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Research Article

Lessons from the PROTECT-CH COVID-19 platform trial in care homes

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Abstract

Background: Coronavirus disease-2019 was associated with significant mortality and morbidity in care homes in 2020–1. Repurposed antiviral drugs might reduce morbidity and mortality through reducing viral transmission, infection, replication and inflammation. We aimed to compare the safety and efficacy of potential antiviral drugs in care home residents.

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Methods: We designed a cluster-randomised, open-label, blinded end-point platform trial to test drugs in a postexposure prophylaxis paradigm. Participants aged 65+ years from United Kingdom care homes, with or without nursing, were eligible for participation. Care homes were to be allocated at random by computer to administer 42 days of antiviral agent (ciclesonide or niclosamide) plus standard care versus standard care alone to residents. The primary outcome at 60 days after randomisation comprised the most serious outcome, which was defined as all-cause mortality, all-cause hospitalisation, severe acute respiratory syndrome coronavirus 2 infection or no infection. Analysis would be by intention to treat using ordinal logistic regression. Other outcomes included individual components of the primary outcome, transmission, plus health economic and process evaluation outcomes. The planned sample size was 300 care homes corresponding to 9600 residents. With ~40% of care homes predicted to develop an outbreak during the trial, we needed to recruit 750 homes/24,000 residents.
Results: We initiated the trial including protocol, approvals, insurance, website, database, data algorithms, intervention selection and training materials. We built a network of principal investigators and staff (91) and care homes (299) to support the trial. However, we never contracted care homes or general practitioners since the trial was stopped in September 2021, as vaccination in care homes had significantly reduced infections. Multiple delays significantly delayed the start date, such as: (1) reduced prioritisation of pandemic trials in 2021; (2) cumbersome mechanisms for choosing the investigational medicinal products; (3) contracting between National Institute for Health and Care Research and the investigational medicinal product manufacturers; (4) publicising the investigational medicinal products; (5) identification of sufficient numbers of care homes; (6) identification and contracting with several thousand general practitioners; (7) limited research nurse availability and (8) identification of adequate insurance to cover care homes for research. Generic challenges included working across the four home nations with their different structures and regulations.
Limitations: The feasibility of contracting between the sponsor and the principal investigators, general practitioners and care homes; screening, consent and treatment of care home residents; data acquisition and the potential benefit of postexposure prophylaxis were never tested.
Conclusions: The success of vaccination meant that the role of postexposure prophylaxis of coronavirus disease-2019 in care home residents was not tested. Significant progress was made in developing the infrastructure and expertise necessary for a large-scale clinical trial of investigational medicinal products in United Kingdom care homes.
Future work: The role of postexposure prophylaxis of coronavirus disease-2019 in care home residents remains undefined. Significant logistical barriers to conducting research in care homes need to be removed urgently before future studies are possible. Further work is required to develop the infrastructure for clinical trials of investigational medicinal products in care homes. Serious consideration should be given to building and then hibernating a pandemic-ready platform trial suitable for care home research.
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Introduction

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Since 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease has spread around the world, causing more than 676 million cases and 6.9 million deaths [coronavirus disease-2019 (COVID-19) Dashboard, Johns Hopkins University, www.arcgis.com/apps/dashboards/bda7594740fd40299423467b48e9ecf6; last accessed 26 July 2024].[2] In the UK, 24.7 million cases and 220,721 deaths have been recorded to date.[2]

Prior to the introduction of vaccines, SARS-CoV-2 infection was devastating in care homes, causing profound morbidity, mortality and disruption of daily routines to the detriment and well-being of residents, families and staff. By the end of 2020, England had recorded 19,179 deaths due to COVID-19 in care home residents,[3] which explains ~30% of the excess mortality associated with COVID-19. In Scottish care home residents, COVID-19 reduced life expectancy by approximately half a year.[4] The implementation of hygiene measures, such as prevention of visiting by friends and family of residents, routine testing for COVID-19, use of personal protection equipment by staff and changes in government policy

so that the patients were not moved from hospitals into care homes without SARS-CoV-2-testing, helped reduce infection. Nevertheless, outbreaks of infection continued, and prophylaxis measures were introduced, especially pre-exposure prophylaxis (PrEP) with vaccination.[5,6] By December 2021, more than 126 million doses of vaccine had been delivered in the UK, including first, second, third and booster injections, a figure that rose to 172 million by March 2023.[2] Vaccination of residents (and staff) started in early 2021 using the Pfizer (Pfizer Inc., New York, NY, USA) and AstraZeneca vaccines. Although there were concerns that vaccines might be less effective in older people with multiple comorbidities and immunosenescence, this fact was not observed and vaccination of more than 90% of care home residents and 80% of staff significantly reduced the COVID-19 disease, especially that leading to hospitalisation and death. Although vaccines were developed against the Wuhan/wild-type virus, they have also been sufficiently effective against Alpha, Beta, Gamma, Delta and Omicron variants (European Centre for Disease Prevention and Control, https://covid19-vaccines-efficacy.ecdc.europa.eu; last accessed 26 July 2024).

The work outlined in this report was conceived before vaccine roll-out, commenced in parallel with the beginning of mass vaccination at the time when the efficacy of vaccination in care home populations remained uncertain and concluded once the efficacy of vaccination had been established, rendering the proposed work unfeasible. Specifically, Prophylactic Therapy in Care Homes Trials (PROTECT-CH) was designed in October 2020 using data from the significant wave of excess deaths seen in care homes due to the first/Wuhan wave of infection in March–May 2020; apart from a smaller wave related to the alpha variant in January–February 2021, there were no other periods of excess deaths in care homes. This pattern of excess deaths differs from that seen for deaths at home and in hospital. Although vaccination has been phenomenally successful, a modest reduction in efficacy, say due to further SARS-CoV-2 variants, would lead to substantial morbidity and mortality; hence, there may yet be a need for interventions that prevent infections and transmission in care homes.

The literature relating to COVID-19 prevention and treatment is fast moving, and the state of knowledge at the time the trial was designed (in late 2020) and was planned to run (in 2021; *Table 1*) was far behind than what is now known in 2024. Since 2021, the efficacy of multiple antiviral interventions has been demonstrated, for example molnupiravir;[7,8] more recently, combination therapy has been tested (e.g. nirmatrelvir/ritonavir[9]) and comparative head-to-head comparisons have been reported (e.g. nirmatrelvir/ritonavir vs. molnupiravir[10]). Long-COVID is now a well-recognised, even if suboptimally understood, complication of COVID-19, but it was not a target of the PROTECT-CH trial.

This report covers the design and initial startup of the National Institute for Health and Care Research (NIHR)-commissioned PROTECT-CH trial. The trial never commenced recruitment due to numerous logistical challenges. Most of these had been surmounted by the autumn of 2021, but some barriers remained, which we

TABLE 1 State of knowledge about COVID-19 treatments in 2020 and 2021. Only large trials are quoted. No trials focused on care home participants

	Prevention	Treatments	
Time	**Effective**	**Effective**	**Ineffective**
Reported in 2020	Vaccine, Pfizer[5,a]	Dexamethasone[11,b]	Lopinavir and ritonavir[12,b]
	Vaccine, AstraZeneca[6,a]	Hydrocortisone[13,b]	Hydroxychloroquine[14,b]
Reported in 2021	Vaccine, Moderna[15,a]	Tocilizumab[16,17,b]	Aspirin[18,b]
	Vaccine, J&J[19,a]	Casirivimab and imdevimab[20,b]	Convalescent plasma[21,b]
	Vaccine, Novavax[22,a]	Budesonide[23,a]	Azithromycin[24,b]
	Molnupiravir[7,8,a]		
	PF-07321332[25,26,a]		

a Community-based.
b Hospital-based.

outline in this study. Ultimately, the trial became infeasible once vaccination led to a dramatic reduction in care home COVID-19 outbreaks.

Methods

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The following text briefly describes the trial rationale, aims and methods. Further details on the protocol, analysis plans and dummy tables, training materials, database design, study oversight, newsletters, correspondence, approvals, participant information and consent forms and frequently asked questions are given at: www.protect-trial.net/resources (accessed 26 July 2024).[1] A summary is given at the funder website https://fundingawards.nihr.ac.uk/award/NIHR133443 (accessed 26 July 2024). Detailed information on the trial has been published as a pre-print[1] and brief comments on challenges are shared in print.[27]

Rationale

The PROTECT-CH was designed in late 2020 and was predicated on multiple observations:

1. A high risk of SARS-CoV-2 transmission and COVID-19 disease existed in care homes.
2. Treatment of care home residents who have been potentially exposed to an index case of SARS-CoV-2 with an effective antiviral agent [postexposure prophylaxis (PEP)] might reduce the viral spread and disease severity.
3. There were no proven antiviral agents to treat or prevent SARS-CoV-2 in 2020. Hence, PEP with an antiviral agent might reduce both transmission within care homes and disease severity in residents.

