CONTROL COVID

CONTROL OF COVID-19 OUTBREAKS IN LONG TERM CARE

FULL TITLE:	**Control of COVID-19 outbreaks in long term care (CONTROL-COVID-Favipiravir)**
Protocol No.	CONTROL-COVID-Favipiravir-1
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Study Sponsor(s):	Appili Therapeutics
ClinicalTrials.gov Identifier:	pending
Version No.	2.0
Date:	4-June-2020

GCP Statement

This clinical study will be conducted in accordance with applicable Health Canada regulations, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on current Good Clinical Practice (GCP), and the Declaration of Helsinki.

Confidentiality Statement

This clinical study protocol contains information which is of a confidential, trade-secret or proprietary nature. The protocol is for the use of the Sponsor-Investigator and designated representatives participating in the investigational trial. It is not to be disclosed to any other person or party without the prior written approval of the Sponsor-Investigator.

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1. INVESTIGATOR AGREEMENT

Protocol Title: Control of COVID-19 outbreaks in long term care (CONTROL-COVID-Favipiravir)
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Date: 4-June-2020

This clinical study will be conducted in accordance with applicable Health Canada regulations, ICH guidelines on current GCP, and the Declaration of Helsinki.

I confirm that I have read and understand this protocol and I agree to conduct this clinical study in accordance with the design and specific provisions of the protocol, with the exception of a change intended to eliminate an immediate hazard to participants. Any deviation from the study protocol will be documented in the case report form.

I agree to promptly report to the applicable ethics boards any changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without prior ethics and Sponsor-Investigator approval, except where necessary to ensure the safety of study participants.

Name	Signature	Date (dd-mmm-yyyy)

2. STUDY CONTACT DETAILS

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Data safety board	Pending

3. PROTOCOL SYNOPSIS

Full Title	**Control of COVID-19 outbreaks in long term care**
Short Title	CONTROL-COVID-1
Protocol Number	**CONTROL-COVID-Favipiravir-1**
Version Number and Date	Version 2.0, June 4, 2020
Study Duration	Enrollment period: May 10, 2020 to Oct 31, 2020
	Study period: April 1, 2020 to March 31, 2021
Principal Investigator	Allison McGeer
Number of Centers	60 screened, 16 enrolled
Number of participants	Estimated: 760
Study Design	Placebo-controlled cluster-randomized trial
Primary Objective	Evaluate the efficacy of favipiravir chemoprophylaxis for control of outbreaks of COVID-19 in long-term care homes (LTCH).
Secondary Objectives	To compare the following secondary outcomes between study arms: 1. The proportion of residents of included LTCH units who die up to day 40, and up to day 60 2. The proportion of residents of included LTCH units who were uninfected at baseline and develop new symptomatic microbiologically confirmed COVID-19 up to day 40 3. The proportion of exposed staff uninfected at baseline in whom SARS-CoV-2 infection is identified up to day

	14 and up to day 40 4. The proportion of residents of included LTCH units hospitalized up to day 40 5. The proportion of residents of included LTCH units who discontinue study medication due to adverse events 6. The proportion of LTCH staff of included LTCH units who discontinue study medication due to adverse events. 7. The occurrence of new microbiologically confirmed COVID-19 infections in residents in other units of the facility up to day 40 (dichotomous, at LTCH level) 8. The proportion of previously unaffected LTCH units of the remainder of the facility in which a case of COVID-19 is identified 9. The proportion of residents in the remainder of the facility who develop COVID-19 infections up to day 40
Sample Size	8 units per arm (16 units in total)
Randomization	Cluster trial with probabilistic minimization
Study Population	Residents and staff of LTCH for older adults, Ontario
Investigational Product Description	Favipiravir 200 mg tablets
Control	Placebo
Administration and Dosing	Favipiravir 1600 mg orally twice daily on day one then 800 mg orally twice daily for prophylaxis, and 2000 mg orally twice daily on day one then 1000 mg orally twice daily for treatment
Duration of Treatment	Starting once a COVID-19 outbreak in an LTCH unit (>=2 symptomatic microbiologically confirmed COVID-19 cases) has been identified and continuing until day 25
Outcome Measures	Primary outcome: Control of outbreak, defined as no new cases of COVID-19 in residents for 24 consecutive days up to day 40 after the

	start of prophylaxis Secondary outcomes: 1. The proportion of residents of included LTCH units who die up to day 40, and up to day 60 2. The proportion of residents of included LTCH units who were uninfected at baseline and develop new symptomatic microbiologically confirmed COVID-19 up to day 40 3. The proportion of exposed staff uninfected at baseline in whom SARS-CoV-2 infection is identified up to day 14 and up to day 40 4. The proportion of residents of included LTCH units hospitalized up to day 40 5. The proportion of residents of included LTCH units who discontinue study medication due to adverse events 6. The proportion of LTCH staff of included LTCH units who discontinue study medication due to adverse events. 7. The occurrence of new microbiologically confirmed COVID-19 infections in residents in other units of the facility up to day 40 (dichotomous, at LTCH level) 8. The proportion of previously unaffected LTCH units of the remainder of the facility in which a case of COVID-19 is identified 9. The proportion of residents in the remainder of the facility who develop COVID-19 infections up to day 40
Statistical Analysis	Primary outcome: Fisher's exact test (two-sided) comparing control of outbreak in homes receiving study drug versus placebo

4. INTRODUCTION, BACKGROUND, AND STUDY RATIONALE

4.1 Overview and Study Rationale

A novel coronavirus, SARS-CoV-2, emerged in December 2019 in Wuhan, China.[1,2] Causing a febrile respiratory illness known as COVID-19, this is the third zoonotic coronavirus of the past two decades to infect humans, after SARS-CoV and MERS-CoV.[3]

COVID-19 is spreading far more rapidly than its predecessors, having infected over 2,300,000 persons worldwide as of April 18th.[4] Rapid transmission has been fuelled by the high intrinsic reproductive number of 2-2.5,[5-7] burgeoning community transmission,[8-10] and the potential for occult transmission during the pre-symptomatic incubation period.[11-13]

As the scale of the ongoing COVID-19 reaches pandemic proportions, intensive public health efforts are underway to control the outbreak. Governments have instituted travel bans, intensified airport screening, implemented case isolation, contact tracing and quarantine of at-risk contacts.[14-16] While such interventions appear to have reduced the effective reproductive number,[17] and slowed ongoing transmission within China, international cases continue to grow. Public health control measures such as symptomatic case-isolation and quarantine of at-risk patients may be insufficient to control the pandemic,[14,18] particularly in light of evidence of transmission from minimally symptomatic or subclinical cases.[11,13,19]

Canada was amongst the first countries outside of China to identify a case of COVID-19,[20] and has already begun to see rising case numbers.[21] It is likely that continuing local transmission will result in on-going infection across the country.

In China, nearly one-fifth of infected patients experience severe or critical illness as a result of COVID-19,[22] with an overall 2.3% case fatality rate and up to 6.1% of patients experiencing severe complications (intensive care unit admission, invasive ventilation, or death).[23] While patients across all age-categories have been infected by SARS-CoV-2,[22,24,25] the elderly are disproportionately bearing the consequences of this pandemic.[26] Most patients dying are ≥60 years of age, with case fatality rising drastically from 0.2% for individuals < 40 years of age to 14.8% for those ≥ 80.[22]

The first evidence of Canadian community transmission of SARS-CoV-2 was found in a nursing home in British Colombia, leading to the first death in Canada.[27] Similarly, in the United States a significant outbreak has been reported in a Seattle-based nursing home.[28] While guidelines and many preventive strategies have been implemented in long term care homes (LTCHs), an increasing number outbreaks are being reported in many countries, including across Canada. Given the structure of LTCHs, and the evidence of difficultly preventing outbreaks and limiting the spread of other respiratory viruses, it is highly likely that many outbreaks of COVID-19 will occur in LTCHs, with devastating consequences for residents and their families.

The long-term care population reflects a particularly frail and elderly subset of patients, with a median age of 86 years across Canada. Despite a significantly lower typical case fatality rates for influenza as compared to COVID-19, case fatality rates for influenza outbreaks in LTC facilities have been identified to be as high as 55%.[29] Outbreaks of COVID-19 are escalating in Canadian LTCHs, with strikingly high case fatality rates. Residents of LTCHs comprise nearly half of all Canadian COVID-19 deaths.[30] In Ontario, as of April 15, 2020, 114 of 631 Ontario LTCHs have declared COVID-19 outbreaks and 145 COVID-19-related deaths have been reported in these homes.

Given the severity of COVID-19 amongst the elderly, and the evidence of ongoing transmission with severe outcomes in LTCHs for the elderly, it is critical to develop interventions to minimize the spread of disease in this setting. As vaccines and treatment for COVID-19 remain unavailable, all possible alternative interventions must be explored.[31] Chemoprophylaxis of at-risk individuals has been identified as an important potential control strategy.

