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Keywords:	Influenza, Oseltamivir, Primary Health Care, Cost-Benefit Analysis, Adaptive Clinical Trial

Antivirals for influenza-like illness? Protocol for a randomized controlled trial of clinical and cost effectiveness in primary care (ALIC^{4}E)

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Abstract

Introduction

Effective management of seasonal and pandemic influenza is a high priority internationally. Guidelines in many countries recommend antiviral treatment for older people and individuals with co-morbidity at increased risk of complications. However, antivirals are not often prescribed in primary care in Europe, because its clinical benefit has been insufficiently demonstrated by non-industry funded and pragmatic studies.

Methods and analysis

ALIC^{4}E is a European multi-national, multi-centre, phase IV, open-labelled, non-industry funded, pragmatic, adaptive-platform, randomised controlled trial (RCT). Initial trial arms will be best usual primary care, and best usual primary care plus treatment with oseltamivir for five days. We aim to recruit at least 2500 participants ≥1 year old presenting with influenza-like illness (ILI), with symptom duration ≤72 hours in primary care over three consecutive periods of confirmed high influenza incidence. Participant outcomes will be followed-up to 28 days by diary and telephone. The primary objective is to determine whether adding antiviral treatment to best usual primary care is effective in reducing time to return to usual daily activity with fever, head- and muscle-ache reduced to minor severity or less. Secondary objectives include determining cost-effectiveness, benefits in subgroups of participants according to age (<12, 12-64, >64 years), severity of symptoms (low, medium, high), comorbidity (yes/no), and duration of symptoms (≤48hours/>48-72 hours), decrease in

complications (hospital admission and pneumonia), reduction in the use of additional prescribed medication, including antibiotics, and effects on the use of over-the-counter medicines and self-management of ILI symptoms.

Ethics and dissemination

Research ethics committee (REC) approval was granted by the NRES Committee South Central (Oxford B) and Clinical Trial Authority (CTA) approval by The Medicines and Healthcare products Regulatory Agency. All participating countries gained national REC and CTA approval as required. Dissemination of results will be through peer reviewed scientific journals and conference presentations.

Trial Registration

ISRCTN27908921

Strengths and limitations of this study

- ALIC^{4}E will be the first publically funded, multi-country, pragmatic study determining whether antivirals should be routinely prescribed for influenza like illness (ILI) in primary care.
- ALIC^{4}E aims to go beyond determining the average treatment effect in a population to determining effects in patients with combinations of pre-specified characteristics (age, symptom duration, illness severity, and co-morbidities).
- The platform design allows the study to remain relevant to evolving circumstances, with the ability to add treatments arms.
- Response adaptation allows the proportion of participants with key characteristics allocated to study arms to be altered during the course of the trial according to emerging outcome data, so that participants' information will be most useful, and increasing their chances of receiving the intervention that will be most effective for them.
- Because the possibility of taking a placebo influences participant expectations about their treatment, and determining effects of the interventions on patient behaviour in real-world care is critical to estimates of cost effectiveness, ALIC^{4}E is an open-labelled trial.

Keywords

Influenza, Oseltamivir, Primary Health Care, Cost-Benefit Analysis, Adaptive Clinical Trial

Background

The influenza virus is highly contagious and represents a common cause of respiratory infection with local and systemic symptoms. Annual influenza epidemics account for considerable morbidity and mortality [1] and influenza outbreaks have the potential to become pandemics [2]. Effective control and management of seasonal and pandemic influenza is a high priority for national governments. Routine use of antiviral agents is rare in European primary care [3]. General practitioners (GPs) in Europe usually advise patients who consult with influenza-like illness (ILI) to take paracetamol or non-steroidal anti-inflammatory agents (NSAIDs), either as required or at regular intervals. They may also provide advice about other over-the-counter (OTC) medicines and self-management of ILI symptoms, e.g. maintaining fluids, bed rest and taking time off work or school. This broad approach is currently considered best usual care for the empirical management of ILI in Europe [4-6].

Currently, the most suitable antiviral agent available for pragmatic evaluation in ALIC^{4}E is oseltamivir (Tamiflu®), a neuraminidase inhibitor (NI). The US Food and Drug Administration (FDA) approved oseltamivir in 1999. Oseltamivir was classified by the WHO as an essential medicine until 2017 [7 8], and many countries have stockpiles of the drug to ensure it is readily available to treat seasonal and pandemic influenza [3].

Oseltamivir phosphate is an oral pro-drug which undergoes hydrolysis by hepatic esterase to form active oseltamivir carboxylate. Oseltamivir carboxylate acts by selective inhibition of influenza A and B viral neuraminidase. This enzyme normally promotes release of the virus from infected cells by cleaving terminal sialic acid residues on the surface of host cells and influenza virus envelopes, and facilitates viral movement within the respiratory tract. By blocking the activity of the enzyme, oseltamivir prevents new viral particles from being released [9 10]. Oseltamivir might also modify the immune response to influenza infection by reducing levels of pro-inflammatory cytokines which might, in turn, modulate symptoms of influenza [11].

Industry-sponsored trials (or studies), efficacy studies and clinical study reports of NIs, most often oseltamivir, have been the subject of many systematic reviews and meta-analyses, including individual patient meta-analyses[12-14]. In two meta-analyses differing in methodology and primary outcome measures but based on almost the same set of trials, Jefferson *et al.* found that oseltamivir improved the mean time to first alleviation of symptoms over the placebo by 16.8 hours [11] and Dobson *et al*. found oseltamivir improved the median time to alleviation of all symptoms over the placebo by 17.8 hours [13]. The reviewers also found that oseltamivir reduced the risk of self-reported, non-verified pneumonia but not for clinically diagnosed pneumonia [11 13]. Dobson *et al.* furthermore indicated that treatment with oseltamivir might reduce the risk of lower respiratory tract infection complications and hospitalization in patients testing positive for influenza [13]. However, increased nausea and vomiting were found to be likely associated with oseltamivir use [11 13]. Even with a possible reduction in symptomatic period (compared to a placebo) the value of oseltamivir treatment of previously healthy individuals with non-severe seasonal influenza is questionable. Conversely, circumstances of some individuals, for example those needing to return to work and parents and other carers, may mean that a reduction in function-limiting symptoms of a day may be hugely beneficial. The UK Academy of Medical Sciences recently reviewed current evidence and advise that cost-effectiveness analyses related to the virulence and severity of symptoms of the circulating strain considering a societal perspective are needed to further inform such judgements [15].

Since 1999, oseltamivir has generated sales in excess of $18bn (£11bn; €13bn). The United States stockpiled 65 million treatments at a cost of $1.3bn. The United Kingdom spent £424m on a stockpile of 40 million doses. By 2009, 96 countries possessed enough oseltamivir for 350 million people [4]. In 2017 the WHO downgraded oseltamivir in the list of essential medicines from a “core” drug to one that is “complimentary”—a category of drugs considered less cost-effective [7 8]. However, there has never been a large-scale, international, publically funded, pragmatic RCT of its cost-effectiveness in primary care, and so the evidence base either to support or not support the routine use of this agent in primary care is inadequate and raises the question: does the effect found in previous efficacy studies translate into a meaningful benefit in every day primary care? Specifically, what are the overall costs and benefits of this possible shortened symptom duration from the perspective of the individual sufferer, the health services, and for society? Do patients considered to be at higher risk for complications of influenza (for example due to age, duration and severity of

symptoms, or relevant co-morbidity) benefit more from antiviral treatment in primary care? Answering these questions will reduce important clinical uncertainty for primary care clinicians about whether to prescribe antiviral agents for ILI, and whether or not to prioritise antiviral treatment for subgroups of primary care patients.

The ALIC^{4}E trial will be delivered as work package (WP) 4 of the Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE: www.prepare-europe.org) consortium grant. PREPARE is a European Commission funded network for the rapid and efficient delivery of harmonised, large-scale clinical research studies on infectious diseases (ID) [16]. ALIC^{4}E will be a randomised controlled trial of investigational medicinal products (CTIMP) in primary care that will determine the clinical- and cost-effectiveness of adding antiviral agents to best usual primary care for patients with specific characteristics suffering from ILI, and thus enable clinicians to better individualise prescribing decisions.

The primary objective of ALIC^{4}E is therefore to determine whether adding antiviral treatment to best usual primary care is effective in reducing time taken to return to usual daily activity. Secondary objectives will be to determine whether antiviral treatment is cost-effective; benefits pre-specified subgroups of participants; decreases hospital admissions; decreases complications related to ILI, especially pneumonia; improves the health-related quality of life, decreases (repeat) attendance at the GP, or other health services; decreases time to first reduction, time to alleviation, and new/worsening of ILI symptoms; reduces the use of over the counter (OTC) and prescribed medication, including antibiotics, and; affects the self-management of ILI symptoms.

Methods/Design

The protocol for ALIC^{4}E, is reported according to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines.

ALIC^{4}E is a European multi-national, multi-centre, phase IV, open-labelled, pragmatic, adaptive-platform, randomised controlled trial (RCT). The trial was granted research ethics committee (REC) approval by the NRES Committee South Central (Oxford B) and Clinical Trial Authority (CTA) approval by The Medicines and Healthcare products Regulatory Agency, i.e. the competent authority in the UK. All participating countries gained national REC and CTA approval as required and when needed. All participants will provide written

informed consent before participation. The study will be conducted (using Good Clinical practice guidelines) according to the principles of the Declaration of Helsinki and in accordance with other relevant national guidelines, regulations, and acts. An independent Data Monitoring Committee (DMC) will review efficacy and safety data by treatment allocation, and a Trial Steering Committee will provide oversight of the trial.

Networks and participants

21 primary care clinical research networks in 15 European countries will recruit participants (Figure 1), and each network will co-ordinate the recruiting sites within their network.

Recruitment will be over three consecutive flu seasons, Q4 2015 to Q1/2 2018. Each season's start and end of recruitment will be based on local influenza-like illness incidence rising above (or falling below) pre-specified thresholds, using information supplied by the European Centre of Disease Prevention and Control (ECDC) [17], local and regional sources for each network.

We aim to recruit a minimum of 2500 participants through recruiting sites (GP Practice, primary care Out of Hours (OOH) service or Paediatric Centres within primary care). Potential participants will be identified when they present to the recruiting sites with symptoms of ILI, or when they telephone for an appointment or advice about their symptoms. Participants must meet the inclusion criteria (including symptom onset of 72 hours or less) and have none of the exclusion criteria (Table 1). If eligible and willing to participate, the participant will complete the rest of the initial trial procedures either within the same visit, or at a second appointment with a recruiter at the recruiting site, or at home.

Table 1. Eligibility criteria

Inclusion	Exclusion

- Male or Female, aged at least one year
- Presenting with ILI* in primary care during a period of increased influenza activity.