Aims

We aimed to set in place a research and governance platform 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, which would allow the dropping of unsuccessful candidate investigational medicinal products (IMPs) and addition of new ones in their place. This would 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.

In addition, we aimed to assess the: (1) 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 and symptomatic), time to symptomatic infection and safety through serious adverse reactions (SARs); (2) effects of trial treatments on transmission of SARS-CoV-2 infection; (3) cost-effectiveness of trial treatments and (4) contextual factors that influence trial processes, including adherence to intervention and outcome measurement regimens, and that might impact on subsequent implementations of PrEP or PEP for COVID-19 in care homes.

Design

The study comprised a multiarm, multistage platform design based on a single master protocol to allow multiple different treatments to be evaluated both in parallel and in series. Cluster randomisation of care homes would use equal probability between all active treatments and control, and all comparative analyses would be based on contemporaneously enrolled care homes. The number of active treatments was to be limited to three at any time to ensure that the platform assessed safety and efficacy in a timely manner, in particular to limit the duration required to determine an answer for each intervention. Both trials of PrEP (i.e. before the care home has a case) and PEP (once the care home has a new case equivalent to an outbreak occurring in a closed setting) would be supported by the platform. The plan was to start with PEP interventions, but have a platform design that would support PrEP, as necessary.

As part of continuous monitoring, the Data Monitoring Committee (DMC) was to be provided with regular confidential reports by trial arm, including information on recruitment, protocol compliance, safety data, interim assessments of outcomes (between-group estimates of differences in efficacy and/or safety outcomes) and conditional power for futility assessment if necessary. The DMC was then to inform the Platform Steering Committee (PSC) if, in its view, there was evidence or reason why the comparison within the platform should be modified or terminated prematurely, for example, if the conditional power at a given point was low. Under such circumstances, where unblinded information on efficacy was necessary and randomisation of care homes was still

ongoing, the impact on the type I error would be taken into consideration. If the PSC and sponsor then decided that the recommended changes should be implemented, then this would be done via a study protocol amendment. No early stopping for benefit was planned.

New treatments were to be added to the platform by recruiting additional care homes or rerandomising previously enrolled care homes that had completed follow-up and provided that the prophylactic effect of the previous treatment was expected to have washed out (which would be quick for some candidate drugs but might take months for others, e.g. synthetic antibodies). Care homes were to be randomised (1 : 1 : 1 allocation ratio) between two active and standard of care (SoC) groups versus a SoC control group using dynamic allocation. New potential treatments were only to be added to the platform, provided that there were no more than two treatments already being assessed. If the study was already investigating three active treatments, then inclusion of a new treatment would be delayed until one of the existing treatment comparisons had concluded a 60-day follow-up for all residents.

All design discussions and decisions involved members of the patient and public involvement (PPI) team (MG and VL). For their diligence and hard work, they received the 'Community volunteer of the year' award, in 2021, from the University of Nottingham.

Participants

Eligibility criteria covered both care homes (the unit of randomisation) and residents (see *Appendix 1*). Briefly, care homes had to:

- be based in the UK and be for older people (with or without nursing)
- have at least 20 beds (so they could gain expertise in trial delivery)
- not be deemed as inadequate in performance by the Care Quality Commission (CQC; or equivalent in devolved administrations).

Since the trial was initially to study PEP interventions, any enrolled care home would only be allocated to treatment on the development of a positive polymerase chain reaction (PCR) or lateral flow test (or equivalent) for SARS-CoV-2 in any resident and/or staff member within the previous 4 weeks.

Residents within an enrolled care home for older people could be recruited if they were aged ≥ 65 years, had capacity to give informed consent or had a personal legal representative if they lacked capacity. They were excluded if they had entered end-stage palliative care, had been admitted to the care home for short-term respite care or had a general practitioner (GP) who was unable to support their involvement in the trial. Similarly, they were excluded if they were currently taking all of the trial interventions, had a contraindication to all of the trial interventions or were in the treatment phase of another COVID-19 prevention or treatment trial. Apart from the minimum age of 65 years, there were no other restrictions on the protected characteristics of age, sex and race ethnicity to ensure equality, diversity and inclusion.

Investigational medicinal products

As a NIHR-commissioned trial, the choices of IMP, inhaled ciclesonide and inhaled niclosamide, were selected by the NIHR prophylaxis oversight group (POG). Another NIHR committee, the UK COVID-19 therapeutics advisory panel (UK CTAP), also discussed potential interventions that might be tested, including inhaled heparin and intravenous convalescent plasma.

Two drugs were recommended for testing by POG, ciclesonide in late December 2020 and niclosamide in early January 2021. Ciclesonide[28] was to be administered once daily via inhalation for 42 days; specifically, administration would require two actuations (320 µg) inhaled via mouth sequentially (with participants who were unable to tolerate a face mask using a spacer mouthpiece) and then via nose (with participants who were unable to tolerate a face mask not receiving the intranasal actuation). Niclosamide[29] (1% in 20 ml) was to be administered for 42 days intranasally as a spray into each nostril twice daily (140 µl, equivalent to a total daily dose of 4.7 mg of niclosamide free acid). Further information on these two drugs is given in *Appendix 1*. Both ciclesonide and niclosamide were to be given in addition to standard care and compared with standard care alone, for example, there was to be no placebo. Further information on both drugs is given in *Appendix 1*.

Randomisation

As a cluster-randomised trial, care homes were to be randomised dynamically using a probabilistic minimisation algorithm to balance across important baseline care home characteristics: type (residential vs. mixed residential/nursing vs. nursing), prior SARS-CoV-2 infection at any time, size (< 30 residents, 31–50, > 50) and capacity to give oxygen and/or dexamethasone when clinically indicated (a practice that was emerging in some parts of the UK at the time of the study). The probability of allocating to the group that minimised the imbalance was 90%. Eligible nursing homes were to be assigned in a 1 : 1 : 1 ratio to receive ciclesonide and standard care,

niclosamide and standard care or standard care alone. Residents who had a definite need for or contraindication to either drug were not included in analyses of that comparison with standard care. Residents, care home staff and GPs would be aware of the assigned treatments, that is allocation concealment was to be ensured by enrolling care homes and residents prior to allocation. Care homes were to be randomised once they had an indication of a developing infection, for example, recent positive PCR or lateral flow test (or equivalent) in any resident or member of staff (index case).

Outcomes, primary

The primary efficacy outcome was to be a four-level, ordered, categorical (ordinal) scale with participants classified by the most serious event they experienced during the 60-day period following randomisation:

1. all-cause mortality
2. all-cause hospitalisation
3. SARS-CoV-2 infection (diagnosed using PCR, lateral flow test or equivalent) without admission to hospital
4. no SARS-CoV-2 infection.

Outcomes were to be assessed at 60 days (and 120 days in a secondary analysis) following randomisation, and information on events would be obtained from UK routine data, with national sources shown in *Table 2*.

The primary efficacy outcome was designed to 'capture the ability of the drug candidate to prevent/reduce morbidity and mortality from COVID-19 in individuals, and to reduce transmission in care home settings', thereby addressing the NIHR Commissioning brief [www.nihr.ac.uk/documents/20111-commissioning-brief-for-prophylaxis-platform-study-in-care-homes/25902; accessed 26 October 2020 (no longer available)]. Hence, the outcome needed to include asymptomatic and symptomatic transmission, morbidity assessed as healthcare interventions, hospitalisation and mortality. This approach followed the World Health Organization's recommendation to use ordinal outcomes in COVID-19 trials,[30] a recommendation that was followed by many such studies.[31] We adapted the ordinal scale to fit the care home context.

Using an ordinal outcome had additional advantages. First, it allowed the effect of treatment to be assessed on the severity of recurrent events as well as their rate. In general, interventions that reduce the risk of events also reduce the severity of those events that do occur;[32,33] conversely, interventions that increase events also increase the severity of those events.[34] Second, using an ordinal outcome improves statistical power as compared to using a dichotomous outcome for a given sample size.[35]

Outcomes, secondary

Secondary outcomes at day 60 following randomisation were to include:

1. time to healthcare referral for COVID-19; for example, discussion outside of care home with GP (excluding routine visit); 111, 999/ambulance paramedic or emergency department (ED) assessment (without admission) and remote hospital consultation
2. time to use of dexamethasone in the care home for COVID-19
3. time to use of oxygen in the care home for COVID-19
4. time to SARS-CoV-2 infection – positive PCR or lateral flow test (or equivalent)
5. time to first admission to hospital
6. cause-specific hospital admission
7. time to death
8. days alive and not in hospital
9. cause-specific mortality, including COVID-19, stroke, pulmonary embolism and myocardial infarction
10. electronic frailty index.