The use of chemoprophylaxis, both pre- and post-exposure to a known case is well established for the prevention of viral infections such as influenza and human immunodeficiency virus.[32-34] Post-exposure chemoprophylaxis for seasonal influenza has been identified to significantly reduce incident cases in several meta-analyses,[35-37] and is a critical component of outbreak control in LTCHs.[33] Further, observational data has indicated potential benefits for post-exposure chemoprophylaxis for another coronavirus infection, the Middle East Respiratory Syndrome.[38] Another evidence-based chemoprophylaxis strategy, pre-exposure prophylaxis (PrEP), involves administering an antimicrobial agent to people at high risk before exposure has been confirmed, and is widely used for the prevention of malaria and HIV infection.[34] Chemoprophylaxis is also used in the control of outbreaks of group A streptococcal infection in long term care, and in the prevention of transmission to close contacts of patients with streptococcal toxic shock syndrome.[39,40]

In Ontario, current recommendations are that any resident or staff member of a LTCH who develops symptoms of an upper respiratory tract infection be tested for COVID-19, and that any resident transferred to an acute care hospital with symptoms compatible with COVID-19 be tested. An outbreak is defined as the identification of a single case of COVID-19 in a LTCH; however, in some circumstances, single cases in either residents or staff have not progressed to involve additional resident or staff cases. These recommendations are intended to ensure that all cases are identified in LTCH, so that additional measures can be instituted early. Despite these measures, new outbreaks in LTCHs are being reported daily in Ontario, and most outbreaks are continuing. We expect that both individual cases of disease and already established outbreaks will be identified in many LCTHs over the coming months.

To address the need to intervene to prevent the spread of COVID-19 in long-term care facilities, we propose a cluster-randomized placebo-controlled trial of chemoprophylaxis in LTCHs experiencing COVID-19 outbreaks.

4.2 Current Treatment Options and rationale for studying Favipiravir

At the time of writing, definitive therapies for established COVID-19 remain to be defined. Significant interest exists in repurposing existing antiviral agents for use against COVID-19.

Favipiravir is a purine nucleoside analogue, which acts as a competitive inhibitor of RNA-dependant RNA polymerase.[41] It has activity against influenza A and B including activity against oseltamivir and zanamivir-resistant influenza viruses, several agents of viral hemorrhagic fever, and SARS-CoV-2 *in vitro.*[41-43] Favipiravir is approved for novel epidemic influenza strains unresponsive to standard antiviral therapies in Japan.

Favipiravir was identified to have activity *in vitro* against SARS-CoV-2, albeit a high concentration was required as compared to chloroquine or remdesivir (EC_{50} = 61.88 µM).[42] Despite a similarly elevated EC_{50} identified for favipiravir and Ebola virus, it was identified in previous animal models to be highly effective as post-exposure prophylaxis for mice exposed to an Ebola virus challenges, with rapid virologic response preventing mortality.[44,45] Based on the

dosing strategies and pharmacokinetic data from human influenza trials, a intensified dosing strategy of 6000 mg loading on day 1 followed by 1200 mg PO BID maintenance therapy for 10 days was employed in a single-arm clinical trial for Ebola virus disease in Guinea.[46]

In a retrospective analysis of 124 patients with Ebola virus disease in Sierra Leone, those treated with favipiravir had a significantly higher survival rate compared to patients receiving supportive management (56% v. 35.3%, p=0.027).[47] Patients received favipiravir 800 mg PO BID on day 1 and 600 mg PO BID for days 3-11. Viral loads were quantified for 35 patients twice during their hospitalization and were significantly reduced amongst patients receiving favipiravir.

Favipiravir has also been used as pharmacologic post-exposure prophylaxis for Ebola virus disease.[48] In a case series of four healthcare workers with higher risk Ebola virus exposures, including two hollow-bore needle stick injuries, none of the patients who received 10 days of high-dose favipiravir developed Ebola virus disease.

Early clinical experience with favipiravir for COVID-19 is promising. An open-label nonrandomized trial of 80 patients with COVID-19 in China identified a significant reduction in the time to SARS-CoV-2 viral clearance in patients treated with favipiravir compared to historical controls treated with lopinavir/ritonavir.[49] Patients with mild or moderate COVID-19 were enrolled within 7 days from disease onset; those with severe or critical disease, ≥ 75 years old, chronic liver disease, or end-stage renal disease were excluded. Patients in the intervention arm received Favipiravir 1600 mg PO BID on day 1 followed by 600 mg PO BID on days 2-14. Both arms were co-treated with inhaled IFN- α1b 60 μg BID and therapy was continued until viral clearance, up to a maximum of 14 days. Thirty-five patients were assigned to favipiravir and 45 patients to lopinavir/ritonavir, with a median age of 47 (IQR 35.8-61); 13.7% were ≥ 65 years old. There was a significant reduction in the median time to viral clearance with favipiravir (4 days; IQR 2.5-9) as compared to lopinavir/ritonavir (11 days; IQR 8-13; p <0.001). Further, by day 14, 91.4% of patients in the favipiravir arm had radiographic improvement versus 62.2% of the lopinavir/ritonavir arm. There was a significantly lower rate of adverse events in patients receiving favipiravir (11.4% v. 55.6%, p<0.01).

In an open-label randomized trial in China, 240 patients with confirmed COVID-19 were randomized to favipiravir or arbidol.[50] Favipiravir was given at 1600 mg PO twice on day 1 followed by 600 mg PO BID until day 7-10. The clinical recovery rate by day 7 of treatment was higher amongst patients receiving favipiravir, albeit not achieving statistical significance (61.21% v. 51.67%, p=0.1396). Amongst patients with moderately severe disease, there was a significantly higher rate of clinical recovery by day 7 with favipiravir (71.43% v. 55.86%).

Given the demonstrated in-vitro of activity of favipiravir against SARS-CoV-2 and signals of benefit in early clinical experience for COVID-19, further studies are urgently needed. To address this need, there are several active clinical trials to assess the therapeutic efficacy for COVID-19. However, no trials to date have focused on outbreak control, an area of significant need. It is critical to evaluate the efficacy of favipiravir as chemoprophylaxis against COVID-19 using a placebo-controlled randomized trial.

As over three hundred trials are currently registered for treatment of COVID-19 in China, and in-vivo data may emerge during the conduct of this study for the therapeutic efficacy for particular pharmacotherapeutics. The study team will monitor findings from ongoing treatment trials, and if an alternative agent is identified to be more effective at study initiation,

consideration will be given to altering the study drug. Any such modification would require a formal amendment to the study protocol, regulatory approvals, and ethical approvals.

4.3 Potential Risks and Benefits to Human Participants

Overall, more than 40 clinical studies with favipiravir have been conducted globally, mainly in the US and Japan. Favipiravir has been well tolerated in studies in adults and elderly subjects with uncomplicated influenza. A consistent safety profile composed of relatively low frequencies of mild to moderate adverse events clustering around the system organ classes of gastrointestinal disorders has been characterized. Mild to moderate transient, asymptomatic elevations in serum uric acid and mild to moderate diarrhea are the two most common adverse events known to occur with favipiravir. Favipiravir has been safely studied with therapy durations up to 22 days (JP120, Phase 1 study).

Favipiravir is considered a safe drug. No related serious adverse events occurred in licensure studies of favipiravir.[71] Preclinical and animal studies show no direct suppression of white blood cell types or immunosuppression by favipiravir. Genotoxicity studies indicate that favipiravir does not pose a clinical genotoxic risk; however, based on the results of embryo-fetal toxicity studies, favipiravir is not recommended for use in pregnant females, those who may become pregnant, or those who are nursing. Though an inhibitor of CYP 2C8 and aldehyde oxidase, few drugs are contra-indicated. Overall, the safety of favipiravir suggests that the potential benefit to human participants exposed to a confirmed case of COVID-19 generally outweighs potential risks.

5. DEFINITIONS

Chemoprophylaxis

When an outbreak of COVID-19 is declared in a LTCH the state of LTCH unit residents who do not have COVID-19 can be classified into 1 of 3 categories: Category 1) not exposed and therefore not incubating (likely representing the majority of the unit residents), Category 2) exposed and incubating but with no detectable virus, Category 3) exposed, incubating with detectable virus. "Chemoprophylaxis" in this study refers to the use of a pharmacologic agent for either pre-exposure (category 1) or postexposure prophylaxis (category 2), or for pre-emptive therapy (category 3). When an outbreak is identified in a LTCH, it is difficult or impossible to assess the degree of exposure for individuals; most often many individuals have had relatively low risk exposure and it is not possible to predict which of them will develop disease. Often, several days of undetected exposure have occurred. Thus, all residents and staff should be considered as incubating and about to develop disease. The term chemoprophylaxis is therefore intended to cover all at-risk individuals in this context. Infected residents will also receive study drug. Infected staff will be excluded from work and, if possible, referred to trials of treatment.

Chemoprophylaxis period

Chemoprophylaxis for all unit residents will be started as early as a COVID-19 outbreak has been recognized at a unit (2 or more symptomatic residents with positive COVID-19 test within 7 days). Chemoprophylaxis will be continued until day 25.

Long term care home for the elderly (LTCH)

"Long-term care home" mean a resident that is licensed as a long-term care home under the Long-Term Care Homes Act, 2007.[72] LTCHs serving older adults which are not so licensed but which have units in which medication can be delivered from a central source and adherence can be monitored are also eligible for inclusion.

***Microbiologically confirmed COVID-19*:**

Detection of SARS-CoV-2 RNA in any patient specimen (mid-turbinate swab, nasopharyngeal swab, oropharyngeal swab, sputum specimen, endotracheal aspirate, bronchoalveolar lavage specimen, stool, blood etc.).

Outbreak in LTCH

Two or more cases of acute illness due to COVID-19 in residents on one unit, with onset within 7 days.