  * ILI=sudden onset of self-reported fever, with at least one respiratory symptom (cough, sore throat, running or congested nose) and one systemic symptom (headache, muscle ache, sweats or chills or tiredness), symptom duration of 72 hours or less

- Is able and willing to comply with all trial requirements
- Participant or legal guardian(s) of a child is willing and able to give informed consent
- Agrees not to take antiviral agents apart from study antiviral agents according to patient randomisation

- Chronic renal failure e.g. known or estimated creatinine glomerular filtration rate <60 ml/min (known = recorded in participant's clinical records)
- Condition or treatment associated with significant impaired immunity (e.g. long-term oral steroids, chemotherapy, or immune disorder) (known=recorded in participant's clinical records)
- Those who in the opinion of the responsible clinician should be prescribed immediate antiviral treatment
- Allergic to oseltamivir or any other trial medication
- Scheduled elective surgery or other procedures requiring general anaesthesia during the subsequent two weeks
- Participant with life expectancy estimate by a clinician to be less than 6 months
- Patient with severe hepatic impairment
- Responsible clinician considers urgent hospital admission is required
- Any other significant disease or disorder which, in the opinion of the responsible clinician, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or may affect the participant's ability to participate in the trial
- Involvement, including completion of any follow up procedures, in another clinical trial of an investigational medicinal product in the last 90 days
- Previous ALIC^{4}E trial participation
- Patients unable to be randomised within 72 hours after onset of symptoms
- Requirement for any live viral vaccine in the next 7 days
- *Optional according to specific country legislation:*
  - Pregnant, lactating or breastfeeding women

The local implementation of the trial has built-in flexibility and local network recruitment processes vary. For example, medical students may assist with recruitment tasks in certain practices, while others will incorporate triage systems or additional trial specific clinics and/or research support staff in their recruitment processes.

Randomization and blinding

After obtaining consent, participants will be randomised at the point of care using a remote online electronic data capture (EDC) system (Research Online 2). Emergency randomisation procedures will be available should this web-based facility be temporarily unavailable. Randomisation will initially be a 1:1 ratio between the two arms, with stratification by subgroup according to ECDC definitions of those at higher risk of complications from influenza, namely their age (<12, 12-64, >64 years), severity of symptoms (low, medium, high), any relevant comorbidity[i] (yes/no), and duration of symptoms since onset (≤48hours/>48-72hours). The proportions randomised to study arms may be altered during the course of the trial following a pre-specified Bayesian, response adaptive approach [18].

ALIC^{4}E is an open trial. The participant, the recruiting clinician and the study personnel will be aware of the participant's allocation. An open pragmatic trial was chosen because this design is better for determining effects in routine care when patients are much less tightly supervised. Estimates of effect from efficacy trials may not translate into similar effect sizes when interventions are taken up into routine clinical care. Knowledge of what medication one is taking influences help-seeking behaviour, and decisions to re-consult may substantially affect cost-effectiveness. In addition, efficacy estimates have already been repeatedly determined in efficacy trials with tightly controlled inclusion criteria, in which children, the elderly and people with co-morbidities have been under represented [19]. Clinicians do not prescribe placebos, and so the credible comparator is current best practice [20]. Therefore, no un-blinding or code breaking is required in the event of a relevant emergency. However, the trial team will be blind to treatment allocation at the aggregate level. The recruiter will create equipoise for the participant about the two arms which will be carefully covered in trial specific training, and each arm of the trial will be supported as in routine practice; previous open pragmatic trials have been able to minimise placebo effects using this approach [21 22].

Intervention

Participants randomised to best usual primary care plus oseltamivir arm will be given a dose of 75 mg oseltamivir twice a day for five days by the oral route (capsules) for those ≥13 years. For those who are ≥1 year but <13 years the doses will be twice daily for 5 days in suspension, administered orally, according to weight: 10-15 kg = 30 mg; >15-23 kg = 45 mg; >23-40 kg = 60 mg; >40 kg = 75 mg. Children weighing >40 kg and who are able to swallow

capsules may receive treatment with the adult dosage of 75 mg capsules twice daily for five days as an alternative to the same dose of oseltamivir suspension. Weight will be measured in children ≤12 years of age during the recruitment visit for medication dosing. All other participants will be asked about their weight at the baseline assessment and measured in case of uncertainty.

Endpoints

The primary outcome is patient reported time to having both returned to usual daily activity, and 'fever', 'headache' and 'muscle-ache' symptoms all rated as ≤minor problem. For non-verbal children, 'clinginess' will replace 'headache' and 'muscle ache', when both are unanswered.

Secondary outcomes will include (collected up to day 28):

- Cost-effectiveness measures through health care resource use and health-related quality of life
- Effectiveness in subgroups of participants (based on age bands, initial illness severity, relevant co-morbidity, duration of symptoms, and laboratory confirmed influenza A/B positivity)
- Hospital admissions (overnight stay)
- (Re-) attendance at GP Practice, hospital emergency care, primary care OOH services or Paediatric Centres
- Complications related to ILI and/or potential relevant complications such as pneumonia
- Time to first reduction, time to alleviation of, and new/worsening ILI symptoms
- Use of prescription medications, including antibiotics
- Use of over-the-counter medications
- Participant reported self-management and usual daily activities

Procedures and assessments

Table 2 outlines the ALIC^{4}E Schedule of Procedures according to the SPIRIT guidelines.

Table 2. ALIC^{4}E Schedule of Procedures

	Screening	Baseline Day 1	Day 1-14	Day 14 - 28	Post day 28
Eligibility assessment[1]	✓				
Informed consent [1+2]		✓			
Baseline CRF[1]		✓			
Physical examination[1]		✓			
Swab(s)[1]		✓			
Randomisation[1]		✓			
Dispensing of trial drugs[1]		✓			
Symptom Diary[2]			✓		
Day 2-4 Phone Call[3]			✓		
Day 14 -28 Phone Call[3]				✓	
After day 28 Phone Call[3]					✓
Clinical notes Review*[3]					✓
Adverse event assessments [3]			✓		✓
SAE Follow-up[3]			✓		✓

*Country dependent
[1]Completed by recruiter
[2]Completed by participant, includes standardised written health–related quality of life assessment and documents resource use
[3]Completed by trial team (CI/PI/coordinator), Day 28 call includes standardised verbal health–related quality of life assessment

Baseline Assessment (Day 1)

After obtaining written, informed consent, recruiters will complete a baseline Case Report Form (CRF). This will include the required information for randomisation: age; relevant comorbidities; duration of symptoms; clinician's rating of severity of ILI as mild, moderate or severe. In addition, the CRF will ascertain participant's/parent's severity grading for: fever, running or congested nose, sore throat, headache, cough, shortness of breath, muscle ache and pains, sweats/chills, diarrhoea, nausea and/or vomiting, abdominal pain, low energy/tired, not sleeping well, dizziness, feeling generally unwell (grading = no, minor, moderate, major problem); information about any usual care advice given to the participant; and type of health care coverage (e.g. public, private or mixed). The symptom questions will

be supplemented with child-specific questions so that the Canadian Acute Respiratory Illness Flu Scale will be completed for children ≤12 years of age [23].

Additionally, clinical examination findings will be recorded including: temperature and the way it was measured (oral, ear or axilla); use of antipyretics in the last 4 hours; pulse rate; weight (≤12 years of age or in cases of uncertainty); height; smoking status; gender; and whether they have had flu vaccination within six months and pneumococcal vaccination within five years.

The recruiter will provide antiviral medication according to the participant's group allocation and standardised instructions on how to take the medication. The recruiter will also take an oropharyngeal and a nasal swab (COPAN®) from those <16 years of age and a nasopharyngeal swab (COPAN®) from those ≥16 years of age. All swabs will be placed in 3mL universal transport media (UTM) and transported to a local laboratory for storage. Finally, they will instruct participants how to complete the Symptom Diary and give information about telephone follow-up assessments.

Diary (Day 1 – 14) and Follow-up

There is no requirement for participants to attend a face-to-face follow-up visit as part of their study participation, as all subsequent measurements will be ascertained by self-completed diary-based questionnaires and through telephone calls from the local trial team.

Participants (or their legal guardian or their carer) will be asked to complete a Symptom Diary from day 1 (baseline) through to day 14 after randomisation. The following data points are collected once: expectations of treatment benefit; ethnicity; employment status; cohabitation; pregnancy and stage; and current long-term medication. The following data points are collected daily in the diary: severity of selected ILI symptom; quality of life (EQ Visual Analogue Scale (VAS)); return to usual daily activity; prescription medication use (including antibiotics); use of OTC medication or remedies; adherence to trial medication and potential side-effects (up to day 7). The following data points are collected weekly: quality of life (using EQ 5D 5L index (respondents >12 years) or EQ 5D 3Y (respondents ≤12 years)); effect of the participants' symptoms on usual daily activities; health care resource use; out-of-pocket expenditure; and ILI state of people in the same household.

Participants and legal guardians will be telephoned on day three (+/- one day) (with day one defined as the day they were recruited into the study) to offer support with Symptom Diary completion and to check for any urgent issues. They will also be telephoned on day 14 (up to day 28) and asked on what day they returned to their usual daily activity, if and when their fever, head- and muscle-ache symptoms reduced to minor severity or less to ensure the primary end point is collected for all participants, and to ascertain any Serious Adverse Events (SAEs) in the preceding two weeks. Participants will receive a final telephone call on or after day 28 to complete a verbal EQ-5D-5L/3Y and VAS, to answer remaining questions about symptom resolution if needed, and about their trial participation and consent process as part of a process evaluation (see below). The trial team will ask whether participants have had a recurrence of their symptoms during this time and whether they have been admitted into hospital as a result of their symptoms.

Participants who have visited the hospital with complications possibly related to ILI and who have had a chest X-ray will have their primary care clinical records examined by the trial team for confirmation of relevant diagnoses of complications, including pneumonia.

Laboratory testing and point of care test (POCT)

Once the swabs have been received at local laboratories, samples will be frozen and stored at -70°C (-20°C is acceptable if there is no deep-freezer). After each flu season, samples will be transported to the Laboratory of Medical Microbiology, University of Antwerp, Belgium for analysis. Each participant's swab(s) will be analysed using a Multiplex RT-PCR for detection of pathogen genes by TaqMan® technology to identify whether or not the participant is infected with influenza A or B, with other respiratory viruses[ii], or with bacteria[iii].

Interviews and Qualitative assessment

As part of the day 28 telephone call to the participants or legal guardians or carers, questions will be asked about motivation for participating in the ALIC^{4}E study, what influenced that decision, and questions related to research participation during a pandemic.

All participating clinicians will be asked to complete a brief questionnaire, and a sub-sample of approximately 50 will be interviewed using a semi-structured topic guide to obtain their perspectives on the trial process, their views of influenza management in primary care, and participation in pandemic research.

Response Adaptive-Platform Trial Design

An "adaptive platform trial" enables multiple interventions for the same indication to be tested simultaneously within a master protocol, and often includes the capacity to add, or drop, study arms while the study is in progress [24 25]. Platform trials provide an effective framework to study patient heterogeneity in outcomes, with the goal of determining the best treatment for various subgroups of patients. In addition, platform trial designs can incorporate response adaptive randomization in order to randomize more participants to the best performing interventions during the course of the trial. This can increase statistical power and efficiency of the trial, as well as lead to better patient outcomes over the course of the study [26].

We chose an adaptive platform trial design because it provided flexibility to evaluate additional interventions in the trial, should interventions emerge that are suitable to pragmatic evaluation in primary care. Additionally, the design provides the ability to prospectively identify particular subgroups of interest that may receive benefit from antiviral agents, as opposed to estimating a single overall effect. This is done by incorporating a Bayesian modelling approach, combined with response adaptive randomization based on pre-specified participant characteristics. There will be multiple interim analyses during recruitment; planned every 750 patients and between flu seasons.