The primary outcome would also be collected at 120 days following randomisation. At the care home level, the number of SARS-CoV-2 infections in residents, including those not participating in PROTECT-CH, would be recorded.

Safety evaluation

Serious adverse reactions (excluding primary and secondary outcomes, suspected unexpected SARs) and adverse events relevant to the interventions were to be collected.

Blinding

As a cluster open-label trial, care homes were either randomised to active treatment/standard care or standard care alone. Hence, residents, their family and care home staff would all to be unblinded. By contrast, the primary outcome was to be blinded, since it was to be derived from national routinely collected health data. Externally facing co-ordinating staff were to be unblended, while those managing and analysing data would be blinded, apart from two statisticians who were supporting the DMC.

Study oversight

The trial was conceived and designed by the grant applicants who wrote the protocol. The study was given NIHR Urgent Public Health level 1 badging (once we had

TABLE 2 Organisational challenges in working across the four UK nations

Issue	Challenge	England	Northern Ireland	Scotland	Wales
CH chains	Most CH medium-large chains not present across all of UK. Most small CH groups are regional	Barchester Four Seasons HC One	Four Seasons	Barchester Four Seasons HC One	Barchester Four Seasons HC One
CH inspectorates and registers	Different organisations in each country, so no common list or classification of CHs	CQC	Regulation and Quality Improvement Authority	Care Inspectorate Scotland	Care Inspectorate Wales
ENRICH	Different organisations in each country, with generally, limited funding	ENRICH, England	Not applicable	ENRICH, Scotland	ENRICH, Cymru
Sources of routine data[a]	Accessing data from multiple different sources				
Death		NHS Digital	HSCNI	PHS	SAIL
Hospitalisation		NHS Digital	HSCNI	PHS	SAIL
SARS-CoV-2		NHS Digital	HSCNI	PHS	SAIL
Primary care		NHS Digital	HSCNI	Albasoft	SAIL
Other		–	HSBNI	–	–

ENRICH, Enabling Research in Care Homes; HSBNI, Honest Brokerage Service NI; HSCNI, Health and Social Care Trusts NI; PHS, Public Health Scotland; SAIL, Secure Anonymised Information Linkage.

a The Dundee Trusted Research Environment (TRE) would curate central data from these sources (with uploads obtained every 2–4 weeks) and trial data from the Nottingham REDCap database. Statistical analyses would then be run from Nottingham and Cambridge, with code run in the Dundee TRE.

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clarified that we had two IMPs to test, dated 1 March 2021); approved by the Medicines and Healthcare products Regulatory Agency [MHRA, UK competent authority, clinical trial authorisation (CTA) 03057/0073/001-0001, 15 May 2021], UK Research Ethics Committee (REC) and Health Research Authority (HRA, 21/SC/0166, dated 17 May 2021); and registered (EudraCT 2021-000185-15).

The trial was overseen (*Figure 1*) by:

- an independent PSC: to provide oversight for the platform study on behalf of the sponsor and funder; provide advice to the Platform Management Group (PMG), the funder (National Institute for Health Research) and Nottingham Clinical Trials Unit (NCTU) on all aspects of the study; review progress, including adherence to the protocol, participant safety and considerations for new information; and receive and consider recommendations made by the independent DMC
- an independent DMC: to safeguard the interests of potential or actual trial participants, their relatives and carers, investigators and the sponsor; to assess the safety and efficacy of the intervention(s) being investigated; to monitor the platform's overall conduct and so protect its validity and credibility; to receive and review the progress and accruing data of the comparison(s) under investigation and provide advice on the conduct of the comparison(s) to the PSC
- PMG: to manage the trial addressing strategic and logistical decisions
- Executive Committee (based at the PROTECT-CH Co-ordinating Centre at the NCTU): to manage the day-to-day conduct of the trial.

Membership of the committees/groups is listed at the end of the report.

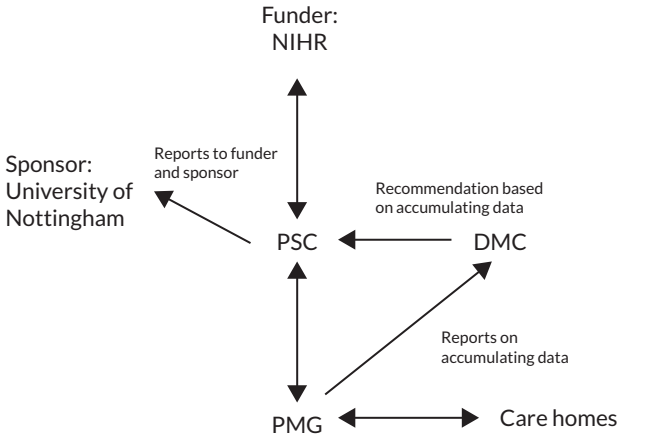


FIGURE 1 Trial management structure. Inter-relationships between the funder (NIHR), sponsor (University of Nottingham), PSC, DMC, PMG and care homes.

Statistical analysis

The analysis and reporting of the trial were to be in accordance with Consolidated Standards of Reporting Trials guidelines for adaptive and cluster designs,[36,37] with the primary comparative analyses being conducted according to randomised allocation (intention to treat). All comparative analyses were to be based on contemporaneously randomised care homes. Primary comparative analyses would employ a multilevel ordinal logistic regression model with adjustment for minimisation factors and individual-level covariates (age, sex and vaccination status) and a random effect to adjust for clustering within care homes. The treatment comparison would be presented as an adjusted common odds ratio (OR; with 95% confidence intervals) for a shift in the direction of a better outcome on the ordinal scale.[32,33,35,38,39] Pre-specified analyses of the primary outcome were to be performed in subgroups defined by the factors: care home type, prior SARS-CoV-2 infection in the care home, care home size (number of residents), capacity to give oxygen, age, sex and vaccination status. Secondary outcomes were to be analysed using appropriate regression models dependent on data type (binary, categorical, continuous and time-to-event), adjusted similarly and accounting for clustering within care homes. All *p*-values would have been two-sided and reported without adjustment for multiple testing. Analyses were to be performed using Stata® (StataCorp LP, College Station, TX, USA) and R (The R Foundation for Statistical Computing, Vienna, Austria). The full statistical analysis plan is available at www.protect-trial.net/files/resources/protect-sap-final-v1-0-08oct2021-signed-1.pdf; dummy tables are available at www.protect-trial.net/files/resources/protect-dummy-tables-final-v1-0-20211008-signed-1.pdf (both accessed 26 July 2024).

Sample size

A total of 530 residents per group were required to detect an OR of 0.67 for a four-level ordinal primary outcome (with assumed proportions: no infection 60%, infection and remain in care home 15%, all-cause hospitalisation 10%, all-cause mortality 15%), assuming a two-sided significance level of 5% and 90% statistical power, with no adjustment for clustering.[40,41] Care homes of varying size were to be included, with an average of 40 beds per care home.[42] We assumed that not all residents would take part in the study, and so we expected that approximately 32 (range 20–60, coefficient of variation for care home size 0.49[43]) residents would be recruited from each participating care homes. Let us assume that an intracluster correlation of 0.11 gave a design effect or inflation factor of 5.25.[44] Therefore, to compare a single active treatment versus standard care, we would need around 174 care homes and in excess of 5500 residents. Allowing for the uncertainty

surrounding the parameters listed above, we proposed a sample size of 200 care homes involving 6400 residents.

Therefore, a comparison of two active (unrelated) treatments versus standard care (in a 1 : 1 : 1 allocation ratio) would require 300 care homes in total, corresponding to around 9600 residents. Since only ~40% of care homes might have a resident and/or staff member who would test positive for SARS-CoV-2 infection during the trial, we would need to recruit 2.5 times these numbers, for example, 750 homes and 24,000 residents, and then we would randomise the first 300 care homes that reported an infection. We would then re-estimate the sample size during the trial once the 60-day outcome data were available for at least 75% of care homes randomised to standard care.