Rationale: In contrast to influenza which has an estimated serial interval of 2.2-2.8 days,[73] COVID-19 has been identified to have a serial interval ranging from 4.4-7.5 days, justifying the use of a longer-time span between cases for the purposes of outbreak definition.

Outbreak control

Outbreak control is defined as no new cases of COVID-19 in residents for 24 consecutive days up to day 40 after the start of prophylaxis.

Rationale: The experience with oseltamivir for influenza is such that when it is given for post-exposure prophylaxis, it also has activity for pre-emptive therapy. As a result, oseltamivir

can both prevent incident cases and resolve pre-symptomatic infections, leading to a rapid termination of an outbreak with universal prophylaxis with oseltamivir. Nonetheless, pre-emptive therapy is often incompletely effective, and it is common to see new cases of influenza with onset within the first 2-4 days (one incubation period) of influenza, and occasionally, a single case occurs later.

We do not yet know if any drugs are effective for therapy of COVID-19 or pre-emptive therapy of subclinical COVID-19. It is possible that drugs may be effective for prophylaxis but not pre-emptive therapy. For COVID-19, if the therapy is effective for prophylaxis but ineffective for pre-emptive therapy, new cases may continue to be observed during the first incubation period (median 5 days, 95th percentile of 12.5 days) after prophylaxis is started. If prophylaxis is completely effective, then no cases should occur after this point. However, if individual level prophylaxis is incompletely effective, or if transmission occurs to residents or staff not able to take prophylaxis, then some transmission might occur without compromising outbreak control. Assuming that the period of infectivity is 10 days, and the maximum incubation period is 14 days, then an outbreak can be considered controlled (or ended) if no cases occur for 25 days after the day of onset in the last case.

Study Day 1

Day 1 is defined as the first day of receipt of chemoprophylaxis in the LTCH.

Symptomatic microbiologically confirmed COVID-19 disease in residents: a respiratory specimen (e.g. nasopharyngeal swab) yielding SARS-CoV-2 RNA in association with new onset fever (≥37.8ºC) OR cough OR one or more of the following other respiratory or systemic symptoms (fatigue, myalgias, arthralgias, shortness of breath, sore throat, chills, loss of appetite, vomiting or diarrhea, change in level of responsiveness or capacity for activities of daily living (ADL)), OR requirement for hospitalization OR death.

Symptomatic microbiologically confirmed COVID-19 disease in staff: fever (≥38.0ºC or cough or two or more of the following other respiratory or systemic symptoms (fatigue, myalgias, arthralgias, shortness of breath, sore throat, chills, loss of appetite, anosmia, vomiting or diarrhea).

Unit

A unit is the section of the LTCH experiencing an outbreak which will be randomized to study drug. Units are sections within the LTCH which have a nursing station and shower room and on which residents and most staff can be reliably physically separated from residents of other units for the duration of the outbreak. Units with >32 residents will be excluded.

6. STUDY OBJECTIVES AND DESIGN

6.1 Overall Study Design (figure 1)

This study is a partially blinded, placebo-controlled cluster randomized trial of chemoprophylaxis to control outbreaks of COVID-19 in LCTHs for the elderly. The unit of analysis is a ward/unit. This design is selected to mimic the current approach to outbreaks of other respiratory viral infections, both because this approach has proven effective for these other viruses, and because it is standard practice and therefore feasible to implement.

Eligible LTCHs will be asked to report outbreaks to the study in addition to the legally-required reporting to their local public health unit; public health units will also be asked to discuss the study with LTCHs reporting outbreaks. In addition, study staff will contact the infection control practitioner in each of the screened LTCHs twice weekly, to ensure the prompt identification of outbreak units.

Either pre-study, or at baseline (identification of the outbreak), residents and staff will be assessed for contraindications to enrollment and informed consent will be obtained for residents and staff to receive the allocated intervention, and to be followed up individually for clinical outcomes, adherence and safety during the outbreak. Favipiravir or placebo will be offered to all residents and staff who will be working on the unit during the chemoprophylaxis period, according to the allocation. Surveillance for infection will occur as usual for resident illness within each facility; staff will be asked to report symptoms and will be screened for symptoms each time they enter the building. Consenting residents and staff will be screened at day 0, day 14 and day 40 to identify asymptomatic infections and to assess duration of viral shedding. The primary outcome will be control of the outbreak, defined as no new microbiologically confirmed case of COVID-19 for 24 consecutive days up to day 40.

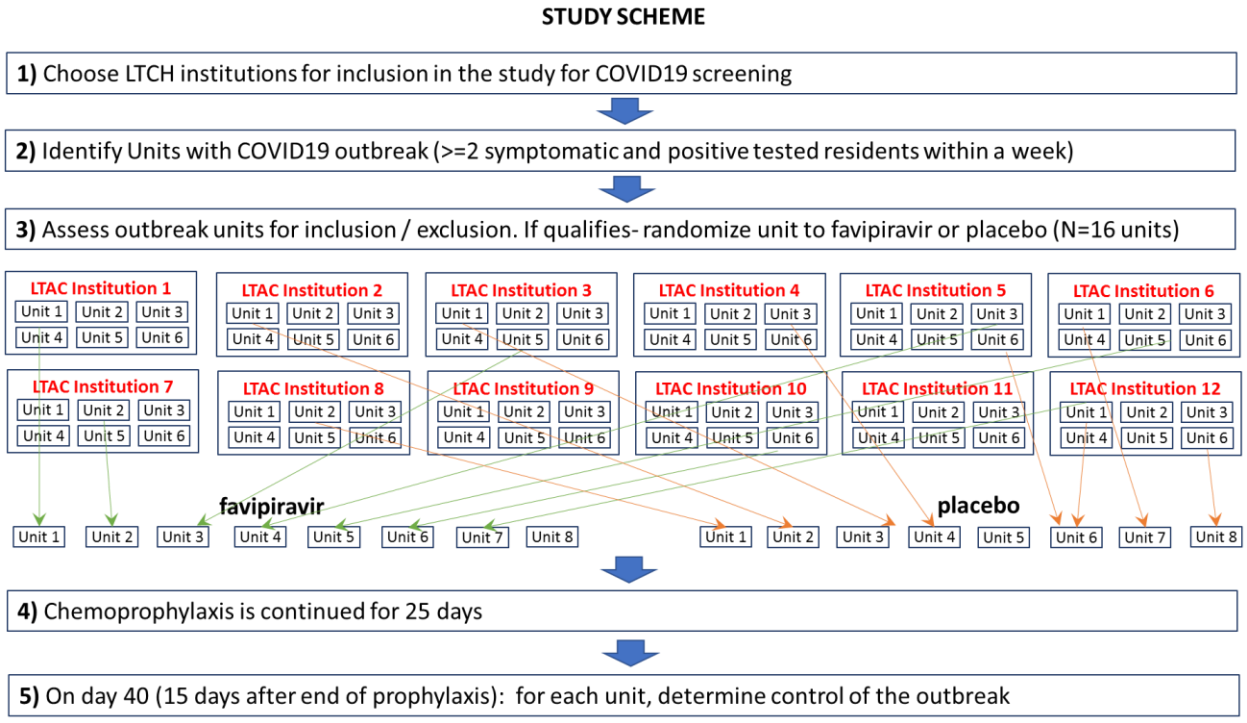

Figure 1: a scheme of study flow.

6.2. Primary objective

The primary objective of this trial is to evaluate the efficacy of favipiravir compared with placebo as chemoprophylaxis for control of outbreaks of COVID-19 in LTCHs.

6.3 Secondary objectives

Secondary objectives are to compare the following secondary outcomes between study arms:

1. The proportion of residents of included LTCH units who die up to day 40, and up to day 60
2. The proportion of residents of included LTCH units who were uninfected at baseline and develop new symptomatic microbiologically confirmed COVID-19 up to day 40
3. The proportion of exposed staff uninfected at baseline in whom SARS-CoV-2 infection is identified up to day 14 and up to day 40
4. The proportion of residents of included LTCH units hospitalized up to day 40
5. The proportion of residents of included LTCH units who discontinue study medication due to adverse events
6. The proportion of LTCH staff of included LTCH units who discontinue study medication due to adverse events.
7. The occurrence of new microbiologically confirmed COVID-19 infections in residents in other units of the facility up to day 40 (dichotomous, at LTCH level)
8. The proportion of previously unaffected LTCH units of the remainder of the facility in which a case of COVID-19 is identified
9. The proportion of residents in the remainder of the facility who develop COVID-19 infections up to day 40

6.4 Endpoint Assessment

The primary outcome (primary endpoint) will be control of outbreak, defined as no new cases of COVID-19 in residents for 24 consecutive days up to day 40 after the start of prophylaxis. This outcome is dichotomous (yes/no) and will be determined at the level of the cluster (LTCH unit).

Secondary outcome measures (endpoints) are:

1. The proportion of residents of included LTCH units who die up to day 40, and up to day 60
2. The proportion of residents of included LTCH units who were uninfected at baseline and develop new symptomatic microbiologically confirmed COVID-19 up to day 40
3. The proportion of exposed staff uninfected at baseline in whom SARS-CoV-2 infection is identified up to day 14 and up to day 40
4. The proportion of residents of included LTCH units hospitalized up to day 40
5. The proportion of residents of included LTCH units who discontinue study medication due to adverse events
6. The proportion of LTCH staff of included LTCH units who discontinue study medication due to adverse events.
7. The occurrence of new microbiologically confirmed COVID-19 infections in residents in other units of the facility up to day 40 (dichotomous, at LTCH level)
8. The proportion of previously unaffected LTCH units of the remainder of the facility in which a case of COVID-19 is identified
9. The proportion of residents in the remainder of the facility who develop COVID-19 infections up to day 40

7. SELECTION AND ENROLLMENT OF PARTICIPANTS

The trial will enroll resident and staff in 16 LTCH units with outbreaks of COVID-19 in Ontario. LTCH units will be allocated to receive favipiravir or placebo.