In ALIC^{4}E, participants will be initially randomised in a 1:1 ratio to the two arms, with stratification by subgroup and random blocks. Each arm will maintain at least a 10% probability of randomisation within each subgroup throughout the course of the trial. Arm superiority will be assessed by subgroup and may be declared superior in some subgroups, but not within others. If, at an interim analysis, an arm meets the superiority criterion for one of the treatments, randomization probabilities may be modified for those subgroups such that a minimum of 10% of participants are allocated to the inferior arm, with the remaining allocation to the superior arm (a maximum of 90%, if two arms). In this event, stratification and blocking will no longer occur within these subgroups. This will ensure the majority of participants receive the best-known therapy, yet the trial design will still allow the assessment of seasonal variation and population changes in the study population over time. In addition, we will still be able to collect data about costs and health related behaviours (including health care seeking) associated with a poorly performing arm.

New comparator arms may enter the trial as determined by the Trial Steering Committee. Eligible therapies will include newly approved treatments for ILI or therapies recommended by public health agencies during an influenza pandemic. If an arm is added to the trial, there is a pre-specified algorithm determining randomization ratios, and for activating response adaptive randomization within subgroups to the respective treatment arms. The operating characteristics of the trial will be updated via simulation; however the general structure of the trial does not change. Response adaptive randomization may be activated in subgroups without satisfying superiority criterion only if the number of interventions is greater than two.

Justification of sample size

A sample size calculation for the planned design is not available using traditional formulas. Instead, simulations must be used to estimate the operating characteristics of the adaptive algorithm, including estimates of how many participants with particular characteristics are required in order to detect differences in treatments. In these simulations, the pre-specified algorithm will be applied such that the randomization of participants with particular pre-specified characteristics will depend on the number of arms and the collected outcome data. In addition, the algorithm will determine when arms are dropped for futility, when an intervention is declared superior, and will have a process for adding a new intervention to the platform trial.

Between 2500 and 4500 participants will be recruited during three consecutive winters. This range of numbers has been chosen to ensure sufficient power for comparisons in the overall population, as well as within the pre-specified subgroups. Given the nature of the study's adaptive design and the desire to ensure sufficient power for multiple hypotheses across several subgroups, the number of participants needed to be recruited is a complex multi-dimensional calculation. Hence, numerous simulations were conducted to calculate power under various plausible scenarios. The maximum target of 4500 participants was chosen from these simulations because it gave over 80% power for many of the subgroup analyses with a one day benefit in terms of symptoms relief from oseltamivir. 2500 participants will provide over 99% power for comparing the primary end point in the overall study population where there is at least one day benefit of oseltamivir for participants with confirmed influenza. This number will also provide >80% power for all subgroups if there is a 2-day benefit of oseltamivir in participants with confirmed influenza. We based these simulations on the

assumption that 50% of patients will have confirmed influenza and 50% of patients will have ILI originating from another viral infection.

Statistical Analysis

The primary analysis will be intention to treat (ITT) and will include all randomised participants in the treatment arm they were assigned regardless of treatment taken. Secondary analyses will include the subset of the ITT population with confirmed influenza. As accrual to the trial is on-going, there will be frequent interim analyses that may update the randomization probabilities depending on interim results and the number of arms in the study.

The composite primary endpoint of return to usual activities with resolution of any fever, muscle- and headache to a minor problem or less will be modelled according to a Bayesian piece-wise exponential model. This is a survival time model that allows the baseline hazard to vary across follow-up. The hazard for reaching the primary endpoint will be modelled during four time intervals – 0-2 day, 3-5 days, 6-10 days, and 11 or more days. Participants not reaching the primary endpoint by 28 days (including participants that die) will be considered censored at 28 days. Participants who withdraw, are lost to follow-up, or not evaluated for the primary endpoint for any reason will be considered censored at their last contact date or 28 days, whichever is earlier.

Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) will compare the direct medical costs and health outcomes (in terms of number of days where ILI limits usual activities and in terms of Quality Adjusted Life Years gained) between the different arms. The analysis will use data from the trial (resource use, EQ-5D-5L, EQ-5D-3Y and VAS scores), and other relevant data from the countries in which the trial is set (e.g., unit costs, and type of health care provided within each country). Potential differences in repeated measures (EQ-5D-5L, EQ-5D-3Y and VAS) between arms will be investigated on a per-participant basis using mixed effects models. Valuation of quality of life (using a standardized instrument for measuring generic health status) will be done in accordance with the guidelines of the Euroqol group [27], using the 'EQ-5D-5L Crosswalk Index Value Calculator'.

Uncertainty will be explored using bootstrapping to represent clouds of Incremental Cost-effectiveness Ratios (ICERs) on the cost-effectiveness plane, as well as cost-effectiveness

acceptability curves. Subgroup analyses will be performed to acknowledge heterogeneity within each arm of the trial (e.g., age, severity, country). Value of perfect information analysis may also be performed to identify which sources of uncertainty should be reduced through additional research to efficiently improve decision making.

Discussion

The ALIC^{4}E Trial will be the first large-scale, international, non-industry sponsored, pragmatic, randomised trial of (cost-)effectiveness of adding oseltamivir to best usual primary care for people suffering from ILI. It will be an open trial in order to approximate effects in conditions close to those of usual care in order to determine real-world estimates of (cost-) effectiveness.

The lack of cost-effectiveness analyses alongside clinical trials, and given that children, older people and people with co-morbidities are underrepresented in studies that have been done, has once again been highlighted after the WHO's decision to downgrade the status of oseltamivir [7 28]. Despite the lack of trial evidence, the 2017 WHO Model List of Essential Medicines states that the use of oseltamivir should be restricted to severe illness due to confirmed, or suspected influenza virus infection in critically ill hospitalised patients [8]. Another report quoting the WHO states: "unless new information supporting the use in seasonal and pandemic outbreaks is provided, the next Expert Committee might consider oseltamivir for deletion" [7]. The current UK and US guidelines recommend treatment of defined subgroups of frail patients and patients with increased risk for complications [4 29]. Because the evidence base for these recommendations is incomplete, withholding treatment from these or other patients may possibly deny them benefit. By including a 'best usual primary care' arm, our study will determine the added benefit of antiviral agents over and above current practice for seasonal and potentially pandemic influenza. This information will be of great importance to the delivery of primary care for ILI, as well as enhance the evidence base around advocating self-care. In many EU countries, patients with ILI symptoms are advised not to consult but to self-manage, and patients with additional risk factors are seldom routinely treated with an antiviral agent. This is largely because of an absence of evidence about the cost-effectiveness overall and in sub-groups of interest.

The virulence, spread and type of circulating influenza strains varies from season to season. ALIC^{4}E aims to recruit over three winter/influenza seasons in 15 countries, thereby obtaining

widely applicable data. Furthermore, the aim is to include a wide age-range of participants, as well as those with co-morbidities. Additionally, in the event of an influenza pandemic, or should additional intervention arms be included, a decision could be made to increase the maximum sample size.

The adaptive design offers several advantages over a traditional study design. Recruitment into a particular arm can be stopped once a pre-determined level of certainty about the effectiveness or non-effectiveness of treatment in that arm has reached a pre-defined estimated precision. Adaptive randomisation will increase the chances of participants being allocated to arms where their information will be most useful and to the intervention that is most effective for them. This can lead to better patient care and better patient outcomes as the trial progresses. Secondly, the platform design allows new intervention arms to be added to the trial, benefiting from comparisons with existing treatment arms in a head to head way. This flexibility extends to a potential pandemic situation where additional or alternative interventions may be added according to governmental or public health recommendations. In this way, the study will remain current and relevant to clinical practice and evolving circumstances throughout.

ALIC^{4}E will be novel in many ways. It will provide critical information about the clinical and cost-effectiveness of adding oseltamivir to best known ILI management in conditions that approximate usual care both overall and in important, pre-specified subgroups. ALIC^{4}E will directly impact current practice, either it will confirm best usual primary care, or it will lead to adaptations.

Figure 1. ALIC^{4}E European Networks. Coordinating centres are in Oxford, UK and Utrecht, The Netherlands. A number of the primary care research networks had already established collaborations through the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe; www.grace-lrti.org) Network of Excellence. [30 31] They were sustained through TRACE (Translational Research on Antimicrobial resistance and Community-acquired infections in Europe; www.esf.org/trace) and were complemented by PREPARE for ALIC^{4}E with six additional primary care research networks. The ALIC^{4}E networks include: Belgium (Antwerp, Ghent); Czech Republic; Denmark; France; Greece;

Hungary; Ireland; Lithuania; Netherlands, Norway; Poland (Bialystok, Lodz); Spain (Barcelona, Catalonia, Santiago de Compostela); Sweden; Switzerland; and the UK (Oxford, Southampton and Cardiff).

Declarations

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CB and TV are co-chief investigators of this trial and act as guarantors of the study in its entirety. CB and TV led the development of the research question, study design and obtaining the funding along with AV, JC, PB, HG, MJ and PL. EB, JC and AV manage the trial and coordinate the operational delivery of the study protocol to the networks co-ordinating centres. BS and JH are the trial statisticians. PB provides health economics input. MI provides support with sampling and analysis. RMA, CBr, SCh, SC, AC, MD, MDP, ADS, NF, DG, MGC, ML, FMT, AM, JP, MP, RRJ, PDS, TT, AT, PTL, DV are representatives of the collaborating co-ordinating centres responsible for their networks participation in the trial. EB and AV wrote the manuscript, supervised by CB. All other authors provided critical review and final approval of the manuscript.

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Trial Status

Recruitment started in January 2016 and is expected to be completed by May 2018. The first two seasons assessed only oseltamivir as an antiviral. There are currently no other antivirals available to evaluate within this trial. The current protocol is version 4.1 02-DEC-2017.

