)

Each consenting resident will have their GP supporting the trial:

- GPs will be contracted with the trial, be provided log-in access to the trial database and receive recompense for time spent on the trial.
- GPs will confirm stage 1 eligibility (section 4.2) and share the summary care record with the trial database.
- GPs will report Serious Adverse Events if they are involved with the management of these in the care home.
- If the GP is unable to support the trial, then none of the residents that fall under their care will be eligible to join the trial.

14.9. Role of Event Adjudicators (EAs)

The trial will be supported by a number of registered doctors to assess outcome and adverse events:

- EAs will be contracted with the trial, be provided log-in access to the trial database and receive recompense for time spent on the trial.
- EAs will review outcome events and SAEs using the trial database system in the order that events are reported.
- EAs will ask trial managers to liaise with care homes for more information about events if insufficient information has been provided.
- EAs will confirm whether events are: i) part of the primary outcome (death, hospitalisation, SARS-CoV-2 positivity); ii) a suspected unexpected serious adverse reaction (SUSAR, i.e. not an outcome or expected event listed in the protocol or its appendices); iii) a serious adverse reaction (SAR); iv) a serious adverse event (SAE); v) a targeted adverse reaction (as listed in the protocol and its appendices); or vi) none of these.
- EAs may not downgrade SUSARs unless the source (care home, PI or GP) confirms that the event was submitted in error. EAs will report SAEs as a SAR if they consider it to be definitely or probably related to IMP. EAs may downgrade SAEs if they consider the event does not fulfil the definition of a SAE.

14.10. Role of Research Nurses (RNs)

Each care home will have a regionally-based Research Nurse who will support the care home throughout the trial:

- RNs will be contracted with the trial, be provided log-in access to the trial database and receive recompense for time spent on the trial.
- RNs will approach residents, or their personal legal representative if the resident lacks capacity, to inform them about the trial and obtain consent.

15. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, and its amendments (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2017, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004) and subsequent amendments and the Data Protection Act 2018 and Guidelines for Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the REC prior to circulation.

16. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018. Participants will always be identified using only their unique trial identification number on the Case Report Form and correspondence between the NCTU and the participating care home. Participants will give their explicit consent for the movement of their consent form electronically, giving permission for NCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

Care homes and trial doctors (PIs or delegates) must maintain trial related documents (e.g. source documents) not meant for submission to NCTU in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, if participant confidentiality is protected. if participant confidentiality is protected.

The University of Nottingham will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party where consent has not been gained for this disclosure. The research team, Sponsor and regulatory authorities may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will always be respected.

17. Insurance and Indemnity

The University of Nottingham will act as Sponsor for the trial. Delegated responsibilities will be assigned to NCTU. Insurance and indemnity for NHS trial staff is covered by the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96) 48, (England and Wales), the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS) (Scotland) or the clinical negligence scheme for GPs (CNSGP). Care Homes are expected to hold appropriate insurance policies to indemnify themselves for losses incurred in the event of a litigious claim against them for their acts or errors of omission or neglect. There are no special compensation arrangements, but trial participants may have recourse to the NHS complaints procedure.

The University of Nottingham has appropriate and typical insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, Employer's Liability and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity.

The University of Nottingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

18. Dissemination Plan

Dissemination of findings will include regular newsletter updates to care home staff and residents, Sponsor hosted events, community meetings, peer-reviewed publications and presentations at academic conferences.

The results of the principal comparisons will be reported first to the trial collaborators. The main reports will be drafted by members of the PROTECT-CH writing committee, and the final version will be agreed by the PSC before submission for publication, on behalf of the collaboration. The trial will be reported in accordance with the relevant Consolidated Standards of Reporting Trials (CONSORT) guidelines. Findings will be disseminated through publication in academic journals and presentations at academic conferences. Results of the trial will be made available via the trial website and results newsletters to care homes for dissemination to participants and/or personal legal representatives as applicable. Oral/poster presentations and workshops at sponsor hosted events, community meetings and professional/stake holder/user conferences will be targeted. The results of the trial will be disseminated regardless of the direction of effect.

The trial team will seek to disseminate in a way to support best practice. They will liaise with the Enabling Research in Care Homes (EnRICH) network to identify potential research users, other

researchers, policy makers, commissioners, clinicians, care home managers and staff, care home residents and relatives. Dissemination outputs will be tailored towards each group including peer reviewed journal articles, evidence summaries, briefing papers and video clips. Media coverage will be sought in the form of local newspapers, television and radio outlets and social media. This will be enabled further via connecting with the university's specialist experts in information technology and communication departments. Requests will be sent to relevant agencies to feature the research project in their newsletters and websites.

19. Publication Policy

Primary responsibility for preparing all main outputs (including pre-prints, press releases and journal articles) for publication will lie with the CI. Results of this each pairwise comparison will be submitted for publication in a peer reviewed journal. A writing committee drawn from the co-investigators (trial grant holders), trial managers and others substantially involved in execution, analysis and interpretation will be named authors on the principal publications arising from the trial provided they meet the authorship criteria used by most high impact peer-reviewed journals (see http://www.icmje.org).

Principal Investigators will be named formally as collaborators on the main publications; other trial personnel with significant input to the running of the trial will be named in the Acknowledgements in publications. The Chief Investigator will nominate and agree appropriate authorship on all publications prior to commencement of writing.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the writing committee. Secondary publications must always follow the primary publication for each comparison chronologically.

Authors must acknowledge that the platform was performed with funding from the NIHR (standard citation) and the support of The University of Nottingham Sponsor. Individual participant data will be shared with the Virtual International care homes Trials Archive held in Glasgow (Robertson Institute).

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