7.1 Eligibility Criteria

7.1.1 Inclusion criteria for LTCHs

1. LTCH in Ontario with >80% of residents being adults ≥65 years of age.
2. Residents are or can be routinely assessed at least daily by staff.
3. LTCH has not previously had a unit enrolled in this study
4. Outbreak of COVID-19 declared on at least one nursing unit, requiring all of the following:
    a. ≥2 to ≤4 residents who develop PCR-confirmed symptomatic COVID-19 infection on the same unit within ≤ 7 days at the time when the outbreak is identified as eligible.
    b. ≤21 days from symptom onset in the index case at the time when the outbreak is identified as eligible.
    c. Cumulative attack rate in residents on the affected unit since the beginning of the pandemic ≤25% at the time when the outbreak is identified as eligible.
    d. ≤20% of residents with microbiologically confirmed COVID-19 or line-listed as a presumptive case in a COVID-19 outbreak and not tested for COVID-19 in prior outbreaks within the last six months.
    e. Nursing unit with ≥16 and ≤32 residents.
    f. Nursing home agrees to work with study coordination to minimize the number of persons who provide care on the unit
5. Mechanism exists for delivery of medication and recording of administered medication for all residents.
6. ≥80% of residents on outbreak unit are eligible and they or their substitute decision makers consent to participate in the study.
7. Written informed consent of Medical Director, Administrator and a delegate of the Residents' Council of the LTCH for LTCH to be included in the cluster trial.

7.1.2 Inclusion criteria for LTCH residents

1. Informed consent from resident or substitute decision maker (SDM),

7.1.3 Inclusion criteria for LTCH staff

1. Expected to work at least two 8-hour shifts, or the equivalent time (16 hours on the unit) during the outbreak period.
2. Informed consent.

7.2 Exclusion criteria

7.2.1 Exclusion criteria for LTCHs

1. Inability to deliver medication to consenting residents within 96 hours of identification of the outbreak.
2. Inability to define a physically separate unit with ≤32 residents.
3. Any of facility management, medical advisory committee or resident council do not approve participation.

7.2.2 Exclusion criteria for LTCH Residents and Staff

1. Pregnancy (females < 55 years of age require a negative urine pregnancy test at enrollment, and either menopause or two concurrent reliable methods of contraception need to be confirmed)
2. History of abnormalities of uric acid metabolism, other than gout.
3. History of hypersensitivity to remdesivir or favipiravir
4. Previous diagnosis of hepatic cirrhosis
5. Current use of the following medications, which cannot be discontinued for the duration of the study: pyrazinamide, hydralazine, more than 3000 mg of acetaminophen per day

7.3 Consent and Enrollment

The Medical Director, the LTCH Administrator and a delegate of the Residents' Council of the LTCH will give written informed consent for the LTCH to be included in the cluster trial. The LTCH Administrator will then delegate the personal distribution of a fact sheet describing the trial to all potentially eligible LTCH staff, residents and SDMs. The fact sheet will indicate that LTCH staff, residents and their SDMs would be contacted by research personnel in case of a COVID-19 outbreak in the LTCH, and offer them the possibility to opt out from being contacted by research personnel by calling or emailing the administration of the LTCH. In addition, posters about the trial will be placed in all staff locker rooms, lounges and nursing stations, and in public areas of the home.

LTCH staff, residents and their SDMs who did not opt out within 5 calendar days after receipt of the fact sheet will be contacted by research personnel. The study will be explained to each person, and written informed consent or e-consent will be obtained. This consent will include all features required for obtaining full informed consent, as outlined in the 2nd edition of the Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS2).[66] LTCH staff and competent residents who provide written informed consent or e-consent at this stage may be enrolled into the trial. Residents who have been assessed as not competent to make their own medical decisions in their capacity evaluation (https://collections.ola.org/mon/24004/300799.pdf) may be enrolled into the trial if their SDM provided written informed consent or e-consent.

For this trial, time to randomization and treatment is of considerable importance for outbreak control; thus, if written informed consent or e-consent has not been obtained prior to an outbreak being declared, informed consent will occur in two stages to minimize delays. LTCH staff, residents and/or their SDMs who have not opted out, but have not yet given written informed consent or e-consent, will therefore be asked to give preliminary consent by telephone or video call ≥24 hours after receipt of the fact sheet describing the trial. This consent will also include all features required for obtaining full informed consent, as outlined in the 2nd edition of

the Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS2),[66] and will be fully documented by the research personnel. Those who provide preliminary verbal consent at this stage may be enrolled into the trial. LTCH staff and competent residents who provide preliminary consent at this stage may be enrolled into the trial. Residents who are not considered competent to provide consent (see above) may be enrolled into the trial if their SDM provided preliminary consent. A second stage of the consent process in participants with preliminary consent will involve obtaining a signed copy of the REB-approved written informed consent form, either in electronic or hard copy, or e-consent. This stage should be done as soon as possible after the verbal preliminary consent is obtained, and research personnel will obtain a signed copy of the consent form or e-consent no later than 40 days after randomization

As new staff may be needed on the unit over time, any new staff starting work on the outbreak LTCH unit will be identified by the facility and referred to the trial for consenting and enrolment on an ongoing basis using the process described above.

7.5 Co-enrollment Guidelines

Co-enrollment into other Health Canada-regulated clinical trials of COVID-19 prevention is permitted, but details of the co-intervention must be documented in the study database. For participants who develop microbiologically confirmed COVID-19 infection, enrollment in trials of treatment other than favipiravir is permitted, but details of the co-intervention must be documented in the study database.

8. WITHDRAWAL OF PARTICIPANTS

8.1 Withdrawal criteria, and criteria for discontinuation of study drug

Participants may be withdrawn from the study if the Sponsor terminates the trial. Participants who are discovered to be pregnant will have the study drug discontinued due to potential teratogenicity; however, given the age distribution of LTCH residents (<3% under 65 years of age), pregnancy in this patient population is extremely unlikely. If a new health condition emerges in a participant that requires medication contraindicated by the protocol, then decisions regarding dose modification or discontinuation of the study drug can be made at the discretion of the study investigators and/or the attending physician, but the participant will be retained in the study for ascertainment of the primary and secondary outcomes.

Participants or their most responsible physician may discontinue study drug at any time if severe adverse events thought to be due to study drug are identified. Participants will continue in the study if this occurs, and the reason discontinuation of study drug will be noted in the study database. Participants may withdraw from the study at any point for any reason.

9. ALLOCATION AND BLINDING PROCEDURES

9.1 Allocation

Each nursing home unit will only be randomized once all members of the unit or their substitute decision makers (SDMs) give preliminary consent, decline or are classified as not contactable; at least 80% of residents or their SDMs within the unit must give consent to take the study medication (favipiravir or placebo) for unit eligibility for randomization. Every effort will be made to contact residents and/or their substitute decision makers within 48 hours. Those who cannot be contacted within 96 hours will not be eligible to receive study drug. LTCH staff may be enrolled on a continuing basis, recognizing that new LTCH staff may be needed to start work on the unit during the outbreak.

As LTCH units will be enrolled prospectively, we will use probabilistic minimization on the baseline COVID-19 attack rate on the unit to allocate units 1:1 (8 intervention units, 8 control units) to the 2 groups. Probabilistic minimization will be performed by an independent statistician at the Applied Health Research Centre (AHRC) at St. Michael's Hospital using the R package *minirand* (R Foundation for Statistical Computing, Vienna, Austria). Consent of LTCH staff and residents prior to randomization of the cluster, and use of placebo as a control intervention will help minimize the risk of "empty" clusters or the use of interventions that are not part of this protocol.

Each person for whom written informed or preliminary verbal consent was obtained will be entered in the electronic case report form (eCRF) so that an adequate number of uniquely coded study drug bottles/blister packes for all consenting members of the LTCH unit can be prepared. An automated audit trail will record the time, date, allocation, and participant identification numbers. Those who withdraw preliminary consent or decline study drug will be asked to consent to be followed-up for primary and secondary outcome. Those who also decline follow-up will be excluded from intention-to-treat analyses. Waiver of consent will be requested of participating sites to record the number of non-participating residents and LTCH staff, and the number and date of onset of cases of symptomatic microbiologically confirmed COVID-19 in these two groups.

9.2 Blinding

The trial will be blinded with the use of placebo controls. Favipiravir will have a placebo which is similar in size and shape, but can be distinguished because of color differences and an imprint on the surface of favipiravir tablets which could not be matched for the placebo given the timelines of this trial. However, favipiravir and placebo will be packaged in blister packages of identical appearance.

Drug supply will be dispensed by external pharmacies, which supply multiple LTCHs, therefore we will not be able to completely rule out that pharmacists dispensing medication will remain blinded. In addition, both placebo and favipiravir can be crushed before administration, which is necessary for some residents, and will not be identical in appearance when crushed. However, since favipiravir is not otherwise available in Canada, residents of included LTCHs will only receive one type of intervention (either drug or placebo, depending on the allocation of the LTCH unit), and no information will be provided by external pharmacies, research personnel or investigators to the LTCHs about, color, imprinting, appearance after crushing, and about the allocated intervention. Therefore, it is unlikely that LTCH staff and residents will be unblinded.