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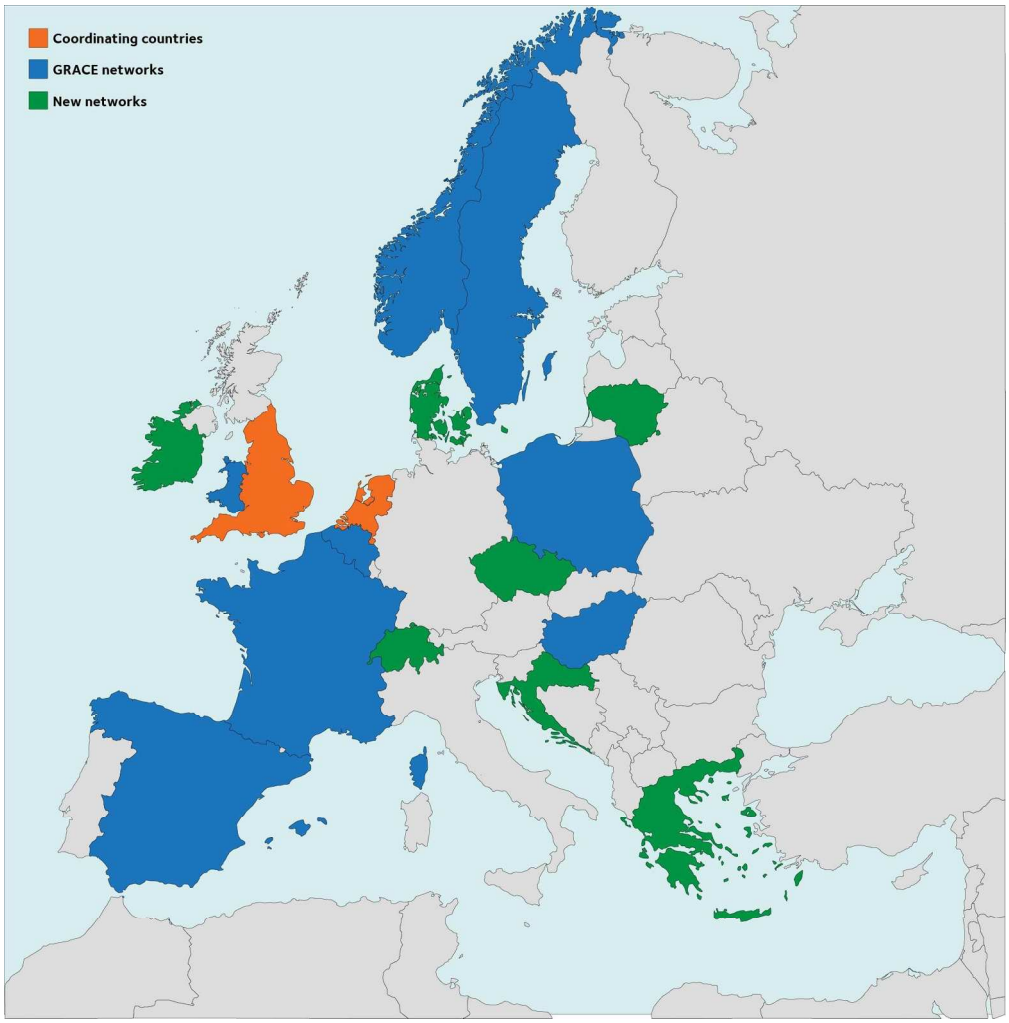
Endnotes

[i] Heart Disease/ Diabetes/Chronic respiratory condition (e.g. asthma, COPD)/Hepatic, hematologic, neurologic or neurodevelopmental condition/Stroke or Transient Ischemic Attack/Overnight hospital admission in the last year.
[ii] Rhinovirus, Coronavirus (NL63/229E/OC43/HKU1), Parainfluenza (1, 2, 3, 4), Human Metapneumovirus A/B, Bocavirus, Respiratory Syncytial Viruses A/B, Adenovirus, Enterovirus, Parechovirus.
[iii] *Mycoplasma pneumoniae, Chlamydia pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae type B, Staphylococcus aureus*.



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Antivirals for influenza-Like Illness? A randomized Controlled trial of Clinical and Cost effectiveness in primary CarE (ALIC4E): The ALIC4E Protocol

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Antivirals for influenza-Like Illness? A randomized Controlled trial of Clinical and Cost effectiveness in primary CarE (ALIC^{4}E): The ALIC^{4}E Protocol

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Abstract

Introduction

Effective management of seasonal and pandemic influenza is a high priority internationally. Guidelines in many countries recommend antiviral treatment for older people and individuals with co-morbidity at increased risk of complications. However, antivirals are not often prescribed in primary care in Europe, because its clinical and cost effectiveness has been insufficiently demonstrated by non-industry funded and pragmatic studies.

Methods and analysis

ALIC^{4}E is a European multi-national, multi-centre, open-labelled, non-industry funded, pragmatic, adaptive-platform, randomised controlled trial (RCT). Initial trial arms will be best usual primary care, and best usual primary care plus treatment with oseltamivir for five days. We aim to recruit at least 2500 participants ≥1 year old presenting with influenza-like illness (ILI), with symptom duration ≤72 hours in primary care over three consecutive periods of confirmed high influenza incidence. Participant outcomes will be followed-up to 28 days by diary and telephone. The primary objective is to determine whether adding antiviral treatment to best usual primary care is effective in reducing time to return to usual daily activity with fever, head- and muscle-ache reduced to minor severity or less. Secondary objectives include estimating cost-effectiveness, benefits in subgroups according to age (<12, 12-64, >64 years), severity of symptoms (low, medium, high), comorbidity (yes/no), and duration of symptoms (≤48hours/>48-72 hours), complications (hospital admission and pneumonia), use of additional prescribed medication including antibiotics, and use of over-the-counter medicines and self-management of ILI symptoms.

Ethics and dissemination

Research ethics committee (REC) approval was granted by the NRES Committee South Central (Oxford B) and Clinical Trial Authority (CTA) approval by The Medicines and Healthcare products Regulatory Agency. All participating countries gained national REC and CTA approval as required. Dissemination of results will be through peer reviewed scientific journals and conference presentations.

Trial Registration

ISRCTN27908921

Strengths and limitations of this study

- ALIC^{4}E will be the first publically funded, multi-country, pragmatic study determining whether antivirals should be routinely prescribed for influenza like illness (ILI) in primary care.
- ALIC^{4}E aims to go beyond determining the average treatment effect in a population to determining effects in patients with combinations of pre-specified characteristics (age, symptom duration, illness severity, and co-morbidities).
- The platform design allows the study to remain relevant to evolving circumstances, with the ability to add treatments arms.
- Response adaptation allows the proportion of participants with key characteristics allocated to study arms to be altered during the course of the trial according to emerging outcome data, so that participants' information will be most useful, and increasing their chances of receiving the intervention that will be most effective for them.
- Because the possibility of taking a placebo influences participant expectation about their treatment, and determining effects of the interventions on patient behaviour in real-world care is critical to estimates of cost effectiveness, ALIC^{4}E is designed as an open-labelled trial.

Keywords

Influenza, Oseltamivir, Primary Health Care, Cost-Benefit Analysis, Adaptive Clinical Trial

Background

The influenza virus is highly contagious and represents a common cause of respiratory infection with local and systemic symptoms. Annual influenza epidemics account for considerable morbidity and mortality[1-4] and influenza outbreaks have the potential to become pandemics[2]. Effective control and management of seasonal and pandemic influenza is a high priority for national governments. Routine use of antiviral agents is rare in European primary care[5]. General practitioners (GPs) in Europe generally advise patients who consult with influenza-like illness (ILI) to take paracetamol or non-steroidal anti-inflammatory agents (NSAIDs), either as required or at regular intervals. They may also provide advice about other over-the-counter (OTC) medicines and self-management of ILI symptoms, e.g. maintaining fluids, bed rest and taking time off work or school. This broad approach is currently considered best usual care for the empirical management of ILI in Europe[6-8].

Currently, the most suitable antiviral agent available for pragmatic evaluation in ALIC^{4}E is oseltamivir (Tamiflu®), a neuraminidase inhibitor (NI). The US Food and Drug Administration (FDA) approved oseltamivir in 1999. Oseltamivir was classified by the WHO as an essential medicine until 2017[9,10], and many countries have stockpiles of the drug to ensure it is readily available to treat seasonal and pandemic influenza[5]. Oseltamivir could therefore be used for the management of ILI on assumption that many cases of ILI may be caused by influenza, the probability of this being higher during confirmed periods of heightened influenza based on national reports of ILI consultations and laboratory confirmed influenza cases.

Oseltamivir phosphate is an oral pro-drug which undergoes hydrolysis by hepatic esterase to form active oseltamivir carboxylate. Oseltamivir carboxylate acts by selective inhibition of influenza A and B viral neuraminidase. This enzyme normally promotes release of the virus from infected cells by cleaving terminal sialic acid residues on the surface of host cells and influenza virus envelopes, and facilitates viral movement within the respiratory tract. By blocking the activity of the enzyme, oseltamivir prevents new viral particles from being released[11,12]. Oseltamivir might also modify the immune response to influenza infection by reducing levels of pro-inflammatory cytokines which might, in turn, modulate symptoms of influenza[13].

Industry-sponsored trials (or studies), efficacy studies and clinical study reports of NIs, most often oseltamivir, have been the subject of many systematic reviews and meta-analyses, including individual patient meta-analyses[14-16]. In two recent meta-analyses that differed in their methods and the primary outcome measures used, but that included almost the same set of trials, Jefferson *et al.* found that oseltamivir improved the mean time to first alleviation of symptoms over the placebo by 16.8 hours[13] and Dobson *et al*. found oseltamivir improved the median time to alleviation of all symptoms over the placebo by 17.8 hours[15]. The reviewers also found that oseltamivir reduced the risk of self-reported, non-verified pneumonia but not for clinically diagnosed pneumonia[13,15]. Dobson *et al.* furthermore indicated that treatment with oseltamivir might reduce the risk of lower respiratory tract infection complications and hospitalization in patients testing positive for influenza[15]. However, increased nausea and vomiting were found to be associated with oseltamivir use[13,15]. Even with a possible reduction in symptom duration (compared to a placebo) the value of oseltamivir treatment of previously healthy individuals with non-severe seasonal influenza is questionable. Conversely, circumstances of some individuals, for example those urgently needing to return to work and parents and other carers, may mean that a reduction in function-limiting symptoms of a day may be considered very worthwhile. The UK Academy of Medical Sciences recently reviewed current evidence, and they advised that cost-effectiveness analyses that take virulence and severity of the circulating strain into account form a societal perspective are required to further inform such judgements[17].

Since 1999, oseltamivir has generated sales in excess of $18bn (£11bn; €13bn). The United States stockpiled 65 million treatments at a cost of $1.3bn. The United Kingdom spent £424m on a stockpile of 40 million doses. By 2009, 96 countries possessed enough oseltamivir for 350 million people[18]. In 2017 the WHO downgraded oseltamivir in the list of essential medicines from a “core” drug to one that is “complimentary”—a category of drugs considered less cost-effective[9,10]. However, there has never been a large-scale, international, publically funded, pragmatic RCT of its cost-effectiveness in primary care, and so the evidence base either to support or not support the routine use of this agent in primary care is inadequate and raises the question: does the effect found in previous efficacy studies translate into a meaningful benefit in every day primary care? Specifically, what are the overall costs and benefits of this possible shortened symptom duration from the perspective of the individual sufferer, the health services, and for society? Do patients considered to be at higher risk for complications of influenza (for example due to age, duration and severity of

symptoms, or relevant co-morbidity) benefit more from antiviral treatment in primary care? Answering these questions will reduce important clinical uncertainty for primary care clinicians about whether to prescribe antiviral agents for ILI, and whether or not to prioritise antiviral treatment for subgroups of primary care patients.

The ALIC^{4}E trial will be delivered as work package (WP) 4 of the Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE: www.prepare-europe.eu/) consortium grant. PREPARE is a European Commission funded network for the rapid and efficient delivery of harmonised, large-scale clinical research studies on infectious diseases (ID)[19]. ALIC^{4}E will be a randomised controlled trial of investigational medicinal products (CTIMP) in primary care that will determine the clinical- and cost-effectiveness of adding antiviral agents to best usual primary care for patients with specific characteristics suffering from ILI, and thus enable clinicians to better individualise prescribing decisions.

The primary objective of ALIC^{4}E is therefore to determine whether adding antiviral treatment to best usual primary care is effective in reducing time taken to return to usual daily activity. Secondary objectives will be to determine whether antiviral treatment is cost-effective; benefits pre-specified subgroups of participants; decreases hospital admissions; decreases complications related to ILI, especially pneumonia; improves the health-related quality of life, decreases (repeat) attendance at the GP, or other health services; decreases time to first reduction, time to alleviation, and new/worsening of ILI symptoms; reduces the use of over the counter (OTC) and prescribed medication, including antibiotics, and; affects the self-management of ILI symptoms.