Protecting against bias

Multiple measures were to be taken to minimise bias:

- recruitment according to pre-defined inclusion/exclusion criteria
- exclusion of patients enrolled in other trials
- central data registration with real-time data validation
- concealment of allocation
- research staff trained in trial protocol and processes
- analysis by intention to treat
- analyses adjusted for baseline prognostic variables, including minimisation factors.

Training

All PROTECT-CH care home staff were to be trained in the trial protocol and processes and assessment scales. The training included an introduction to good clinical practice (GCP) with increased detail covering aspects relevant to staff, for example consent and IMP management. (More information on this follows.)

Care home monitoring was to be performed remotely by the NCTU Co-ordinating Centre, with the aim of ensuring quality control of the delivery of the protocol, collection of data and adherence with national regulations and ethics. Remote monitoring to confirm the presence of the participant and their consent, eligibility criteria, selected data critical to the trial (demographics and prescription of interventions) and report serious adverse events were planned. In-person monitoring visits were to be performed as deemed necessary by the Co-ordinating Centre.

Central statistical monitoring of the data was to be performed according to Buyse *et al.*[45] during the trial and prior to locking of the data. Checks would include logic and range checks, digit preference, comparison of univariate data between sites and comparison of multiple variable models between countries. The monitoring procedures would have been compliant with the requirements of the sponsor, the national ethics committees and MHRA and fulfilled GCP requirements.

Health economic evaluation and process evaluation

These are described in *Appendix 1*.

Observations and discussion

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The disproportionate effect of the pandemic in a vulnerable, frail and unvaccinated group in care homes led to high death rates in 2020. This meant that the UK needed to address this problem specifically and the early success of the randomised evaluation of COVID-19 therapy (RECOVERY) platform trial[46] suggested that a platform trial focussing on care homes and their residents would provide a practical solution. The trial was designed, its infrastructure was built and an initial 300 care homes were identified. Although the trial was close to being ready to start in April 2021, the dramatic fall in COVID-19 rates in care homes due to the success of vaccination meant the trial never commenced formal recruitment and contracting with care homes and GPs. For this reason, further trial activity was stopped and the funding grant was closed. Nevertheless, multiple and serious logistical problems were identified[27] and it is questionable whether the trial could ever have started (other than perhaps as a pilot study) since many of these issues appeared insurmountable in mid-2021. These trial-specific internal and external challenges are now highlighted.

The early success of vaccination in 2021 reduced the scientific need for the trial, which become increasingly obvious in quarter 2 of 2021. By then, significant impediments to trial progress had become obvious and it is highly questionable whether the trial could have ever

progressed with its design unless these obstructions were removed. Key blockages related to: trial design, choice of IMP, IMP contracting, research nurses (RNs) and GPs.

Internal challenges

Multiple trials versus platform trial

The NIHR commission was for a platform trial and so we did not consider setting up multiple parallel arm trials. The benefits of platform trials for common disease/conditions are well rehearsed and these include the need, overall, for fewer patients, shorter time to obtaining an answer for a given intervention, ability to drop ineffective interventions early and introduce new arms more quickly and a greater probability of success.[47,48] Advantages have been seen prior to the pandemic, for example in oncology, with STAMPEDE.[49] During the COVID-19 pandemic, platform trials achieved the biggest gain in knowledge and identified beneficial, ineffective and hazardous interventions (see *Table 1*), as seen in RECOVERY,[11,12,14] REMAP-CAP,[13] PRINCIPLE[23] and PANORAMIC.[50] It is highly unlikely that multiple parallel arm trials would have achieved the same impact in the equivalent time period. It is equally likely that the same conclusion would apply to pandemic trials running in the care home sector.

Cluster versus individual randomisation

Although randomisation of individual residents would require a smaller sample size, this might not have been feasible because of the administrative and logistical burden associated with individualised randomisation and administration for care home staff – all at a time when their burden of work was already substantially increased by the pandemic. In the event of an outbreak, study staff would have been unable to enter to the care home to help, placing this burden substantively on care home staff. Hence, cluster randomisation was considered to be particularly relevant to a care home trial.

Cluster designs are especially relevant to care home trials since they:

- are more likely to provide a clear answer than a trial using individual randomisation because reducing virus transmission is so fundamental to prophylaxis – a critical mass of 'susceptible' individuals is typically needed for disease transmission and so the impact of a useful drug will be amplified if it is used widely
- reduce the risk of bias due to contamination, whereby residents receive the wrong intervention[51]
- allow 'real-world' investigation of transmission
- facilitate recruitment
- enable simpler drug management and delivery
- ease identification/attribution of serious adverse events
- best reflect the manner that prophylactic interventions would be implemented in care homes, for example for all residents (and potentially staff) following an outbreak.

In view of these clear practical advantages, especially in a research naive environment in a pressurised situation, we elected to use a cluster trial design. Nevertheless, a cluster trial design leads to a much larger trial than when using individual randomisation in the case of PROTECT-CH by a factor of more than 5 (see earlier sample size calculation above). As a result, we would needed to have engaged, contracted, trained and supported many hundreds of care homes and thousands of GPs and recruited tens of thousands of residents.

Some might argue that we should have used individual randomisation and accepted this less optimal design, a case of 'best is the mortal enemy of the good' (Montesquieu in 1726);[52] this would have required recruitment of only 1000–2000 residents from fewer than 100 care homes. But, since mortality and transmission were the most important outcomes, an individually randomised trial may not have answered the research question adequately. Future care home trials will need to consider this dilemma of cluster versus individual randomisation carefully.

Training

Care home staff are largely new to research, and it was vital that they received adequate training and retraining. Mandatory training covered background to the trial, trial-specific GCP, data protection, safety and guidance on COVID-19 outbreaks. Role-dependent training covered consent and enrolment, data entry, interventions, assessments and follow-up and close out and archiving. Training modules covering these areas were uploaded to the trial website (they are still present at www.protect-ch.net) and were to have been delivered in webinars. Further training would have been delivered face to face at the care homes by RNs.

Additionally, most of the research delivery team, based predominantly in a Clinical Trials Unit, were new to working with care homes. They had to learn about how care homes were funded, commissioned, managed and staffed. They had to assimilate a plethora of new legislation surrounding care delivery in care homes and regularly recalibrate in light of frequently changing guidelines as government and care providers adjusted to rapidly shifting clinical circumstances. The coinvestigators had substantial expertise in the sector and how to work with care home

staff. This facilitated, for example, the establishment of regular education and update sessions for care home staff involved with the study to keep them informed and engaged (materials available on request). However, due to clinical trial of investigational medicinal products (CTIMPs) being largely unexplored in this sector, the team was frequently breaking new ground.

Designing and developing the training materials was a significant task and the workload should not be underestimated in any future large care home trial. As discussed below, it is not clear that there are enough RNs in the UK who can cover care home research, including delivery of some on-site training.

Co-ordination and staffing

Co-ordinating a care home trial in a pandemic is complex, involving care homes, GPs, medical principal investigators (PIs), RNs, central pharmacy and the trial co-ordinating centre/clinical trials unit. Twenty-four multidisciplinary working groups based in a hub-and-spoke model and covering the UK managed the process, and this involved 91 individuals comprising academic, clinical and methodologists from 25 organisations.[53] The remit of these groups was to localise implementation and delivery of trial protocols, taking account of local variation in how care homes, primary and community care interacted. Thus, each working group performed similar functions by way of making the study feasible locally; duplication was minimised by regular online meetings with the core study team in Nottingham which was attended by representatives of all working groups.

Future care home trials, especially those addressing pandemic needs, will inevitably involve multiple organisations and staff members and so will need the appropriate structure and funding.

Quality assurance

Quality assurance (QA) of a trial during remote working and within a care home setting posed several difficulties from a regulatory oversight perspective. High-risk CTIMP trials (such as those conducted within a vulnerable population with an unlicensed IMP) would normally involve a risk-based assessment and then an increased level of on-site monitoring during initiation and conduct. This intensity of monitoring and oversight was not going to be possible due to government restrictions and COVID-19 prevention measures in care homes. The risk assessment was drafted taking this into account, proposing the use of novel central monitoring systems where possible. In order to ensure that a risk-based level of oversight and monitoring was accounted for, the QA function was involved in all stages of database design, e-consent, electronic trial master file (eTMF) and safety reporting. Database forms were designed to allow the highest level of central monitoring was possible, enabling review of consent forms, IMP charts, and safety events. While the trial was never initiated, new forms and database models can be used going forward for this purpose.

The use of an eTMF for the trial also enabled the QA function to perform a remote audit of essential documents, approvals and amendments to ensure that all were accounted for and filed correctly.