All study investigators will be blinded, except for an independent statistician from AHRC who will be responsible for probabilistic minimization, but will otherwise not be involved in the conduct of the trial. Outcome assessors, who will extract outcome data from the LTCHs' administrative data, will be blind to treatment allocation. The statistician conducting the analysis will also be unaware of treatment allocation.

9.3 Emergency unblinding

Code breaks should occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient. The resident's attending physician and/or the LTCH Medical Director or Directors of Nursing are encouraged to discuss with the Principal Investigator if they believe that unblinding is necessary. If unblinding is considered necessary, the Principal Investigator will contact the independent statistician at the AHRC, who will do the code break as deemed necessary and communicate it directly to resident's attending physician. Similarly, a staff member's family or attending physician will be encouraged to consult with the Principal Investigator the need to unblind for LTCH staff.

Medical directors, investigators and research personnel are encouraged to maintain the blind as far as possible. The actual allocation must not be disclosed to LTCH staff or patients and/or other research personnel, investigators or sponsors. In addition, there should not be any disclosure of the code in any of the corresponding patient documents. Medical director and Principal Investigator must report all code breaks with reason as they occur on the corresponding CRF page. Unblinding should not necessarily be a reason for study drug discontinuation.

10. STUDY INTERVENTIONS

10.1 Favipiravir

The study intervention is a 25-day course of favipiravir/placebo for LTCH residents and staff, to be initiated immediately after recognition of the LTCH outbreak.

Favipiravir was approved for novel influenza strains unresponsive to standard antiviral therapies in Japan in 2004, under the trade name Avigan®.[71] It is manufactured by Fujifilm Toyama Chemical Co., Ltd. Favipiravir is a purine nucleoside analogue, which acts as a competitive inhibitor of RNA-dependant RNA polymerase.[41] It has in-vitro activity against influenza A and B including activity against amantadine-, oseltamivir-, and zanamivir-resistant influenza viruses, and several agents of viral hemorrhagic fever, and SARS-CoV-2 *in vitro.*[41-43,71]

The duration of prophylaxis was defined to align with the sum of the periods of infectivity and incubation. The average incubation period ranges between 4-6.4 days (ranging from 0-14 days),[5,23,75,76] with a 95th percentile of 12.5 days.[5] Further, preliminary literature from Germany suggests that the duration of infectivity is 7-10 days from the onset of symptoms.[77] Prophylaxis will continue until day 25.

New staff starting to work on the unit after day 1 who consent to receiving study drug will continue the drug until day 25 of the outbreak.

Residents in the LTCH unit diagnosed with COVID-19 at enrollment will be offered treatment with study drug for 14 days.

10.1.1 Dosing and Administration

The dosage for favipiravir to be used in this study for prophylaxis is 1600 mg (8 x 200 mg tablets) orally twice daily on day 1 followed by 800 mg (4 x 200 mg tablets) orally twice daily. The dose for treatment is 2000 mg orally twice daily on day 1, the 1000 mg orally twice daily for 13 additional days.

Favipiravir is provided as 200 mg tablets and dosed orally. Favipiravir is rapidly and completely absorbed after oral administration of the 200 mg immediate release tablets. If necessary, favipiravir may be crushed for administration and can be taken with or without food.

This dosing strategy is increased from the licensed dosing regimen for influenza, to account for the higher in-vitro concentrations required for activity against SARS-CoV-2. Elevated dosing strategies, up to 6000 mg on day 1 followed by 1200 mg BID has been used in published Favipiravir studies for Ebola. Prolonged administration to 22 days has been explored in a phase 1 study in Japan (JP120) with a favorable safety profile (patients received 1800 mg PO BID on day 1 followed by 800 mg PO BID from day 2-21 and a single dose of 800 mg on day 22).

10.1.2 Dosing in special populations

Favipiravir is contraindicated in nursing mothers and pregnant women or women of child-bearing age who are not taking oral contraception due to its potential teratogenicity.

No alteration of dosing is needed in subjects with renal impairment. Total exposure for plasma favipiravir for subjects with severe renal impairment (Stage 4) was 1.3-fold higher compared to subjects with normal renal function. No obvious effect of renal impairment on safety was observed and favipiravir treatment was generally well tolerated in subjects with renal impairment.

No alterations in dosing strategies are required in older adults. The maximum plasma concentration and AUC values in elderly subjects in a single and a multiple-dose study completed in Japan were higher than in young subjects. Comparing AUC values on Day 5, the differences were 40 and 80% after 600 mg once a day and 400 mg BID, respectively. In the companion study completed in the United States of America, there were no differences between young and older populations based on Day 5 AUC comparison in subjects receiving either 600 or 800 mg BID.

Higher drug levels occur in patients with hepatic impairment, and we have excluded patients with cirrhosis.

10.1.3 Formulation and Packaging

Favipiravir will be provided to the study team from the manufacturer (Avigan®; FUJIFILM Toyama Chemical Co., Ltd) via Appili Therapeutics. The medication is supplied as tablets and is orally administered. Appili will supply placebo tablets of similar but not identical appearance, with a formulation equivalent to the active product, minus the active pharmaceutical ingredient.

Favipiravir can be crushed for persons unable to swallow tablets. If necessary, nurses at the bedside will crush favipiravir or placebo tablets immediately before administration and disperse them in water, cranberry juice or apple sauce for administration to residents either orally or by feeding tube (for residents who have pre-existing chronic feeding tubes) who cannot swallow tablets.

Details of the chemical composition and appearance are provided below in Table 1. Favipiravir will be provided in blister packs. All study products (Favipiravir and placebo) will be labeled as Investigational Product in accordance with Health Canada regulations.

Table 1. Formulation, Appearance and Composition of Favipiravir®

	Avigan®
	Tablet
Formulation	C5H4FN3O2; favipiravir
DIN	
Appearance	Light yellow round tablet 8.7 mm in diameter
Non-medicinal ingredients	Colloidal silicon dioxide (diluent), povidone K30 (binder), low-substituted hydroxypropyl cellulose (disintegrant), crospovidone (disintegrant), and sodium stearyl fumarate (lubricant). Film coated with OPADRY, which includes Hypromellose (2910, 6mPas), titanium dioxide, talc, and yellow ferric oxide.

10.1.4 Storage and Stability

Favipiravir is a novel nucleic acid (pyrazine molecule) analogue that interferes with viral ribonucleic acid (RNA) replication. Favipiravir is supplied as a light yellow, film-coated tablet for oral administration containing 200 mg favipiravir. Favipiravir tablets are to be kept in a dry area, stored at 15° C to 30° C and shielded from direct light.

10.1.5 Study Drug Dispensation

For residents, study drug will be provided from a research pharmacy to the dispensing pharmacy for each enrolled LTCH. The dispensing pharmacy will be responsible for packaging and arranging transportation of medications to each LTCH. The medications will then be dispensed to each enrolled resident by the LTCH nursing staff as per routine medication administration processes.

For LTCH staff, the medication will be dispensed from the research pharmacy to research coordinators who will be responsible for arranging transportation to the study participants and documenting this process.

10.1.6 Expected Side Effects

Favipiravir is considered a safe drug. No treatment related serious adverse events occurred in licensure studies of favipiravir.[71] The most common adverse events observed in clinical trials are gastrointestinal (diarrhea 2.3%; nausea 2.1%). A similar proportion of subjects in the placebo (25.4%) and favipiravir (25.3%) groups experienced at least 1 adverse event. Further favipiravir is associated with increased uric acid level which are typically asymptomatic and would be expected to be transient with the duration of treatment to be used in this trial.

10.1.7 Additional Safety Considerations

For the purpose of this trial, the following are exclusion criteria for study drug administration:

1. **Pregnancy**
2. History of abnormalities of uric acid metabolism, other than gout.
3. Subject has a history of hypersensitivity to remdesivir or favipiravir
4. Known hepatic cirrhosis
5. Current use of the following medications, which cannot be discontinued for the duration of the study: pyrazinamide, hydralazine, more than 3000 mg of acetaminophen per day.

The following safety considerations are based on data from individuals taking favipiravir for influenza. They are listed here for reference.

- ***Phototoxicity***: Nonclinical studies have shown mild phototoxicity. One study subject experienced mild photosensitivity (rash) following a tanning bed session. All subjects should avoid excessive exposure to sunlight or artificial ultraviolet light.
- ***Laboratory Values***: Mild to moderate asymptomatic elevations of uric acid and aminotransferase have been observed in healthy volunteers and subjects with influenza treated with favipiravir in clinical studies. The changes have been reversible upon favipiravir discontinuation.
- ***Mutagenesis****:* Favipiravir proved mildly positive under some conditions studied in the mammalian chromosomal aberration test and mouse lymphoma assays at high concentrations. Although the potential for genotoxicity at high exposures cannot be ruled

out, evidence indicates that this risk is minimal at the exposures planned in this clinical study.

- ***GI Tract Lesions:*** In two proof-of-concept studies of orally administered favipiravir against Ebola virus infection in macaques, GI tract lesions were observed that were not consistent with the known natural history of Ebola nor with previous animal and clinical studies of favipiravir. However, evidence suggests that bacterial infections and pre-existing enterocolitis in the treated macaques may have been responsible, and an ongoing risk to patients may not exist.