Methods/Design

The protocol for ALIC^{4}E, is reported according to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines.

Ethics and dissemination

The trial was granted research ethics committee (REC) approval by the NRES Committee South Central (Oxford B) and Clinical Trial Authority (CTA) approval by The Medicines and Healthcare products Regulatory Agency, i.e. the competent authority in the UK. All participating countries gained national REC and CTA approval as required and when needed.

All participants will provide written informed consent before participation. The study will be conducted (using Good Clinical practice guidelines) according to the principles of the Declaration of Helsinki and in accordance with other relevant national guidelines, regulations, and acts. An independent Data Monitoring Committee (DMC) will review efficacy and safety data by treatment allocation, and a Trial Steering Committee will provide oversight of the trial.

A manuscript with the results of the primary outcome will be published in a peer-reviewed journal. Additional manuscripts will be report secondary outcomes, and be submitted for publication in peer-reviewed journals.

Patient and public involvement

The relevance and necessity of the research question, study design and development of patient facing documents including the Consent Forms, Participant Information Sheets, Symptom Diary, all follow up forms and promotional materials have been reviewed by members of the public. The patient and public involvement (PPI) group included a mixture of research experienced and inexperienced people, parents and elderly members of the public.

As part of the Trial Steering Committee (TSC) a representative of the relevant patient group is involved in the continued review of the recruitment to and conduct of the study. A TSC meeting is held at least once per year before each recruiting season.

The intervention arm in ALIC^{4}E is the use of an antiviral in addition to best usual primary care. The burden to participants was assessed by the TSC and considered minimal as the only antiviral currently being assessed in ALIC^{4}E, oseltamivir, is a licensed medication with marketing authorisation globally. In the context of the ALIC^{4}E Trial a standard dose of oseltamivir has been shown to be well tolerated. The study itself is only using the standard does of oseltamivir and is being used according to the marketing authorisation it has been granted.

Trial participants will not be informed of the trial results directly. However, the results will be published on the PREPARE Consortium website (http://www.prepare-europe.eu/) and on the Nuffield Department of Primary Care website (https://www.phc.ox.ac.uk/phctrials), both can be accessed freely.

Networks and participants

ALIC^{4}E is a European multi-national, multi-centre, open-labelled, pragmatic, adaptive-platform, randomised controlled trial (RCT). 21 primary care clinical research networks in 15 European countries will recruit participants (Figure 1), and each network will co-ordinate the recruiting sites within their network. A number of the primary care research networks had already established collaborations through the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe; www.grace-lrti.org) Network of Excellence[20,21]. They were sustained through TRACE (Translational Research on Antimicrobial resistance and Community-acquired infections in Europe; www.esf.org/trace) and were complemented by PREPARE for ALIC^{4}E with six additional primary care research networks.

Recruitment will be over three consecutive flu seasons, Q4 2015 to Q1/2 2018. Each season's start and end of recruitment will be based on reports of local influenza-like illness incidence rising above (or falling below) pre-specified thresholds, using information supplied by the European Centre of Disease Prevention and Control (ECDC)[22], and local and regional sources for each network.

We aim to recruit a minimum of 2500 participants through recruiting sites (GP Practice, primary care Out of Hours (OOH) service or Paediatric Centres within primary care). Potential participants will be identified when they present to the recruiting sites with symptoms of ILI, or when they telephone for an appointment or advice about their symptoms. Participants must meet the inclusion criteria (including symptom onset of 72 hours or less) and have none of the exclusion criteria (Table 1). The definition of ILI used in ALIC^{4}E was based on the European Centre for Disease Prevention and Control (ECDC) definition[23] with flexibility to maximise recruitment of children and the elderly[24,25]. If eligible and willing to participate, the participant will complete the rest of the initial trial procedures either within the same visit, or at a second appointment with a recruiter at the recruiting site, or at home.

Table 1. Eligibility criteria

Inclusion	Exclusion

• Male or Female, aged at least one year • Presenting with ILI* in primary care during a period of increased influenza activity. * ILI=sudden onset of self-reported fever, with at least one respiratory symptom (cough, sore throat, running or congested nose) and one systemic symptom (headache, muscle ache, sweats or chills or tiredness), with symptom duration of 72 hours or less • Is able and willing to comply with all trial requirements • Participant or legal guardian(s) of a child is willing and able to give informed consent • Agrees not to take antiviral agents apart from study antiviral agents according to patient randomisation	• Chronic renal failure e.g. known or estimated creatinine glomerular filtration rate <60 ml/min (known = recorded in participant's clinical records) • Condition or treatment associated with significant impaired immunity (e.g. long-term oral steroids, chemotherapy, or immune disorder) (known=recorded in participant's clinical records) • Those who in the opinion of the responsible clinician should be prescribed immediate antiviral treatment • Allergic to oseltamivir or any other trial medication • Scheduled elective surgery or other procedures requiring general anaesthesia during the subsequent two weeks • Participant with life expectancy estimate by a clinician to be less than 6 months • Patient with severe hepatic impairment • Responsible clinician considers urgent hospital admission is required • Any other significant disease or disorder which, in the opinion of the responsible clinician, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or may affect the participant's ability to participate in the trial • Involvement, including completion of any follow up procedures, in another clinical trial of an investigational medicinal product in the last 90 days • Previous ALIC^{4}E trial participation • Patients unable to be randomised within 72 hours after onset of symptoms • Requirement for any live viral vaccine in the next 7 days • *Optional according to specific country legislation:* o Pregnant, lactating or breastfeeding women

The local implementation of the trial has built-in flexibility and local network recruitment processes vary. For example, medical students may assist with recruitment tasks in certain practices, while others will incorporate triage systems or additional trial specific clinics and/or research support staff in their recruitment processes.

Randomization and blinding

After obtaining informed, written consent, participants will be randomised at the point of care using a remote online electronic data capture (EDC) system (Research Online 2). Emergency randomisation procedures will be available should this web-based facility be temporarily unavailable. Randomisation will initially be a 1:1 ratio between the two arms, with stratification by subgroup according to ECDC definitions of those at higher risk of complications from influenza, namely their age (<12, 12-64, >64 years), severity of symptoms (low, medium, high), any relevant comorbidity[i] (yes/no), and duration of symptoms since onset (≤48hours/>48-72hours). The proportions randomised to study arms may be altered during the course of the trial following a pre-specified Bayesian, response adaptive approach[26].

ALIC^{4}E is an open trial. The participant, the recruiting clinician and the study personnel will be aware of the participant's allocation. An open pragmatic trial was chosen because this design is better for determining effects in routine care when patients are much less tightly supervised. Estimates of effect from placebo-controlled efficacy trials may not translate into similar effect sizes when interventions are taken up into routine clinical care. Knowledge of what medication one is taking influences help-seeking behaviour, and decisions to re-consult may substantially affect cost-effectiveness. In addition, efficacy estimates have already been repeatedly determined in efficacy trials with tightly controlled inclusion criteria, in which children, the elderly and people with co-morbidities have been under represented[27]. Clinicians do not prescribe placebos in routine care, and so the credible comparator is current best practice[28]. Therefore, no un-blinding or code breaking is required in the event of a relevant emergency. However, the trial team will be blind to treatment allocation at the aggregate level. The recruiter will promote equipoise for the participant about the two arms which will be carefully covered in trial specific training, and each arm of the trial will be supported as in routine practice; previous open pragmatic trials have been able to minimise placebo effects using this approach[29,30].

Intervention

Participants randomised to best usual primary care plus oseltamivir arm will be given a dose of 75 mg oseltamivir twice a day for five days by the oral route (capsules) for those ≥13 years. For those who are ≥1 year but <13 years the doses will be twice daily for 5 days in

suspension, administered orally, according to weight: 10-15 kg = 30 mg; >15-23 kg = 45 mg; >23-40 kg = 60 mg; >40 kg = 75 mg. Children weighing >40 kg and who are able to swallow capsules may receive treatment with the adult dosage of 75 mg capsules twice daily for five days as an alternative to the same dose of oseltamivir suspension. Route of administration, dosage and treatment periods follow the manufacturers Summary of Product Characteristics (SPC)[12]. Weight will be measured in children ≤12 years of age during the recruitment visit for medication dosing. All other participants will be asked about their weight at the baseline assessment and measured in case of uncertainty. A daily Symptom Diary and subsequent day 14-28 telephone call will be used to monitor intervention compliance, and together with a telephone call after day 28, will also ascertain a minimal data set for some other outcomes.

Endpoints

The primary outcome is patient reported time to having both returned to usual daily activity, and 'fever', 'headache' and 'muscle-ache' symptoms all rated as '≤minor problem'. For non-verbal children, 'clinginess' will replace 'headache' and 'muscle ache', when both are unanswered.

Secondary outcomes will include (collected up to day 28):

- Cost-effectiveness measures through health care resource use and health-related quality of life
- Effectiveness in subgroups of participants (based on age bands, initial illness severity, relevant co-morbidity, duration of symptoms, and laboratory confirmed influenza A/B positivity)
- Hospital admissions (overnight stay)
- (Re-) attendance at GP Practice, hospital emergency care, primary care OOH services or Paediatric Centres
- Complications related to ILI and/or potential relevant complications such as pneumonia
- Time to first reduction, time to alleviation of, and new/worsening ILI symptoms
- Use of prescription medications, including antibiotics
- Use of over-the-counter medications
- Participant reported self-management and usual daily activities

Procedures and assessments

Table 2 outlines the ALIC^{4}E Schedule of Procedures according to the SPIRIT guidelines.

Table 2. ALIC^{4}E Schedule of Procedures

	Screening	Baseline Day 1	Day 1-14	Day 14 - 28	Post day 28
Eligibility assessment[1]	✓				
Informed consent [1+2]		✓			
Baseline CRF[1]		✓			
Physical examination[1]		✓			
Swab(s)[1]		✓			
Randomisation[1]		✓			
Dispensing of trial drugs[1]		✓			
Symptom Diary[2]			✓		
Day 2-4 Phone Call[3]			✓		
Day 14 -28 Phone Call[3]				✓	
After day 28 Phone Call[3]					✓
Clinical notes Review*[3]					✓
Adverse event assessments [3]			✓		✓
SAE Follow-up[3]			✓		✓

*Country dependent
[1]Completed by recruiter
[2]Completed by participant, includes standardised written health–related quality of life assessment and documents resource use
[3]Completed by trial team (CI/PI/coordinator), Day 28 call includes standardised verbal health–related quality of life assessment

Baseline Assessment (Day 1)

After obtaining written, informed consent, recruiters will complete a baseline Case Report Form (CRF). This will include the required information for randomisation: age; relevant comorbidities; duration of symptoms; clinician's rating of severity of ILI as mild, moderate or severe. In addition, the CRF will ascertain participant's/parent's severity grading for:

fever, running or congested nose, sore throat, headache, cough, shortness of breath, muscle ache and pains, sweats/chills, diarrhoea, nausea and/or vomiting, abdominal pain, low energy/tired, not sleeping well, dizziness, feeling generally unwell (grading = no, minor, moderate, major problem); information about any usual care advice given to the participant; and type of health care coverage (e.g. public, private or mixed). The symptom questions will be supplemented with child-specific questions so that the Canadian Acute Respiratory Illness Flu Scale will be completed for children ≤12 years of age[31].