External challenges

Prioritisation of pandemic trials

At commencement of the pandemic, research was prioritised at all levels, for example, the RECOVERY trial was able to start within 10 days of conception.[46] When PROTECT-CH started in early 2021, many aspects of research were attempting to return to pre-COVID-19 practice and activity, for example, Clinical Research Network (CRN) wanted RNs to return to supporting non-COVID-19 trials. *Table 3* details out the dates for key milestones, and it is clear that progress was far slower than seen for platforms opening in 2020.

No dates were relevant for participant last visit, data entry and cleaning or database lock.

Prioritisation of national resources for pandemic research needs to continue for the duration of the pandemic. All research in a pandemic context is time-critical and will be disproportionately affected by research delays by comparison with more routine research.

Choice of investigational medicinal products

The commission for the trial was to design, set up and deliver the trial but not choose the interventions. Although the IMP was chosen by the NIHR POG, another NIHR group UK CTAP was the primary gatekeeper for suggestions for interventions and made recommendations for other studies. It was unclear whether UK CTAP ever considered ciclesonide and niclosamide as worth testing.

Although we cannot speculate as to which agents might be relevant in a future pandemic, the choice of inhaled drugs such as ciclesonide and niclosamide in a care home setting may be suboptimal, even if attractive superficially. Most residents live with cognitive impairment or dementia and may struggle to understand how to effectively use an inhaler, even with a spacer device attached. Similarly,

TABLE 3 Record of key dates

Event	Date
NIHR call (20/111) announced	20 October 2020
NIHR prospective applicants briefing	22 October 2020
Submission of single-stage grant application	11 November 2020
Interview as a shortlisted application	25 November 2020
Revised application submitted	14 December 2020
NIHR award grant	15 December 2020
MHRA first advisory meeting	16 December 2020
Ciclesonide proposed as an IMP to test	23 December 2020
Grant and project starts	1 January 2021
Niclosamide proposed as an IMP to test	2 January 2021
MHRA second advisory meeting	19 February 2021
Urgent public health level 1	1 March 2021
Joint platform steering/DMC meeting	3 March 2021
Integrated Research Application System submission, protocol version 1.0	29 April 2021
MHRA approval (CTA 03057/0073/001-0001)	15 May 2021
REC/HRA approval (21/SC/0166)	17 May 2021
Protocol amendment version 2.0	1 July 2021
Insurance sourced, contracting commenced	2 July 2021
Protocol amendment: MHRA approval	9 July 2021
NIHR issue close-down notice	22 September 2021
All documentation filed in the eTMF	5 November 2021
Submission of close-down plan to NIHR	10 November 2021
All documents uploaded to the trial website	19 November 2021
Grant close	17 December 2021
Process evaluation	Not completed
Final report submission	This report

many will dislike and even refuse nebulised drugs. Care home residents rooms rarely have space suitable for storing drug spacers and nebulisers and central storage is likely to increase the risk of mixing up drugs, leading to administration errors. Similarly, intravenous interventions (such as convalescent plasma[21]) will be impractical unless being used in a small, highly controlled Phase II feasibility trial with the presence of dedicated healthcare staff to administer and monitor administration. Suppositories are likely to be resisted by many confused residents. While transdermal administration would be attractive, mechanisms capable of delivering adequate systemic doses of antimicrobials are only at the experimental stage. Hence, practically, an oral (or perhaps subcutaneous) drug formulation will ease administration and the reliability of dosing. Nevertheless, any drug will need to involve MHRA approval and so the involvement of GPs, as discussed later.

We received mixed messages from various arms of NIHR (UK CTAP and POG) as to which drugs should be tested, although our contract specified that NIHR POG were to decide. In the future, a single committee should identify preferred drugs; this would reduce confusion, accelerate trial startup and ensure that the Department of Health and Social Care (DHSC) and NIHR are fully behind the trial. For a specialist group of patients such as care home residents, decisions on drugs will need to be tempered by considering aspects such as storage, route of administration and acceptability to people who live with dementia.

Contracting between the National Institute for Health and Care Research and companies manufacturing the investigational medicinal products

Both ciclesonide and niclosamide were in development by their respective manufacturers (Ayrtons, Liverpool, UK; Union Therapeutics, Hellerup, Denmark) and lacked any licence, although both agents were available for other purposes from other companies. The two companies needed data from PROTECT-CH, as well as other trials such as prophylaxis for patients at risk of COVID-19 infection (PROTECT-V),[54] to assist them getting a licence for COVID-19 (assuming the data were positive). As such, they were willing to give drug in exchange for the trial data. However, NIHR could not agree to this due to legalities relating to state aid; in particular, NIHR would not agree to any data exchange until the trials results were available so that they could assess their value. Further, NIHR expected the companies to hand over background intellectual property in case the company withdrew from the market during the trial; both companies declined this. While one company signalled a willingness to sell the drug to the trial in late July 2021, NIHR and the other company had not come to any agreement by this time. Hence, it is possible that the trial could have started with one drug but not before late quarter 3 of 2021. Importantly, more than 6-month delay in contracting significantly limited the progress of all central pharmacy set-up activities. Avoiding these delays would, in all probability, have allowed the platform trial to have started contracting with all parties in May 2021.

We believe that the key driver of patient benefit must underline all processes. NIHR should consider whether companies who provide drugs for free agree to handing

over background intellectual property (IP). Also, NIHR should agree on allowing companies to use trial data for licensing and marketing purposes before the trial starts rather after the results are available. This would reassure companies that they would have access to data and would accelerate licensing, marketing and patient benefit in the event of a positive result. During the NIHR contracting process, we were often excluded from discussions making trial delivery complicated since NIHR was both trial funder and leading on company contracting. NIHR should review how they support trial teams during the contracting process.

Publicising investigational medicinal product

Once the IMP was chosen, we asked NIHR if we could share this information with potential care homes, GPs and the media so that we could publicise the trial and so garner further interest. However, NIHR instructed us not to publicise what IMP was to be tested until contracts with the manufacturers had been signed. With the delay in contracts, this delayed recruitment and contracting with care homes and GPs not knowing our plans, thus reducing our ability to advertise the trial to media and garner their interest in the trial.

Care home identification and governance

The varied ownership of care homes (commercial, charity, social care and NHS) made it challenging to identify suitable homes, and we had to approach multiple commercial and charity chains; often, personal knowledge and relationships were vital. Further, it was challenging to work out who the primary contact for each care home was; the registered manager might not have the authority to scrutinise or sign research contracts,[27] particularly in chain providers where the head office usually made chain-wide decisions. Additionally, changes in personnel and their contact details complicated the process of contacting and building up the relationship with individual care homes.

Unlike UK NHS hospitals, care homes are variously owned by commercial and charitable chains, with a very small and diminishing number being managed by local authorities or the NHS. Ownership patterns, and national umbrella organisations, differ across the four nations. There is no centralised contact list of care homes, and it is necessary to identify them via national organisations such as the Care Providers Alliance, Care England, the Registered Nursing Home Association and the National Care Forum. Local authorities and Integrated Care Systems also hold contact lists for homes in their areas, but finding the right contact in these organisations can be complex and time-consuming. Care homes for older people are also categorised by whether they are residential only (without nursing), mixed residential and nursing or nursing only. This variance makes it challenging to identify suitable care homes for a trial.

Expression of interest was received from 299 care homes (*Figure 2*), 228 of whom were eligible (30% of trial target); discussions were ongoing with 2 large care home chains, with a potential to recruit approximately 100 additional care homes. A significant proportion of care homes who expressed an interest (152/299, 51%) was residential only, presenting challenges for the medical oversight of a CTIMP trial. Overall, 82 care homes agreed to participate and confirmed capacity and capability (see *Figure 2*), while 65 did not answer calls or respond to e-mails/telephone messages.

Considerable efforts were made by the trial management regional leads to contact care home representatives; despite this, we were unable to initiate discussions with 74/228 (32%) of eligible care homes. The reasons for lack of contact reported by the trial team may reflect the considerable pressures that care home staff had experienced throughout the pandemic: manager not available, n = 9; no response received (to telephone calls, e-mails or voicemails), n = 65.