10.1.8 Concomitant and Prohibited Medications

There are no absolute contraindications for using favipiravir with other medications. However, numerous precautions exist. Favipiravir clearance may be reduced in the setting of aldehyde oxidase inhibitors and may increase the plasma concentration of aldehyde oxidase substrates. For the safety of residents, current receipt of the following medications which may have interactions with favipiravir will result in residents not receiving study drug if they cannot be discontinued for the duration of the study: pyrazinamide, hydralazine, more than 3000 mg of acetaminophen per day.

10.2 Control

The comparator arm in this trial will be placebo. No existing pharmacologic agents have been demonstrated to have confirmed clinical activity against COVID-19; some agents have in-vitro activity against SARS-CoV-2 and may have potential benefit in observational studies. In the absence of confirmed evidence for benefit or harm of active pharmacologic agents for treatment or prophylaxis of COVID-19, the use of a placebo is justified.

10.3 Co-Intervention(s)

LTCHs in both arms will implement standard infection prevention and control measures for COVID-19 outbreaks, including case-isolation, visitation limitation, cancellation of activities, handwashing, and use of personal protective equipment per Ministry of Health and Long-Term Care mandates, and in collaboration with their local Public Health Unit, and infection prevention and control from any hospital who is working with the LTCH.

10.4 Participant Access to Study Medication at Study Closure

This study will provide access to the study drug for those randomized to the intervention arm only. In the event that a study participant tests positive for COVID-19 during the follow-up period, efforts will be made to link the individual to ongoing clinical trials of COVID-19 treatment if such trials are enrolling in proximity to the LTCH unit. However, no guarantees of access to investigational product can be made. At the time of writing, there are no known effective treatments for established COVID-19 infection.

11. RISK MANAGEMENT

11.1 Pregnancy

Favipiravir is contraindicated in pregnancy. If a participant becomes pregnant during the study, the Investigator must inform the Sponsor and the study drug will be discontinued. Follow-

up should be continued until study close-out at the study centre. Pregnancy is not an adverse event; however, any complication related to pregnancy should be considered an adverse event.

11.2 Protection of Study Personnel from COVID-19

COVID-19 is transmitted from person-to-person through respiratory droplets and via fomites. While the greatest risk of transmission is believed to occur in the context of respiratory symptoms, transmission from asymptomatic and minimally symptomatic individuals may occur. Participants in this trial will all have been recently exposed to a confirmed case of COVID-19 disease and will thus be at increased risk of having early or incubating infection during the incubation period. They are also residing in a group setting for vulnerable adults, such that introduction of the virus by asymptomatic study personnel is an important risk. For these reasons, several measures will be taken to minimize the risk of transmission to both study personnel and residents.

Where possible, communication with residents and LTCH staff, and in-person visits to LTCHs will be virtual. When study personnel conduct in-person visits during the outbreak, a surgical mask should be placed on the participant if possible, and droplet precautions will be used by LTCH staff during the study visit, including surgical mask, face shield or goggles, disposable gown, and gloves. After the outbreak has been deemed terminated, further visits can be conducted using routine precautions. All study personnel will be excluded from work if they develop a fever or any respiratory symptoms, and will follow public health guidelines regarding any visits to LTCHs. Any study personnel who develop symptoms potentially suggestive of COVID-19 disease will immediately be assessed by occupational health and relieved of study duties until deemed safe to return to work. Study personnel will comply with all requests from public health units related to study visits, practices in the LTCH and submission of swabs for COVID-19 testing.

12. CLINICAL AND LABORATORY EVALUATIONS

12.1 Clinical Evaluations

Once consent is obtained, data on patient underlying illness and medications will be obtained from LTCH medical records and residents/substitute decision makers.

For the study period, daily line lists of new symptoms in residents, and of those who have had specimens sent for COVID-19 testing will be recorded and faxed to the study office. All results of COVID-19 testing, whether in the nursing home or after hospital admission, will be obtained and recorded for the study. The identifying information on this line list is the names of residents. LTCH staff will black out the names of residents not participating in the study before faxing the line list to the study office. The line list will be sent to a secure fax in a locked office at Sinai Health System, where study codes will be immediately applied and resident names blacked out.

Any residents who develop adverse events, and any calls for physician assessment will also be recorded on the line lists. The study will contact physicians to identify the result of their assessment of the resident to determine whether COVID-19 is a possible diagnosis, or whether an adverse effect has occurred. Where possible, study staff will review electronic records of nursing notes daily.

Data will be recorded onto standardized electronic case report forms hosted on secure servers at the Applied Health Research Centre (AHRC) at St. Michael's Hospital.

12.2 Laboratory Evaluations and Specimen Collection

12.2.1 Microbiologic testing for SARS-CoV-2

It is expected that all residents or staff who meet the case definition for COVID-19 will have specimens obtained clinically for testing, the results from which will be recorded. However, if any such cases do not meet criteria for clinical testing, specimens will be submitted to the study laboratory for testing in real time. Any resident who dies in the home during the study period will have a nasopharyngeal swab submitted for COVID-19 testing.

At baseline (day 0) and on day 14 and day 40, participants will undergo collection of nasopharyngeal or nasal swab for RT-PCR testing. Testing will be performed using licensed tests for COVID-19 by research laboratories licensed to perform such tests.

12.3 Questionnaires

See Appendix for questionnaires and data collection forms.

12.4 Stored Research Specimens and Plans for Possible Future Testing

Any respiratory specimens collected from participants for solely study purposes will be stored until no longer needed by the study, then discarded.

13. STUDY PROCEDURES

13.1 Schedule of Events

To protect study and long-term care home staff, residents and substitute decision makers, all efforts will be made to have any contacts be virtual. Where possible, consent will be obtained by telephone or video link, and data will be obtained by telephone, fax, or remote data entry.

13.2 Screening, consenting and initial data collection Visit

The purpose is to rapidly assess participant eligibility and obtain written informed or preliminary verbal consent to participate in the trial, as eligibility and consent are required from at least 80% of residents on the outbreak ward in order to randomize. A nasopharyngeal or nasal swab will be obtained from all residents on day 0, and from all staff as soon as practical.

The study coordinator will:

- Review the patient's chart and medication record to assess eligibility; if possible, this will be performed remotely either via research staff having access to electronic charts, or by having a staff member in the home transmit the information by telephone or fax.
- If written informed consent has not yet been obtained, provide and review the informed consent document via email / fax / telephone / video link with each resident, substitute decision maker or staff person, and obtain and document verbal consent to participate.
- Advise the participant/substitute decision maker that written consent will be required as soon as possible and agree on the method by which this will be done.
- Provide contact information for the study, such that each participant has access to study personnel at any time to answer questions
- Obtain multiple forms of contact information for consenting participants, including multiple telephone numbers, an email address, and a mailing address for study material delivery.
- For study staff:
    - Complete the baseline interview for study staff.
    - Decide whether staff will complete daily diaries online or on paper
    - Review with the participant how to access and complete the symptom/adherence diary and questionnaires, and encourage immediate completion of the baseline questionnaire on the day of the visit.

13.3 Medical Oversight

Confirmation of eligibility, assessment of adherence of study drug/placebo, evaluation of overall participant safety, review/assessment of minor and/or serious adverse events (including classification of adverse events according to seriousness, severity, relatedness and expectedness), and final sign off of data collection will be done by the qualified investigator/principal investigator (Allison McGeer, MD) or a medically qualified and licensed delegated physician.

Table 1. Schedule of Events for Residents

Visit	Screening (Day 0)	Baseline (Day 1)	Day 14±2d	Day 40±4d	Day 60±7d
Visit format	**Remote**	**Remote**	**In person**	**In person**	**Remote or in person**
Eligibility assessment	X				
Informed consent	X				
Cluster randomization		X			
Dispensing study drugs		X			
Assessment for COVID-19		Daily, by LTC staff (fax to study) Chart review by study staff, day 14 & 40			
Concomitant medication assessment	X		X	X	
Adverse event assessment		Daily by LTC staff (fax to study) Chart review by study staff, day 14 & 40			SAE only
Death/hospital transfer document.		Daily by LTC staff (fax to study) Chart review by study staff, day 14 & 40			X
Nasopharyngeal/ nasal swab	X		X	X	
Medication adherence			X	X	

Table 2. Schedule of Events for Staff

Visit	Screening (Day 0)	Baseline (Day 1)	Day 14±2d	Day 40±4d
Visit format	**Remote or in person***	**Remote**	**Remote or in person**	**In person**
Eligibility assessment	X			
Informed consent	X			
Cluster randomization		X		
Dispensing study drugs		X		
Interview by study staff	X		X	X
Concomitant medication assessment	X		X	X
Adverse event assessment			X	X
Daily diary		Daily symptom/adverse event/adherence diary to be completed		
Visit-specific questionnaire	X		X	X
Nasopharyngeal/ nasal swab	X[1]		X	X
Pill count				X

*If staff are willing and able to do their own nasal swab, then visits will be remote. Consents and questionnaires will be returned by mail or fax, or collected at the LTCH. Pill bottles will be returned to a secure location at each LTCH to be collected by study staff.

[1]For staff, nasopharyngeal/nasal swabs may be obtained on day 0-3, as they may not be obtained until the first time that the staff member attends at the LTCH to complete a shift. New staff starting work during the outbreak will be requested to have a swab on the first day that they work.