Additionally, clinical examination findings will be recorded including: temperature and the way it was measured (oral, ear or axilla); use of antipyretics in the last 4 hours; pulse rate; weight (≤12 years of age or in cases of uncertainty); height; smoking status; gender; and whether they have had flu vaccination within six months and pneumococcal vaccination within five years.

The recruiter will provide antiviral medication according to the participant's group allocation and standardised instructions on how to take the medication. The recruiter will also take an oropharyngeal and a nasal swab (COPAN®) from those <16 years of age and a nasopharyngeal swab (COPAN®) from those ≥16 years of age. All swabs will be placed in 3mL universal transport media (UTM) and transported to a local laboratory for storage. Finally, they will instruct participants how to complete the Symptom Diary and give information about telephone follow-up assessments.

Diary (Day 1 – 14) and Follow-up

There is no requirement for participants to attend a face-to-face follow-up visit as part of their study participation, as all subsequent measurements will be ascertained by self-completed diary-based questionnaires and through telephone calls from the local trial team.

Participants (or their legal guardian or their carer) will be asked to complete a Symptom Diary from day 1 (baseline) through to day 14 after randomisation. The following data points will be collected once: expectations of treatment benefit; ethnicity; employment status; cohabitation; pregnancy and stage; and current long-term medication. The following data points are collected daily in the diary: severity of selected ILI symptom; quality of life (EQ Visual Analogue Scale (VAS)); return to usual daily activity; prescription medication use (including antibiotics); use of OTC medication or remedies; adherence to trial medication and

potential side-effects (up to day 7). The following data points will be collected weekly: quality of life (using EQ 5D 5L index (respondents >12 years) or EQ 5D 3Y (respondents ≤12 years)); effect of the participants' symptoms on usual daily activities; health care resource use; out-of-pocket expenditure; and ILI state of people in the same household.

Participants and legal guardians will be telephoned on day three (+/- one day) (with day one defined as the day they were recruited into the study) to offer support with Symptom Diary completion and to check for any urgent issues. They will also be telephoned on day 14 (up to day 28) and asked on what day they returned to their usual daily activity, if and when their fever, head- and muscle-ache symptoms reduced to minor severity or less to ensure the primary end point is collected for all participants, and to ascertain any Serious Adverse Events (SAEs) in the preceding two weeks. Participants will receive a final telephone call on or after day 28 to complete a verbal EQ-5D-5L/3Y and VAS, to answer remaining questions about symptom resolution if needed, and about their trial participation and consent process as part of a process evaluation (see below). The trial team will ask whether participants have had a recurrence of their symptoms during this time and whether they have been admitted into hospital as a result of their symptoms.

Participants who have visited the hospital with complications possibly related to ILI and who have had a chest X-ray will have their primary care clinical records examined by the trial team for confirmation of relevant diagnoses of complications, including pneumonia.

Laboratory testing and point of care test (POCT)

Once the swabs have been received at local laboratories, samples will be frozen and stored at -70°C (-20°C is acceptable if there is no deep-freezer). After each flu season, samples will be transported to the Laboratory of Medical Microbiology, University of Antwerp, Belgium for analysis. Each participant's swab(s) will be analysed using a Multiplex RT-PCR for detection of pathogen genes by TaqMan® technology to identify whether or not the participant is infected with influenza A or B, with other respiratory viruses[ii], or with bacteria[iii].

Interviews and Qualitative assessment

As part of the day 28 telephone call to the participants or legal guardians or carers, questions will be asked about motivation for participating in the ALIC^{4}E study, what influenced that decision, and questions related to research participation during a pandemic.

All participating clinicians will be asked to complete a brief questionnaire, and a sub-sample will be asked their perspectives on the trial process, their views of influenza management in primary care, and participation in pandemic research.

Safety and discontinuation or withdrawal of participants from trial treatment

Oseltamivir has a well-documented safety profile and is a commonly used medication in a primary care setting. As a result, no non-serious adverse events will be recorded in this study. All Serious Adverse Events (SAEs) occurring during the 28 days participants are enrolled on the trial will be recorded. It will be left to the Investigator's clinical judgment to decide whether or not a symptom or side effect is of sufficient severity to require the participant's removal from treatment. If the participant is withdrawn due to an adverse event (AE), the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised or until the end of their trial participation, whichever is later. If the participant is withdrawn due to an AE, follow up data will continue to be collected and their information will be included for the purpose of the intention to treat analysis. Participants have the right to withdraw from the study at any time without any prejudice to current and future health care.

Response Adaptive-Platform Trial Design

An "adaptive platform trial" enables multiple interventions for the same indication to be tested simultaneously within a master protocol, and often includes the capacity to add, or drop, study arms while the study is in progress[32,33]. Platform trials provide an effective framework to study patient heterogeneity in outcomes, with the goal of determining the best treatment for various subgroups of patients. In addition, platform trial designs can incorporate response adaptive randomization in order to randomize more participants to the best performing interventions during the course of the trial. This can increase statistical power and efficiency of the trial, as well as lead to better patient outcomes over the course of the study[34].

We chose an adaptive platform trial design because it provided flexibility to evaluate additional interventions in the trial, should interventions emerge that are suitable to pragmatic evaluation in primary care. Additionally, the design provides the ability to prospectively identify particular subgroups of interest that may receive benefit from antiviral agents, as opposed to estimating a single overall effect. This is done by incorporating a Bayesian modelling approach, combined with response adaptive randomization based on pre-specified

participant characteristics. There will be multiple interim analyses during recruitment; planned after every 750 patients and/or between flu seasons.

In ALIC^{4}E, participants will be initially randomised in a 1:1 ratio to the two arms, with stratification by subgroup and random blocks. Each arm will maintain at least a 10% probability of randomisation within each subgroup throughout the course of the trial. Arm superiority will be assessed by subgroup and may be declared superior in some subgroups, but not within others. If, at an interim analysis, an arm meets the superiority criterion for one of the treatments, randomization probabilities may be modified for those subgroups such that a minimum of 10% of participants are allocated to the inferior arm, with the remaining allocation to the superior arm (a maximum of 90%, if two arms). In this event, stratification and blocking will no longer occur within these subgroups. This will ensure the majority of participants receive the best-known therapy, yet the trial design will still allow the assessment of seasonal variation and population changes in the study population over time. In addition, we will still be able to collect data about costs and health related behaviours (including health care seeking) associated with a poorly performing arm.

New comparator arms may enter the trial as determined by the Trial Steering Committee. Eligible therapies will include newly approved treatments for ILI or therapies recommended by public health agencies during an influenza pandemic. If an arm is added to the trial, there is a pre-specified algorithm determining randomization ratios, and for activating response adaptive randomization within subgroups to the respective treatment arms. The operating characteristics of the trial will be updated via simulation; however, the general structure of the trial does not change. Response adaptive randomization may be activated in subgroups without satisfying superiority criterion only if the number of interventions is greater than two.

Justification of sample size

A sample size calculation for the planned design is not available using traditional formulas. Instead, simulations must be used to estimate the operating characteristics of the adaptive algorithm, including estimates of how many participants with particular characteristics are required in order to detect differences in treatments. In these simulations, the pre-specified algorithm will be applied such that the randomization of participants with particular pre-specified characteristics will depend on the number of arms and the collected outcome data. In addition, the algorithm will determine when arms are dropped for futility, when an

intervention is declared superior, and will have a process for adding a new intervention to the platform trial.

Between 2500 and 4500 participants will be recruited during three consecutive winters. This range has been chosen to ensure sufficient power for comparisons in the overall population, as well as within the pre-specified subgroups. Given the nature of the study's adaptive design and the desire to ensure sufficient power for multiple hypotheses across several subgroups, the number of participants needed to be recruited is a complex multi-dimensional calculation. Hence, numerous simulations were conducted to calculate power under various plausible scenarios. The maximum target of 4500 participants was chosen from these simulations because it gave over 80% power for many of the subgroup analyses with a one day benefit in terms of symptoms relief from oseltamivir. 2500 participants will provide over 99% power for comparing the primary end point in the overall study population where there is at least one day benefit of oseltamivir for participants with confirmed influenza. This number will also provide >80% power for all subgroups if there is a 2-day benefit of oseltamivir in participants with confirmed influenza. We based these simulations on the assumption that 50% of patients will have confirmed influenza and 50% of patients will have ILI originating from another viral infection.

Statistical Analysis

The primary analysis will be intention to treat (ITT) and will include all randomised participants in the treatment arm they were assigned regardless of treatment taken. Secondary analyses will include the subset of the ITT population with confirmed influenza. There will be at least one interim analysis when accrual and data collection for each season is complete and before recruitment opens in the subsequent flu season. If accrual is rapid and large numbers of patients are enrolled, for example in the case of flu pandemic, more than one interim analysis may be conducted during a flu season, each occurring after approximately an additional 750 patients have been enrolled. The adaptive randomisation probabilities may be updated and arms assessed for superiority after each interim analysis.

The composite primary endpoint of return to usual activities with resolution of any fever, muscle- and headache to a minor problem or less will be modelled according to a Bayesian piece-wise exponential model. This is a survival time model that allows the baseline hazard to vary across follow-up. The hazard for reaching the primary endpoint will be modelled

during four time intervals – 0-2 day, 3-5 days, 6-10 days, and 11 or more days. Participants not reaching the primary endpoint by 28 days (including participants that die) will be considered censored at 28 days. Participants who withdraw, are lost to follow-up, or not evaluated for the primary endpoint for any reason will be considered censored at their last contact date or 28 days, whichever is earlier.

Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) will compare the direct medical costs and health outcomes (in terms of number of days where ILI limits usual activities and in terms of Quality Adjusted Life Years gained) between the different arms. The analysis will use data from the trial (resource use, EQ-5D-5L, EQ-5D-3Y and VAS scores), and other relevant data from the countries in which the trial is set (e.g., unit costs, and type of health care provided within each country). Potential differences in repeated measures (EQ-5D-5L, EQ-5D-3Y and VAS) between arms will be investigated on a per-participant basis using mixed effects models. Valuation of quality of life (using a standardized instrument for measuring generic health status) will be done in accordance with the guidelines of the Euroqol group[35], using the 'EQ-5D-5L Crosswalk Index Value Calculator'.

Uncertainty will be explored using bootstrapping to represent clouds of Incremental Cost-effectiveness Ratios (ICERs) on the cost-effectiveness plane, as well as cost-effectiveness acceptability curves. Subgroup analyses will be performed to acknowledge heterogeneity within each arm of the trial (e.g., age, severity, country). Value of perfect information analysis may also be performed to identify which sources of uncertainty should be reduced through additional research to efficiently improve decision making.

Discussion

The ALIC^{4}E Trial will be the first large-scale, international, non-industry sponsored, pragmatic, randomised trial of (cost-)effectiveness of adding oseltamivir to best usual primary care for people suffering from ILI.