A pan-UK accessible register of care homes is needed to facilitate clinical research. Since all residents should have the right to take part in research, care homes should be judged by the CQC (and equivalents across UK), in part, on their willingness to participate in research. Care homes should also have to sign up to NHS research and governance processes to ensure consistency across clinical research. A standardised template, as piloted by ENRICH in Wales (https://healthandcareresearchwales.org/enrich-cymru; accessed 26 July 2024), would assist contracting. In return, a remuneration model will be required to take account of the costs involved with research. This will be different than for NHS providers because care homes are run either by for-profit or not-for-profit providers. Providing an equitable and fair model of reimbursement that recognises the true costs of research will require close working with the care home sector.[27]

General practitioners

Initially, we did not plan to involve GPs in the trial, since trial medics (including several of the authors) would prescribe the IMP via the central pharmacy once a care home developed an outbreak. We were aware that care homes might have a relationship with one GP practice or, alternatively, residents might have their own GP; hence, there might be one or many GPs involved with each care

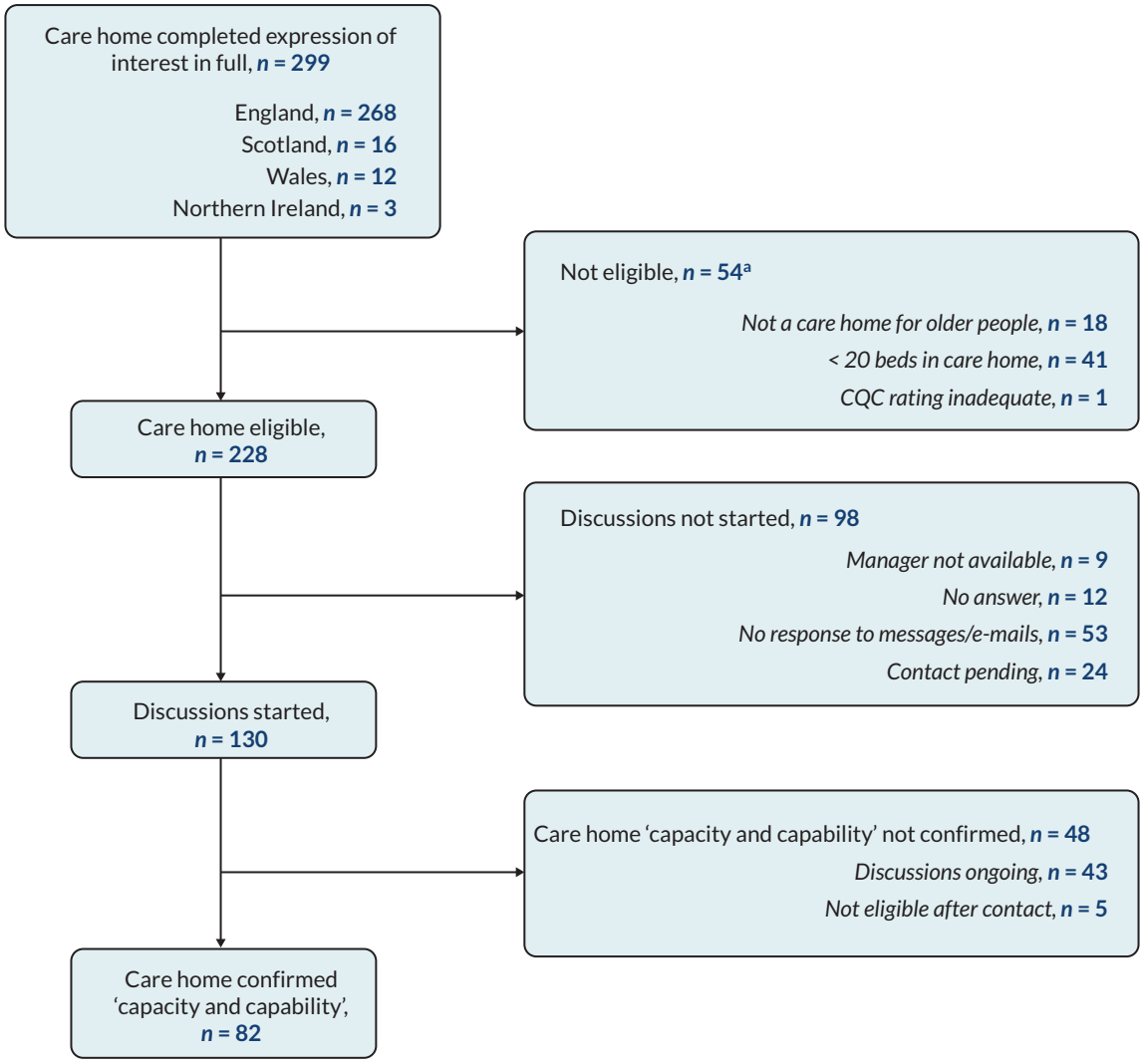


FIGURE 2 Care home eligibility flow diagram. a, Some care homes are ineligible due to multiple reasons; therefore, the number of reasons does not equal the number of not eligible.

home. Additionally, GPs might be responsible for more than one care home. However, MHRA required that all residents must have their GPs participate in the trial through providing information on medical history and potential reasons for exclusion and contributing to safety oversight. Care homes who expressed an interest in the trial were associated with an average of 3 GP practices (range 1–10); with a target recruitment of 750 care homes, contracts would need to have been arranged with over 2000 GP practices to facilitate trial delivery. This was further complicated since until we knew which residents would sign up within each care home to the trial platform, it would not be possible to formally start contracting with GPs. As such, GP contracting and subsequent training were going to become a massive load on the trial.

On the basis of our experience, MHRA is likely to expect the involvement of GPs if unlicensed drugs or licensed drugs for another indication are being tested, particularly since the care home population is vulnerable and many residents lack the capacity to make their own decisions. As such, contracting and subsequent training will be a massive, and potentially insurmountable, load on any large trial in care homes. Testing a repurposed licensed drug (rather than an unlicensed drug) would reduce the need for detailed safety reporting and perhaps involvement of GPs. Testing of a non-IMP[55] would mean MHRA and GPs would not need to be involved at all, which would simplify safety recording and reporting.

Some of the issues of identifying which GPs to contract for a given care home might be addressed through the 'clinical lead' model adopted in England during the pandemic.[56] This identifies one named NHS professional as responsible for co-ordinating with NHS care delivery in a given care home (although residents may continue to see their named GP). At present, there is no need for a clinical lead to be a doctor. Given the work required to develop

care home research infrastructure is described elsewhere in this study, consideration should be given as to how the responsibility for research could be incorporated within the clinical lead role and whether similar arrangements could be introduced in the other nations.

Research nurses

They are an integral part of most trials testing IMPs and especially so in care homes which do not have the staffing or experience to manage studies, especially if the IMP is unlicensed. In hospital-based trials, NIHR CRN RNs and research co-ordinators lead on trial delivery. We worked with the CRN in general, and especially the ENRICH network, to scope out how a care home could be supported, initially, for obtaining consent or consultee assent and then later for initial drug administration once a care home went positive. In reality, no satisfactory solution was arrived at should the trial have ever started recruiting care homes and residents.

Some of the difficulties we faced were due to the difficulties associated with sending outside staff into a care home during a pandemic situation, particularly during an outbreak. However, there are currently insufficient numbers of RNs to support a large care home-based trial platform testing IMP, especially in a PEP design, where several researchers may be needed at very short notice when a care home needs to start immediate treatment. Involving hospital-based RNs is unlikely to help since acute research trusts do not typically have enough RNs to deliver their own studies. Additionally, most hospitals will not have governance arrangements in place to allow their RNs to visit care homes, and most hospital-based RNs lack the experience and training in the care home sector to enable them to deliver research rapidly in this setting. The NIHR CRN needs to assess how more RNs can be made available for such community-based research. Further, future grants should include specific support for care homes to enhance their staffing. It should be recognised that care homes have a number of sector-specific challenges and that nurses require specific competencies or training to work in this sector. If rapid redeployment to support care home research is to be part of pandemic planning, then training materials should be developed in anticipation of this.

Principal investigators

Although no PIs reached the contracting stage of trial set-up, it became evident early on that there would be some challenges in contractual arrangements for the remote network of PIs. Given that the PIs were contracted to an NHS Trust/Board, but conducting a supporting role for a number of care homes (most of which did not fall under NHS management), questions were raised regarding which organisation would be liable in the event of any claims of negligence. A further complication was that several PIs (including some of the authors) had a primary contract with a university rather than hospital trust; universities made it clear that they did not wish to negotiate with independent care homes. Although the university academics also held honorary contracts with NHS Trusts/Boards, again it was unclear whether these NHS Institutions would be willing to responsible for their staff working in a care home-based trial. These issues were largely overcome by multiple, local-level conversations, comparing and sharing responses between employers and negotiating such that risk was shared between organisations. This was not a satisfactory long-term solution.