13.3 Baseline Visit (Day 1)

- **Dispense study drug:**
    - Medications are provided to LTCH residents in Ontario by third-party pharmacies. The pharmacies for participating LTC facilities will be approached in advance to co-ordinate mechanisms for timely distribution of trial drugs. Medications will be distributed from the central research pharmacy to the regional dispensing pharmacy for distribution to the LTCH. All medications will be dispensed and administered by long-term care facility nursing staff as part of routine medication administration.
    - For staff, the medication will be dispensed from the research pharmacy to study research coordinators who will be responsible for arranging transportation to the study participants and documenting this process.

13.4 Data collection Day 2 to Day 40

Efforts will continue to ensure that either an electronic or hard copy of the signed written informed consent form is obtained from each participant or their substitute decision maker. This should be obtained as soon as possible, ideally by day 2.

From day 0 until the outbreak is declared over, the LTCH will fax daily line lists of the outbreak to the study (these will already be being routinely sent to the local public health unit). These lists record all residents and staff who meet the case definition, who are tested for COVID-19, as well as the results of any testing. For this study, we will add to the line list a record of any potential adverse events, and discontinuation of study drug. Study staff will also report any deaths or transfers to hospitals during the outbreak. In addition, the study coordinator responsible for the particular outbreak will participate in all virtual outbreak meetings between public health units and the LTCH, to ensure that no information is missed.

On day 14, a study staff member will visit the home and review charts (remote chart review will occur if possible), to ensure concordance between chart review and records on the line list and testing of residents meeting the case definition. Validation of records of deaths, transfer to hospital, adverse events, and medication compliance will also occur. At this visit, all consenting residents who have not had a nasopharyngeal swab obtained within the last 48 hours will have nasopharyngeal swabs obtained (these may be obtained either by study staff or LTCH staff); participating staff who are working that day will also have an NP swab obtained. Participating staff who are at home on day 14 will obtain a nasal or mid-turbinate swab at home and bring it to the LTCH for testing at the time of their next shift.

The study staff member will also identify the number of residents and staff on other units of the home who have been diagnosed with COVID-19

The day 14 LTCH visit will be by a single staff person who will visit the LTCH, appropriate PPE supplied by the study will be used, and all procedures established by the LTCH and their local public health unit will be followed.

At day 14, all participating staff will be contacted by telephone to check on and encourage daily diary completion and to complete a questionnaire regarding symptoms, potential adverse events and medication adherence.

13.5 Day 40 Visit

For residents, study activities include:

- Chart review (remote chart review will occur if possible), to ensure concordance between chart review and records on the line list and testing of residents meeting the case definition.
- Validation of records of deaths, transfer to hospital, adverse events
- Review of medication compliance.
- Nasopharyngeal swabs from all consenting residents who have not had a nasopharyngeal swab obtained within the last 48 hours
- Documentation of the number of COVID-19 cases which have been identified in non-consenting residents on the outbreak units, and in residents on other units in the facility (no information will be collected about these cases).

For staff, study activities include:

- Interview and questionnaire regarding symptoms, concomitant medications, adverse events, and medication adherence
- Nasopharyngeal/nasal swab from those who have not had a nasopharyngeal/nasal swab obtained within the previous 48 hours
- Review of pill count, and arrangements for return of remaining pills and daily diaries if this has not already happened.
- Documentation of COVID-19 cases which have been identified in staff working on other units in the facility

13.6 Day 60 Visit

At the day 60 visit assessment includes, by telephone from the LTCH or by in person visit:

- SAEs, hospitalizations, deaths for residents
- Number of microbiologically confirmed COVID-19 cases that have been identified in staff and residents to day 60.

13.7 Early Termination Visit

If a participant chooses to withdraw from the study prematurely after the baseline visit but **before day 40,** efforts will be made to complete all study activities required at the day 40 visit. Participants who discontinue study drug prematurely but consent to still be followed up in the study should follow routine protocol-defined procedures.

14. EVALUATION, RECORD, AND REPORTING OF ADVERSE EVENTS

14.1 Definitions

14.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation participant, administered a study medication/intervention, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) study medication/intervention, whether or not related to the medicinal (investigational) study medication/intervention.

During each follow-up visit with the participant, information on AEs will be gathered and documented accordingly. AEs will be graded as mild, moderate, severe or life-threatening and assessed by causality as probably related, possibly related, unlikely to be related or not related to the study drug (investigational arm only).

Stable chronic conditions which are present prior to clinical trial entry and do not worsen are not considered AEs and will be accounted for in the participant's medical history.

14.1.2 Serious Adverse Events (SAEs)

A SAE is defined as an AE meeting one of the following criteria at any dose:

- Results in death during the period of protocol-defined surveillance
- Is a life-threatening event (defined as a participant at immediate risk of death at the time of the event)
- Results in in-patient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance
- Results in persistent or significant disability or incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect

Any other important medical event that may not result in one of the above outcomes, may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Participants will be monitored during the 60-day study period for SAEs. If an SAE is ongoing at the time a participant discontinues/completes the study, the SAE will be followed until the Investigator agrees that the event is satisfactorily resolved, becomes chronic, or that no further follow-up is required.

14.2 AE Descriptions and Recording

Grading of AEs will be done by study staff and investigators according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

For all collected AEs (including SAEs), study investigators will also determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to Investigational Product administration and cannot be explained by concurrent disease or other products or chemicals. The response to withdrawal of the product (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the Investigational Product, is unlikely to be attributed to concurrent disease or other products or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to Investigational Product administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other products or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not related: The AE is completely independent of Investigational Product administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

All SAEs which occur during the course of the study must be reported to the Project Manager within 24 hours of the site becoming aware of the event. The Project Manager will be responsible for reporting SAEs to Health Canada on behalf of the Sponsor. SAEs will be reported to:

Project Manager:	Gurpreet Lakhanpal, MSc, CCRP, PMP
Phone:	416-864-6060 ext. 47835
Fax:	416-864-3014
E-mail:	Gurpreet.Lakhanpal@unityhealth.to

14.3 Follow-up for Adverse Events

Any AE that occurs between the time that a study participant is randomized and the time that s/he departs the study at the end of the final study visit (or at the time of early discontinuation of the participant from the study for any reason) will be captured and recorded.

At each contact with the participant, the investigator (or designate) must seek information on AEs by specific questioning.

All AEs (including SAEs) will be followed until resolution or until the investigator and the clinical/medical monitor are in agreement that the AE has resolved, stabilized or become chronic and no further follow-up is required.

14.4 Pregnancy Follow-up

If a participant becomes pregnant during the study, the Sponsor will collect follow-up data regarding the pregnancy, birth, and status of the child. Follow-up should be continued until study close-out at the study centre. Pregnancy is not an adverse event; however, any complication related to pregnancy should be considered an adverse event. Refer to Section 0.1 to 14.3.

15. STATISTICAL ANALYSES

15.1 General Study Design

This is a placebo-controlled cluster-randomized trial.

15.2 Sample Size Considerations/Justification

The preliminary sample size calculation is based on transmission parameters from historic literature on prior influenza outbreaks and emerging data on COVID-19.

The baseline attack rate of COVID-19 in LTCH is unknown; interim case fatality in a LTCH in Washington state is 33.7%, and the outbreak continues.[30] Outbreaks of febrile respiratory illnesses in long-term care facilities can be explosive, with as many as 70% of residents may develop illness during an outbreak in an epidemic year.[78,79]

Estimates for the attack rate in household settings suggest that the symptomatic secondary attack rate for COVID-19 amongst household members is 10.5% (95% CI = 2.9%–31.4%).[10] The observed attack rate of COVID-19 on the Diamond Princess cruise ship which more closely approximates the close quarters of a long-term care facility, was observed to be 19% (705 cases of 3711 passengers and crew members).[80] However this likely underrepresents the ultimate attack rate in this outbreak as the cruise ship was disembarked as cases continued to climb. Historical long-term care facility outbreaks of influenza in Connecticut experienced attack rates in individual homes ranging from 13% to 49% (median 35%).[81] Given the rapid transmission of COVID-19, fueled by a high intrinsic reproductive number of 2-2.5,[5-7] and lack of pre-existing immunity or vaccination, the ultimate attack rate of COVID-19 in long-term care facilities may be even greater.

Influenza chemoprophylaxis has been identified to be highly effective, resulting in a 55% reduction in symptomatic influenza cases in a meta-analysis of influenza prophylaxis for adults and children.[35] The mass administration of antiviral prophylaxis has been identified to be even greater in long-term care facilities. During the era of amantadine prophylaxis more than 75% of influenza outbreaks were terminated with mass administration of antiviral prophylaxis.[82] Additional studies have supported the notion that the vast majority of influenza outbreaks in long-term care facilities may be terminated with mass chemoprophylaxis.[83-86] In a retrospective analysis of three years of antiviral prophylaxis for influenza outbreaks in long-term care facilities in British Colombia, after 5 days of initiation of antiviral prophylaxis, only 1 case of laboratory confirmed influenza was identified across 352 unit-level outbreaks.[85] Monto et al.[84] analyzed influenza outbreaks in Michigan long-term care facilities; among 8 outbreaks with mass prophylaxis, no further cases were seen in 5 units and terminated after few additional cases in 3 outbreaks. Further, in Ontario long-term care facilities, oseltamivir prophylaxis terminated 8 (100%) outbreaks after amantadine had failed to control the outbreak.