ALIC^{4}E will be an open trial in order to approximate effects in conditions close to those of usual care in order to determine real-world estimates of (cost-) effectiveness. Open trials have been criticised because, should a treatment appear beneficial, it may not be clear if the effect resulted from biological mechanism or because of a placebo effect. When considering the

possible outcomes of ALIC^{4}E, if no benefit is found in the antiviral arm, despite the comparator usual care arm not being enhanced by the possible effects of a placebo, then prescribing the antiviral agent should not be recommended. On the other hand, if a benefit from an antiviral agent is identified in the pragmatic trial, given that the drug's efficacy will have already been demonstrated in many placebo controlled trials and that the drug's mechanisms of action is known and is specific to the condition under study, then it would be obtuse to suggest that any benefit ALIC^{4}E may identify derives from the placebo effect, and not from the antiviral's effect on influenza.

The lack of cost-effectiveness analyses alongside clinical trials, and given that children, older people and people with co-morbidities are underrepresented in studies that have been done, has once again been highlighted after the WHO's decision to downgrade the status of oseltamivir[9,36]. Despite the lack of trial evidence, the 2017 WHO Model List of Essential Medicines states that the use of oseltamivir should be restricted to severe illness due to confirmed, or suspected influenza virus infection in critically ill hospitalised patients[10]. Another report quoting the WHO states: "unless new information supporting the use in seasonal and pandemic outbreaks is provided, the next Expert Committee might consider oseltamivir for deletion"[9]. The current UK and US guidelines recommend treatment of defined subgroups of frail patients and patients with increased risk for complications[6,37]. Because the evidence base for these recommendations is incomplete, withholding treatment from these or other patients may possibly deny them benefit. By including a 'best usual primary care' arm, our study will determine the added benefit of antiviral agents over and above current practice for seasonal and potentially pandemic influenza. This information will be of great importance to the delivery of primary care for ILI, as well as enhance the evidence base around advocating self-care. In many countries, patients with ILI symptoms are advised not to consult but to self-manage, and patients with additional risk factors are seldom routinely treated with an antiviral agent. This is largely because of an absence of evidence about the cost-effectiveness overall and in sub-groups of interest.

The virulence, spread and type of circulating influenza strains varies from season to season. ALIC^{4}E aims to recruit over three winter/influenza seasons in 15 countries, thereby obtaining widely applicable data allowing us to determine whether any benefit or otherwise of antiviral agents is influenced by season. Furthermore, the aim is to include a wide age-range of participants, as well as those with co-morbidities. Additionally, in the event of an influenza

pandemic, or should additional intervention arms be included, a decision could be made to increase the maximum sample size.

The adaptive design offers several advantages over a traditional study design. Recruitment into a particular arm can be stopped once a pre-determined level of certainty about the effectiveness or non-effectiveness of treatment in that arm has reached a pre-defined estimated precision. Adaptive randomisation will increase the chances of participants being allocated to arms where their information will be most useful and to the intervention that is most effective for them. This can lead to better patient care and better patient outcomes as the trial progresses. Secondly, the platform design allows new intervention arms to be added to the trial, benefiting from comparisons with existing treatment arms in a head to head way. This flexibility extends to a potential pandemic situation where additional or alternative interventions may be added according to governmental or public health recommendations. In this way, the study will remain current and relevant to clinical practice and evolving circumstances throughout.

ALIC^{4}E will be novel in many ways. It will provide critical information about the clinical and cost-effectiveness of adding oseltamivir to best current ILI management in conditions that approximate usual care, both overall, as well as in important, pre-specified subgroups. ALIC^{4}E is likely therefore to enhance the evidence base supporting and important and common area of clinical practice.

Declarations

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CCB and TV are co-chief investigators of this trial and act as guarantors of the study in its entirety. CCB and TV led the development of the research question, study design and obtaining the funding along with AV, JC, PB, HG, MJ and PL. EB, JC and AV manage the trial and coordinate the operational delivery of the study protocol to the networks co-ordinating centres. BS and JH are the trial statisticians. PB provides health economics input. MI provides support with sampling and analysis. RMA, CBr, SCh, SC, AC, MD, MDP, ADS, NF, DG, MGC, ML, FMT, AM, JP, MP, RRJ, PDS, AT, PTL, DV are representatives of the collaborating co-ordinating centres responsible for their networks participation in the trial. EB and AV drafted the manuscript, supervised by CCB. All other authors provided critical review and final approval of the manuscript.

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Trial Status

Recruitment started in January 2016 and is expected to be completed by May 2018. The first two seasons assessed only oseltamivir as an antiviral. There are currently no other suitable antivirals available to evaluate within this trial. The current protocol is version 4.1 02-DEC-2017.

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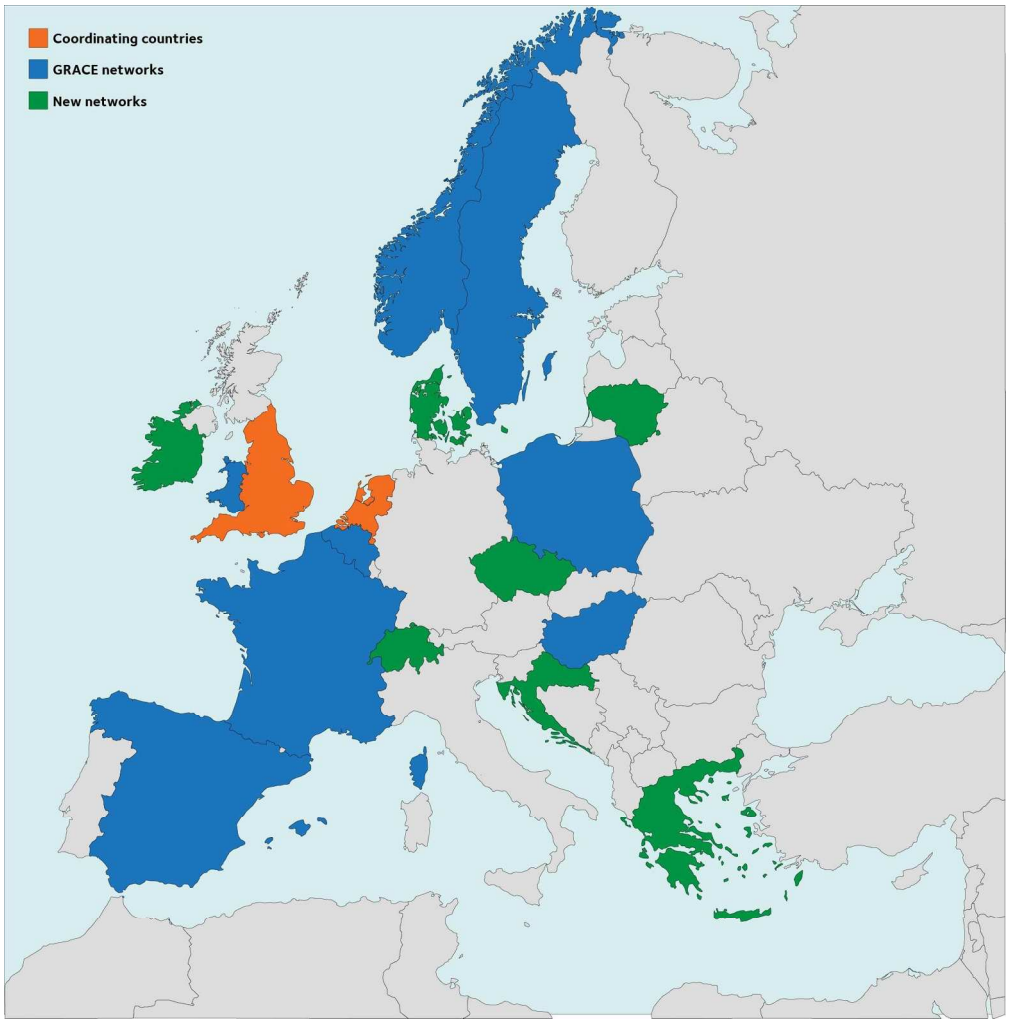
Figure 1. ALIC^{4}E European Networks. Coordinating centres are in Oxford, UK and Utrecht, The Netherlands. The ALIC^{4}E recruiting networks include: Belgium (Antwerp, Ghent); Czech Republic; Denmark; France; Greece; Hungary; Ireland; Lithuania; Netherlands, Norway; Poland (Bialystok, Lodz); Spain (Barcelona, Catalonia, Santiago de Compostela); Sweden; Switzerland; and the UK (Oxford, Southampton and Cardiff).

Endnotes

[i] Heart Disease/ Diabetes/Chronic respiratory condition (e.g. asthma, COPD)/Hepatic, hematologic, neurologic or neurodevelopmental condition/Stroke or Transient Ischemic Attack/Overnight hospital admission in the last year.

[ii] Rhinovirus, Coronavirus (NL63/229E/OC43/HKU1), Parainfluenza (1, 2, 3, 4), Human Metapneumovirus A/B, Bocavirus, Respiratory Syncytial Viruses A/B, Adenovirus, Enterovirus, Parechovirus.

[iii] *Mycoplasma pneumoniae, Chlamydia pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae type B, Staphylococcus aureus*.



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171x173mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	1, 3, 8, 18, 23, 30, 34, 38
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	3, 35
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	3, 7
	5b	Name and contact information for the trial sponsor	7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	33

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	10
	6b	Explanation for choice of comparators	11-14
Objectives	7	Specific objectives or hypotheses	16
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	13
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	19, 32, 38
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	18-24
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	23, 26
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	24
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	24
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	37, 39

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	30
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	30
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	20
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	20
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	20
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	20
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	20
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	20 - 23
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	23, 29

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	32-33
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	27-32
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	27-32
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	30
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	27, 33
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	28, 33
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	25-27
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	33
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	34
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	34

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	34
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	32
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	35
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	35
	31b	Authorship eligibility guidelines and any intended use of professional writers	35
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	separate
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	41

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Antivirals for influenza-Like Illness? A randomized Controlled trial of Clinical and Cost effectiveness in primary CarE (ALIC4E): The ALIC4E Protocol

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Antivirals for influenza-Like Illness? A randomized Controlled trial of Clinical and Cost effectiveness in primary CarE (ALIC^{4}E): The ALIC^{4}E Protocol

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Abstract

Introduction

Effective management of seasonal and pandemic influenza is a high priority internationally. Guidelines in many countries recommend antiviral treatment for older people and individuals with co-morbidity at increased risk of complications. However, antivirals are not often prescribed in primary care in Europe, partly because its clinical and cost effectiveness has been insufficiently demonstrated by non-industry funded and pragmatic studies.

Methods and analysis

ALIC^{4}E is a European multi-national, multi-centre, open-labelled, non-industry funded, pragmatic, adaptive-platform, randomised controlled trial (RCT). Initial trial arms will be best usual primary care, and best usual primary care plus treatment with oseltamivir for five days. We aim to recruit at least 2500 participants ≥1 year old presenting with influenza-like illness (ILI), with symptom duration ≤72 hours in primary care over three consecutive periods of confirmed high influenza incidence. Participant outcomes will be followed-up to 28 days by diary and telephone. The primary objective is to determine whether adding antiviral treatment to best usual primary care is effective in reducing time to return to usual daily activity with fever, head- and muscle-ache reduced to minor severity or less. Secondary objectives include estimating cost-effectiveness, benefits in subgroups according to age (<12, 12-64, >64 years), severity of symptoms at presentation (low, medium, high), comorbidity (yes/no), and duration of symptoms (≤48hours/>48-72 hours), complications (hospital admission and pneumonia); use of additional prescribed medication including antibiotics, and; use of over-the-counter medicines and self-management of ILI symptoms.