Insurance

Three types of insurance were required. First, that covering the sponsor, host institution and their staff and the protocol. The university trial's insurance was not designed to cover a large platform trial such as PROTECT-CH, and it needed to purchase additional cover via the platform grant and that covering participating healthcare staff (medical and nursing staff) for negligent procedures. Discussions with medical defence/protection societies/unions suggested that this cover would extend to PROTECT-CH at no extra cost.

The third type, that covering case care homes and their staff for non-negligent events, was the most complicated. Unlike NHS hospitals and general practices, the majority of care home insurance policies do not cover research and so additional cover would need to be paid for via the platform grant. At the time we commenced the study, insurance costs for care home providers had increased substantially and many providers had attached stringent conditions to new or existing policies.[57] Discussions with several insurance companies providing conventional cover for care homes suggested that none were willing to extend this to cover research.

Primary drivers for this position included the:

1. perceived risk of doing research in research-naive sites
2. perceived risk of a trial testing unlicensed drugs
3. uncertain risk associated with COVID-19 in care homes, taking account of the high death rate in wave 1 of the pandemic
4. opening up of care homes to relatives and visitors with the increased risk of importing infection into the care home.

In the absence of commercial insurance, discussions were held with DHSC, and a fallback position was for Her Majesty's Government to underwrite the trial as part of the Coronavirus Act 2020 (www.legislation.gov.uk/ukpga/2020/7/contents/enacted; last accessed 26 July 2024). Subsequently, DHSC and the University of Nottingham's (UoN) Procurement Office identified separately that Lloyd's, Brokered by Aon UK Ltd and underwritten by the Newline Syndicate, could provide a single insurance covering UoN, care homes and healthcare staff. Contracting for this was commenced but was not completed due to the platform closure.

We recommend that care home insurance should automatically cover clinical research, including randomised controlled trials that involve unlicensed interventions. This should be recognised as an additional cost borne by the sector to be included in discussions about reimbursement already outlined above. Alternatively, a care home financial pool to cover research, as set up between hospitals (NHS Resolution, Risk Pooling Scheme for Trusts), may be necessary. Either way, it is important to note that clinical trials have a very low risk of legal action.

Four nations' working

Care homes and their chains, structures such as CRN and ENRICH, GP data, data sources and regulations each differ across the four UK nations (see *Table 2*), thereby complicating the design and delivery of a care home trial.

Accepting that devolution makes such differences inevitable, PROTECT-CH identifies some of the solutions that will ease future care home trials working across the UK. Where possible, the four nations should work together to enact solutions to ease future care home trials.

National Health Service funding

The PROTECT-CH was funded through a cross-platform scheme, but, as with other funding schemes, such as Health Technology Assessment, comprised core research funding (from NIHR), NHS service support costs (SSCs, broadly those costs that cease once the trial completes) and NHS excess treatment costs (ETCs, those costs, typically related to the intervention and its delivery, that continue on after the trial with implementation of the new treatment). Certain research costs and all SSCs and ETCs are identified in the NIHR Schedule of Events Costs Attribution Tool (SoECAT). SoECAT was primarily developed to collect data relevant to hospital-based studies and was not developed to support care home trials. As such, it was difficult to enter funding data that would lead to care homes receiving money, especially for Scottish care homes.

The SoECAT model needs to be reviewed and made more flexible to allow appropriate funding of care home trials. The review needs to be done in conjunction with care home provider organisations, taking account of how such organisations are funded, the ways in which they are contracted through local authorities and the NHS and the ways in which they remunerate and backfill staff time.

What might we have done differently?

The choice of randomisation unit, for example individual (pragmatic in view of trial size) versus cluster (the more appropriate scientific design), was a continuing source of discussion. We were frustrated throughout by having no role in the choice of IMP and its contracting. Taking account of the principle ascribed to Montesquieu in 1726 ('the best is the mortal enemy of the good'),[52] a choice of a pragmatic intervention (e.g. beetroot juice as a source of nitric oxide and an antimicrobial[55,58]) together with individual randomisation would possibly have enabled a simpler trial that could have, at least, allowed recruitment to have started. Any future pandemic will need to balance the choice of interventions with the practicality of their delivery, bearing in mind that decisions will need to be made rapidly and that a multitude will be suggested, many of which will have little biological plausibility or proof of concept.

The future

The speed of onset of the COVID-19 pandemic suggests that a pandemic-ready trial should be prepared for the Social Care setting. Comparisons can justifiably be made with RECOVERY in the hospital setting. The ability to rapidly set up a pandemic platform trial in hospitals built on the pre-pandemic preparedness work of the NIHR Pandemic Portfolio of studies. Specifically, the Adjuvant Steroids in Adults admitted to hospital with Pandemic influenza (ASAP – NIHR 11/46/14) trial had already primed hospitals, CRN, HRA, MHRA and advisory bodies regarding a pandemic intervention trial and done this outside of the pandemic environment. For instance, the choice of intervention (dexamethasone) pre-2020 was highly contentious, but many of the debates and challenges had already been met during the years when ASAP was in hibernation.[59] Many clinicians and hospital systems had already been 'stress-tested' by ASAP to be able to deliver a pandemic trial. The ethics of consent (making it simple for a pandemic) had been rigorously discussed by the ASAP team with the highest levels of NIHR and HRA. ASAP had alerted NIHR to the likely need to prioritise pandemic studies during a pandemic and to further prioritise among pandemic studies (putting intervention trials first). This preparation and priming of funder, ethics and regulator considerably eased the rapid startup of RECOVERY.

Further, 40 of the ASAP trial sites contributed ~50% of the participants in the dexamethasone comparison (Lim, personal communication, 24 August 2023).

In comparison, PROTECT-CH was set up without any prior priming of funder, care homes and drug regulator and so was, in itself, the vanguard pandemic trial for care homes. While ASAP had many years to prepare the ground, PROTECT-CH had no time since the pandemic was already underway. Hence, based on the learnings of ASAP and PROTECT-CH, NIHR should give serious consideration to funding the preparation of a pandemic-ready trial to run in care homes and then have this put into hibernation,[1] as also suggested by the UK COVID-19 Inquiry.[60] A period of trial hibernation/maintenance may enable investigators to find resolutions to many of the barriers outlined in this report. Finally, we note that neither of the planned interventions, ciclesonide and niclosamide, showed efficacy when tested for other COVID-19 indications.[61,62]

Conclusions and future recommendations

The PROTECT-CH was designed to test interventions that would prevent COVID-19 in care homes and so reduce morbidity and mortality. Vaccination reduced the need for such testing. Nevertheless, in designing and setting-up the trial, multiple challenges and complications were faced, one or more of which could have prevented delivery of the trial if vaccination had been ineffective. We highlight these issues here and suggest potential solutions. Consideration and enactment of these by government, DHSC, NIHR, MHRA, care homes, CQC and insurance companies (and their equivalents in the devolved nations) are vital, if they are not to impede future pandemic and, indeed non-pandemic, care home-based trials. Serious consideration should be given to building and then hibernating a pandemic-ready platform trial suitable for care home research. Otherwise, history will repeat itself. We have made available all the resources we developed on the trial's website.

Additional information

CRediT contribution statement

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Heather Gage (https://orcid.org/0000-0002-2049-9406): Funding acquisition, Methodology (equal), Resources (equal), Software (equal), Writing – reviewing and editing (equal).

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Data-sharing statement

Due to the platform never recruiting nor treating participants, there are no raw participant-level data that can be shared. Further details on the protocol, analysis plans and dummy tables, training materials, database design, study oversight, newsletters, correspondence, approvals, participant information and consent forms and frequently asked questions are available at: www.protect-trial.net/ and www.protect-trial.net/resources. The full statistical analysis plan is available at www.protect-trial.net/files/resources/protect-sap-final-v1-0-08oct2021-signed-1.pdf; dummy tables are available at www.protect-trial.net/files/resources/protect-dummy-tables-final-v1-0-20211008-signed-1.pdf. The full health economics analysis plan is available at www.protect-trial.net/files/resources/protect-ch-economic-analysis-plan-final_v1-0_151021-signed-1.pdf; dummy tables are available at www.protect-trial.net/files/resources/health-economics-dummy-tables.pdf (all accessed on 26 July 2024).

Ethics statement

The study was approved by the UK REC and HRA (21/SC/0166, dated 17 May 2021).

Information governance statement

The University of Nottingham is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Nottingham is the Data Controller, and you can find out more about how they handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer at: www.nottingham.ac.uk/utilities/privacy/privacy.aspx#:~:text=The%20University%20of%20Nottingham%2C%20University,Z5654762.