We therefore predict that in the absence of chemoprophylaxis, there will be failure to control the outbreak in 87.5% of outbreaks. If mass chemoprophylaxis is effective, we anticipate a reduction in failure of control to 12.5% of outbreaks.

We will enroll 8 units in each treatment arm. This will provide >85% power to detect an 75% absolute risk difference in outbreak control, from 12.5% in control clusters (1 out of 8 LTCH units) to 87.5% in experimental clusters (7 out of 8 LTCH units) at a two-sided alpha of 0.05 using Fisher's exact test (two-sided).

15.3 Statistical Analyses

15.3.1 Analysis of Primary Outcome Measures

The primary outcome is the proportion of LTCH units with an outbreak that achieve outbreak control, defined as 24 consecutive days without a microbiologically confirmed case of COVID-19 in the facility up to day 40 after the start of prophylaxis. This is a binary outcome at cluster level (LTCH unit), with proportions of outbreaks controlled in experimental and control clusters compared using Fisher's exact test (two-sided), accompanied by a risk difference with 95% confidence interval.

15.3.2 Analysis of Secondary Outcome Measures

Secondary analyses will include generalized linear mixed models (GLMMs) with logit link to estimate the effect of favipiravir on the probability of the secondary outcomes at participant level, while accounting for clustering of participants in LTCHs. We will also compare the onset of symptomatic disease, hospitalization, and mortality in time-to-event models. All analyses will be by intention-to-treat.

Safety outcomes will include the number of serious adverse events in residents and staff, and the proportion of residents and staff whose study medications are discontinued due to adverse events

15.3.3 Descriptive analyses

Participant and cluster characteristics will be summarized using appropriate descriptive statistics that account for clustering of participants in LTCHs if necessary. Data from the control arm only will be used to characterize the transmission dynamics and natural history of COVID-19 among LTCH in the Canadian context, including estimation of the secondary attack rate in roommates and unit mates, clinical features of COVID-19 in LTCH residents and symptom burden.

15.3.4 Subgroup Analyses

No subgroup analyses will be performed.

16. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with the ICH-GCP Guidelines and the principles in the Declaration of Helsinki. Investigators will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and product monograph.

16.1 Informed Consent

Consent and enrolment were described in Section 7.3. Participants may withdraw consent at any time during the course of the study without prejudice. If a participant withdraws from the medication, but consents to be followed-up, the participant will continue to be followed for primary and secondary outcomes.

16.2 Confidentiality

All participant-related information including Case Report Forms, laboratory specimens, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only accessible to research staff. Participants will be identified only by means of a coded number specific to each participant. All computerized databases will identify participants by numeric codes only and will be password protected.

Upon request, and in the presence of the investigator or his/her representative, participant records will be made available to the study Sponsor, monitoring groups representative of the study Sponsor, representatives of funding groups, and applicable regulatory agencies for the purpose of verification of clinical trial procedures and/or data, as is permissible by local regulations.

16.3 Institutional Review Board, Ethics Committee, or Research Ethics Board

The REB will review all appropriate study documentation to safeguard the rights, safety, and well-being of the participants. The study will be conducted only at sites where ethics approval has been obtained. A copy of the protocol (including protocol amendments), all versions of informed consent forms, other information to be completed by participants such as survey instruments or questionnaires, and any proposed recruitment materials must be reviewed and approved by the REB of each participating centre prior to implementation of the trial. The investigator will be responsible for obtaining REB approval of the annual Continuing Review throughout the duration of the study. The investigator will notify the REB of serious adverse events as applicable. The investigator will seek prior ethics approval for any protocol deviations except when the change is intended to eliminate an immediate hazard to participants. In this case, the protocol deviation will be promptly reported.

17. GENERAL TRIAL CONDUCT CONSIDERATIONS

17.1 Adherence to Protocol

17.1.1 Protocol Amendments

All protocol amendments will be reviewed and approved and if applicable submitted to the applicable regulatory agencies for prior approval or notification. The Investigator must sign and date the amendment prior to implementation. All protocol amendments must also be submitted to the ethics committee.

17.1.2 Protocol Deviations

No deviations from this protocol will be permitted without the prior written approval of the Sponsor, except when the modification is needed to eliminate an immediate hazard or hazards to participants. Any deviations that may affect a participant's treatment or informed consent, especially those increasing potential risks, must receive prior approval from the REB unless performed to remove an immediate safety risk to the participants. In this case it will be reported to the REB and the Sponsor immediately thereafter. Any departures from the protocol must be documented.

17.2 Monitoring & Auditing

17.2.1 Data Safety Monitoring Committee

The DSMC will include infectious diseases, long term care and public health specialists, at least one biostatistician, and researcher expert in clinical trials. The DSMC will review summary data and all resident deaths after each outbreak, and every 2 months. The purpose of the DSMC will be to review safety concerns and review external data that may have bearing on the design of or decision to continue the trial.

17.2.2 Study Monitoring

Each participating LTCH agrees to allow delegates of the trial data coordination centre to have direct access to the study records and medical records from those patients enrolled in the clinical study as well as Investigational Product accountability records, in order to conduct remote risk-based monitoring of this trial. The proposed remote monitoring scheme will be composed of:

1) Review of essential study documents related to participant protection, such as informed consent form signature pages, good clinical practice and protocol training records, delegation log, curriculum vitae and medical license of investigators and Protocol signature page
2) Targeted source data verification (SDV) of case report form data will be performed on 5% of participants chosen at random. For residents, this will include medication administration records, faxed line lists of study related data, and, if accessible remotely, nursing notes monitoring symptoms. Only critical data variables identified through risk assessment which are programmed into the electronic data capture system will be source verified.

The Applied Health Research Centre will provide research staff with a form listing key variables for targeted SDV. Sites will be asked to complete the form and send it to the central coordination team, along with de-identified source documents for listed variables/participants via a dedicated end-to-end secure internet portal. Instructions will be provided on how to complete the form, de-identify source documents, and send these documents to the central coordination team using the secure portal.

Upon receipt of the completed form and appropriate source documents, the central coordination team will review these documents to ensure that the data is consistent with the data entered on eCRF. The review will include checking the case report form entries for accuracy and completeness against source documents. Applied Health Research Centre or delegates will maintain a monitoring log of all patients for whom source documents are requested, received, and verified. Variables will be marked as "verified" in the monitoring log once the review is complete. Urgent issues will be communicated on an ongoing basis as needed with the PIs/Sponsor.

If errors or inconsistencies are noted, a follow up email will be sent to the Principal Investigator and Primary Study Coordinator. The follow up email will include a summary of the issues identified, outline of any corrective actions and/or request an explanation, and a timeline for resolution.

17.3 Record Keeping

17.3.1 Data Collection

The Investigator must maintain detailed records on all study participants. Data for this study will be recorded in the participant's chart and entered into case record forms. Applicable data from the participant's chart should be recorded in the case record forms completely and promptly, taking time to correct any mistakes. Copies of case record forms will remain at the clinical site at the conclusion of the study.

17.3.2 Source Documents

The Investigator must maintain adequate and accurate source documents upon which case record forms for each participant are based. They are to be separate and distinct from case record forms except for cases in which the Sponsor has pre-determined that direct data entry into specified pages of the participant's case record forms is appropriate. These records should include detailed notes on:

- Oral and written communication with participant regarding the study treatment (risks/benefits)
- Participation in trial and signed and dated informed consent forms
- Inclusion and exclusion criteria details
- Visit dates
- Adverse events and concomitant medication
- Laboratory result printouts
- Participant's exposure to any concomitant therapy
- Reason for premature discontinuation (if applicable)
- Enrollment number
- Adherence with the study protocol and protocol deviation information

17.3.3 Data Corrections

Any corrections of data entered on source documents at the LTCH unit should be crossed out with a single horizontal line, initialed and dated.

17.3.4 Data Management

Data management responsibilities for this trial will be assumed by the Applied Health Research Centre. Instructions concerning the recording of study data on case record forms will be provided in a comprehensive study Operations Manual. Detailed aspects of data handling will be described in the Data Management Plan.

17.3.5 Record Retention

The Investigator will maintain all study records according to the ICH-GCP and applicable Health Canada regulatory requirements. Records will be retained for 25 years, in accordance with applicable Health Canada regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and the Sponsor-Investigator notified. The Investigator should ensure that no destruction of medical records occurs without the written approval of the Sponsor-Investigator.

17.4 Steering Committee

The steering committee (SC) will include: Dr. McGeer, Dr. Jüni, Dr. Coomes, Dr. Daneman, Dr. Simor, and Dr. Golan. The SC will meet 1-2 times monthly to discuss epidemic trends/recruitment, consider new sites, ethical issues, and emerging scientific or logistical issues. The steering committee will be advising the sponsor. Final decision-making authority will rest with the sponsor.

18. DISCLOSURE AND PUBLICATION POLICY

18.1 Publication of Study Results

Following completion of the study, the lead Principal Investigator is expected to publish the results of the primary and secondary analyses from this trial in peer-reviewed scientific journals. A detailed authorship policy will be developed and agreed upon by all investigators to determine how best to fairly acknowledge the contributions of relevant parties.

18.2 Data Sharing for Secondary Research

Data from this study may be used for secondary research. All of the individual participant data collected during the trial will be made available after de-identification through expert determination. These data will be made available as soon as possible following publication, with no end date, as part of data sharing requirements from journals and funding agencies, and in the spirit of open data access.

18.3 Conflict of interest

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

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