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List of abbreviations

ASAP	Adjuvant Steroids in Adults admitted to hospital with Pandemic influenza
CH	care home
COVID-19	coronavirus disease-2019
CRN	Clinical Research Network/research delivery network
CQC	Care Quality Commission
CTA	clinical trial authorisation
CTIMP	clinical trial of investigational medicinal product
DHSC	Department of Health and Social Care
DMC	Data Monitoring Committee
ED	emergency department
ENRICH	Enabling Research in Care Homes
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
ETC	excess treatment cost
EQ-VAS	EuroQol-visual analogue scale
eTMF	electronic trial master file
GCP	good clinical practice
GP	general practitioner
HRA	Health Research Authority
HSBNI	Honest Brokerage Service NI
HSCNI	Health and Social Care Trusts NI
ICS	inhaled corticosteroids
IMP	investigational medicinal product
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Nottingham Clinical Trials Unit
NIHR	National Institute for Health and Care Research
PCR	positive polymerase chain reaction
PEP	postexposure prophylaxis
PHS	Public Health Scotland

PPI	patient and public involvement
PrEP	pre-exposure prophylaxis
PROTECT-V	prophylaxis for patients at risk of COVID-19 infection
PI	principal investigator
PMG	Platform Management Group
POG	prophylaxis oversight group
PROTECT-CH	Prophylactic Therapy in Care Homes Trials
PSC	Platform Steering Committee
QA	quality assurance
QALY	quality-adjusted life-year
REC	Research Ethics Committee
RECOVERY	randomised evaluation of COVID-19 therapy
RN	research nurse
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
SoC	standard of care
SoECAT	schedule of events costs attribution tool
SSC	service support cost
UK CTAP	UK COVID-19 therapeutics advisory panel

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Appendix 1

Authorship

The PROTECT-CH trial did not contract with any care homes, GPs or PIs, so there are no other authors to be listed here.

Eligibility criteria

Care home eligibility at trial entry

Inclusion criteria

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

Exclusion criteria

- CQC quality rating as inadequate, or equivalent in devolved administrations.

Care home eligibility at treatment phase

Exclusion criteria

- Positive PCR or lateral flow test (or equivalent) for SARS-CoV-2 in any resident and/or staff within previous 4 weeks.

Resident eligibility at trial entry

Inclusion criteria

- 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.

Exclusion criteria

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

Resident eligibility at treatment phase

Exclusion criteria

- Currently taking all of the trial interventions.
- Contraindication to all trial interventions – see protocol's IMP below.
- In treatment phase of another COVID-19 prevention or treatment trial.

Investigational medicinal products

Numerous interventions have demonstrated in vitro activity against SARS-CoV-2[63] and some have been tested clinically.

Ciclesonide

Ciclesonide, a non-halogenated inhaled corticosteroid used in the prophylaxis of asthma,[64–66] has been shown to block SARS-CoV-2 RNA replication by targeting the viral replication–transcription complex[67] and to inhibit SARS-CoV-2 cytopathic activity.[63] Pharmacodynamic studies have shown that inhaled ciclesonide has potent anti-inflammatory activity in patients with asthma and does not appear to have clinically relevant systemic effects even at high doses. In a case series, ciclesonide treatment was associated with higher blood lymphocyte counts, potentially important since lymphopenia is associated with severe COVID-19.[68] Several uncontrolled case series of ciclesonide use in COVID-19 have been reported, but the lack of control groups, small size and concurrent testing of other potential antiviral agents limit their interpretation.[69–71] A double-blind placebo-controlled Phase III trial (COVIS) of inhaled ciclesonide (320 µg bd) in 400 non-hospitalised patients with symptomatic SARS-CoV-2 infection found that ciclesonide did not alter the primary outcome – time to alleviation of COVID-19 symptoms – but reduced visits to the ED or hospitalisation; this trial was published after the choice of drug. Although licensed in the UK, the version of inhaled ciclesonide made available to PROTECT-CH was an unlicensed version manufactured by Ayrtons, a UK specialist pharmaceutical company. Ciclesonide was originally intended to be tested in the ongoing UK trial PROTECT-V trial.[54]

Since PROTECT-CH closed, other trials of inhaled ciclesonide for COVID-19 have been reported,[72–74] including when given in combination with other drugs.[75] A recent systematic review identified 11 randomised trials of inhaled corticosteroids (ICS) testing ciclesonide, budesonide or fluticasone furoate. While ICS was associated with higher rates of early symptom alleviation,

there was no difference between those receiving ICS versus control for the composite outcome of urgent care, ED visit or hospitalisation or combined hospitalisation or death. There was a non-significant lower risk of death at 28 days with ICS versus control.[76] A separate meta-analysis also suggested the lack of clinical benefit.[61]

Niclosamide

Niclosamide anhydrous is a salicylanilide introduced as an oral anthelmintic in the early 1960s for treating tapeworm infestations, and it was more recently used as a general pesticide in aquaculture. Niclosamide is a multimodal drug that inhibits or regulates multiple signalling pathways and biological processes via pleotropic activities. Recent studies have indicated that niclosamide may have broad clinical applications beyond the treatment of parasites and that it has demonstrated anti-SARS-CoV-2 activity through inhibiting SARS-CoV-2 replication and cellular penetration in vitro[63] and in vivo.[77] Niclosamide has also been shown to have non-steroidal anti-inflammatory activity, both experimentally and clinically.

Oral niclosamide is approved for treating tapeworm infestations and has safety and tolerability data in a Phase I trial in normal volunteers.[78] Although not licensed in the UK, the British National Formulary describes oral niclosamide as the most widely used drug for tapeworm infection (https://bnf.nice.org.uk/treatment-summaries/helminth-infections/; accessed 4 October 2023). Nasal administration as a spray may be most effective as a postexposure prophylactic for early-stage infection when viral load is a main issue. Although niclosamide is a substrate and inhibitor of CYP1A2 in vitro, intranasal administration is unlikely to lead to plasma levels where CYP inhibition is seen. Inhaled niclosamide is an unlicensed formulation being developed by the Danish company, Union Therapeutics. A small trial of oral niclosamide, for example not given by nasal spray, has been reported.[79] Subsequent to PROTECT-CH, the PROTECT-V trial[54] found that inhaled niclosamide did not modify the outcome when tested for the prevention of COVID-19 in patients with renal disease (haemodialysis, renal transplant and inflammatory renal diseases).[62]

Health economic evaluation

The primary economic evaluation planned was a within-trial cost-utility analysis based on outcomes at day 60, adopting an NHS cost perspective. Healthcare resource use collection was designed to be parsimonious and feasible and would be collected by electronic case report form (eCRF) where necessary, in addition to routine data sources. Resource use data collection was to include primary care contacts, use of ambulance services and secondary care attendance or stays. Health-related quality of life measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), EuroQol-visual analogue scale (EQ-VAS) (proxy report) at 60 days was to be measured and EQ-5D-5L presented descriptively in addition to estimating between group differences. Self-reported health-related quality of life was also to be collected where possible. Self-report and proxy report response patterns were to be explored and reporting subgroups (self-report vs. proxy) were examined in the sensitivity analysis.

Statistical analyses were to be conducted in line with other continuous outcomes, using linear mixed-effects models, additionally controlling for differences in the baseline EQ-5D-5L utility, accounting for potential non-normality and correlation between costs and quality-adjusted life-years (QALYs), where appropriate. Missing data were to be assessed and handled appropriately depending on the nature of the missingness.

Incremental costs (including any potential savings) associated with prophylaxis for care home residents were to be estimated. EQ-5D-5L was to be used to compute QALYs and estimate incremental QALYs. Costs and QALYs were to be combined to estimate the incremental cost-effectiveness ratio and present incremental net monetary benefit at various willingness to pay thresholds. Uncertainty would be characterised using bootstrap sampling and cost-effectiveness acceptability curves. A secondary analysis would be performed based on outcomes at 120 days (survival and resource use from routine sources). The full health economics analysis plan is available at www.protect-trial.net/files/resources/protect-ch-economic-analysis-plan-final_v1-0_151021-signed-1.pdf; dummy tables are available at www.protect-trial.net/files/resources/health-economics-dummy-tables.pdf (both accessed 26 July 2024).

Process evaluation

A key substudy was a nested process evaluation that was designed to run concurrently with the trial. The evaluation was to be informed by a realist approach[80–83] with the following objectives:

1. to provide contextualised insight into the delivery of the intervention(s)
2. to consider acceptability of the intervention to staff, residents and their families
3. to reflect upon and inform trial processes (although interviews were performed, the paper has yet to be completed).