Ethics and dissemination

Research ethics committee (REC) approval was granted by the NRES Committee South Central (Oxford B) and Clinical Trial Authority (CTA) approval by The Medicines and Healthcare products Regulatory Agency. All participating countries gained national REC and CTA approval as required. Dissemination of results will be through peer reviewed scientific journals and conference presentations.

Trial Registration

ISRCTN27908921

Strengths and limitations of this study

- ALIC^{4}E will be the first publicly funded, multi-country, pragmatic study determining whether antivirals should be routinely prescribed for influenza like illness (ILI) in primary care and if pre-specified characteristics (age, symptom duration, illness severity, and co-morbidities) influence outcomes.
- The platform design allows the study to remain relevant to evolving circumstances, with the ability to add treatments arms.
- Response adaptation allows the proportion of participants with key characteristics allocated to study arms to be altered during the course of the trial according to emerging outcome data, so that participants' information will be most useful, and increasing their chances of receiving the intervention that will be most effective for them.
- Because the possibility of taking a placebo influences participant expectation about their treatment, and determining effects of the interventions on patient behaviour in real-world care is critical to estimates of cost effectiveness, ALIC^{4}E is designed as an open-labelled trial.
- The open design carries risk of bias in participants' self-reported outcomes; clear explanation of equipoise by recruiters may mitigate this.

Keywords

Influenza, Oseltamivir, Primary Health Care, Cost-Benefit Analysis, Adaptive Clinical Trial

Background

The influenza virus is highly contagious and represents a common cause of respiratory infection with local and systemic symptoms. Annual influenza epidemics account for considerable morbidity and mortality[1-4] and influenza outbreaks have the potential to become pandemics[2]. Effective control and management of seasonal and pandemic influenza is a high priority for national governments. Routine use of antiviral agents is rare in European primary care[5]. General practitioners (GPs) in Europe generally advise patients who consult with influenza-like illness (ILI) to take paracetamol or non-steroidal anti-inflammatory agents (NSAIDs), either as required or at regular intervals. They may also provide advice about other over-the-counter (OTC) medicines and self-management of ILI symptoms, e.g. maintaining fluids, bed rest and taking time off work or school. This broad approach is currently considered best usual care for the empirical management of ILI in Europe[6-8].

Currently, the most suitable antiviral agent available for pragmatic evaluation in ALIC^{4}E is oseltamivir (Tamiflu®), a neuraminidase inhibitor (NI). The US Food and Drug Administration (FDA) approved oseltamivir in 1999. Oseltamivir was classified by the WHO as an essential medicine until 2017[9,10], and many countries have stockpiles of the drug to ensure it is readily available to treat seasonal and pandemic influenza[5]. Oseltamivir could therefore be used for the management of ILI on assumption that many cases of ILI may be caused by influenza, the probability of this being higher during confirmed periods of heightened influenza based on national reports of ILI consultations and laboratory confirmed influenza cases.

Oseltamivir phosphate is an oral pro-drug which undergoes hydrolysis by hepatic esterase to form active oseltamivir carboxylate. Oseltamivir carboxylate acts by selective inhibition of influenza A and B viral neuraminidase. This enzyme normally promotes release of the virus from infected cells by cleaving terminal sialic acid residues on the surface of host cells and influenza virus envelopes, and facilitates viral movement within the respiratory tract. By blocking the activity of the enzyme, oseltamivir prevents new viral particles from being released[11,12]. Oseltamivir might also modify the immune response to influenza infection by reducing levels of pro-inflammatory cytokines which might, in turn, modulate symptoms of influenza[13].

Industry-sponsored trials (or studies), efficacy studies and clinical study reports of NIs, most often oseltamivir, have been the subject of many systematic reviews and meta-analyses, including individual patient meta-analyses[14-16]. In two recent meta-analyses that differed in their methods and the primary outcome measures used, but that included almost the same set of trials, Jefferson *et al.* found that oseltamivir improved the mean time to first alleviation of symptoms over the placebo by 16.8 hours[13] and Dobson *et al*. found oseltamivir improved the median time to alleviation of all symptoms over the placebo by 17.8 hours[15]. The reviewers also found that oseltamivir reduced the risk of self-reported, non-verified pneumonia but not for clinically diagnosed pneumonia[13,15]. Dobson *et al.* furthermore indicated that treatment with oseltamivir might reduce the risk of lower respiratory tract infection complications and hospitalization in patients testing positive for influenza[15]. However, increased nausea and vomiting were found to be associated with oseltamivir use[13,15]. Even with a possible reduction in symptom duration (compared to a placebo) the value of oseltamivir treatment of previously healthy individuals with non-severe seasonal influenza is questionable. Conversely, circumstances of some individuals, for example those urgently needing to return to work and parents and other carers, may mean that a reduction in function-limiting symptoms of a day may be considered very worthwhile. The UK Academy of Medical Sciences recently reviewed current evidence, and they advised that additional pragmatic trials in primary care and cost-effectiveness analyses that take virulence and severity of the circulating strain into account are required to further inform such judgements[17].

Since 1999, oseltamivir has generated sales in excess of $18bn (£11bn; €13bn). The United States stockpiled 65 million treatments at a cost of $1.3bn. The United Kingdom spent £424m on a stockpile of 40 million doses. By 2009, 96 countries possessed enough oseltamivir for 350 million people[18]. In 2017 the WHO downgraded oseltamivir in the list of essential medicines from a “core” drug to one that is “complimentary”—a category of drugs considered less cost-effective[9,10]. However, there has never been a large-scale, international, publicly funded, pragmatic RCT of its cost-effectiveness in primary care, and so the evidence base either to support or not support the routine use of this agent in primary care is inadequate and raises the question: does the effect found in previous efficacy studies translate into a meaningful benefit in every day primary care? Specifically, what are the overall costs and benefits of this possible shortened symptom duration from the perspective of the individual sufferer, the health services, and for society? Do patients considered to be at higher risk for complications of influenza (for example due to age, duration and severity of

symptoms, or relevant co-morbidity) benefit more from antiviral treatment in primary care? Answering these questions will reduce important clinical uncertainty for primary care clinicians about whether to prescribe antiviral agents for ILI, and whether or not to prioritise antiviral treatment for subgroups of primary care patients.

The ALIC^{4}E trial will be delivered as work package (WP) 4 of the Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE: www.prepare-europe.eu/) consortium grant. PREPARE is a European Commission funded network for the rapid and efficient delivery of harmonised, large-scale clinical research studies on infectious diseases (ID)[19]. ALIC^{4}E will be a randomised controlled trial of investigational medicinal products (CTIMP) in primary care that will determine the clinical- and cost-effectiveness of adding antiviral agents to best usual primary care for patients with specific characteristics suffering from ILI, and thus enable clinicians to better individualise prescribing decisions.

The primary objective of ALIC^{4}E is therefore to determine whether adding antiviral treatment to best usual primary care is effective in reducing time taken to return to usual daily activity in patients with ILI. Secondary objectives will be to determine whether antiviral treatment is cost-effective; benefits pre-specified subgroups of participants; decreases hospital admissions; decreases complications related to ILI, especially pneumonia; improves the health-related quality of life; decreases (repeat) attendance at the GP, or other health services; decreases time to first reduction, time to alleviation, and new/worsening of ILI symptoms; reduces the use of over the counter (OTC) and prescribed medication, including antibiotics, and; affects the self-management of ILI symptoms.

Methods/Design

The protocol for ALIC^{4}E, is reported according to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines.

Ethics and dissemination

The trial was granted research ethics committee (REC) approval by the NRES Committee South Central (Oxford B) and Clinical Trial Authority (CTA) approval by The Medicines and Healthcare products Regulatory Agency, i.e. the competent authority in the UK. All participating countries gained national REC and CTA approval as required and when needed.

All participants will provide written informed consent before participation. The study will be conducted (using Good Clinical practice guidelines) according to the principles of the Declaration of Helsinki and in accordance with other relevant national guidelines, regulations, and acts. An independent Data Monitoring Committee (DMC) will review efficacy and safety data by treatment allocation, and a Trial Steering Committee will provide oversight of the trial.

A manuscript with the results of the primary outcome will be published in a peer-reviewed journal. Additional manuscripts will be report secondary outcomes, and be submitted for publication in peer-reviewed journals.

Patient and public involvement

The relevance and necessity of the research question, study design and development of patient facing documents including the Consent Forms, Participant Information Sheets, Symptom Diary, all follow up forms and promotional materials have been reviewed by members of the public. The patient and public involvement (PPI) group included a mixture of research experienced and inexperienced people, parents and elderly members of the public.

As part of the Trial Steering Committee (TSC) a representative of the relevant patient group is involved in the continued review of the recruitment to and conduct of the study. A TSC meeting is held at least once per year before each recruiting season.

The intervention arm in ALIC^{4}E is the use of an antiviral in addition to best usual primary care. The burden to participants was assessed by the TSC and considered minimal as the only antiviral currently being assessed in ALIC^{4}E, oseltamivir, is a licensed medication with marketing authorisation globally. In the context of the ALIC^{4}E Trial a standard dose of oseltamivir has been shown to be well tolerated. The study itself is only using the standard does of oseltamivir and is being used according to the marketing authorisation it has been granted.

Trial participants will not be informed of the trial results directly. However, the results will be published on the PREPARE Consortium website (http://www.prepare-europe.eu/) and on the Nuffield Department of Primary Care website (https://www.phc.ox.ac.uk/phctrials), both can be accessed freely.

Networks and participants

ALIC^{4}E is a European multi-national, multi-centre, open-labelled, pragmatic, adaptive-platform, randomised controlled trial (RCT). 21 primary care clinical research networks in 15 European countries will recruit participants (Figure 1), and each network will co-ordinate the recruiting sites within their network. A number of the primary care research networks had already established collaborations through the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe; www.grace-lrti.org) Network of Excellence[20,21]. They were sustained through TRACE (Translational Research on Antimicrobial resistance and Community-acquired infections in Europe; www.esf.org/trace) and were complemented by PREPARE for ALIC^{4}E with six additional primary care research networks.

Recruitment will be over three consecutive flu seasons, Q4 2015 to Q1/2 2018. Each season's start and end of recruitment will be based on reports of local influenza-like illness incidence rising above (or falling below) pre-specified thresholds, using information supplied by the European Centre of Disease Prevention and Control (ECDC)[22], and local and regional sources for each network.

We aim to recruit a minimum of 2500 participants through recruiting sites (GP Practice, primary care Out of Hours (OOH) service or Paediatric Centres within primary care). Potential participants will be identified when they present to the recruiting sites with symptoms of ILI, or when they telephone for an appointment or advice about their symptoms. Participants must meet the inclusion criteria (including symptom onset of 72 hours or less) and have none of the exclusion criteria (Table 1). The definition of ILI used in ALIC^{4}E was based on the European Centre for Disease Prevention and Control (ECDC) definition[23] with flexibility to maximise recruitment of children and the elderly[24,25]. If eligible and willing to participate, the participant will complete the rest of the initial trial procedures either within the same visit, or at a second appointment with a recruiter at the recruiting site, or at home.

Table 1. Eligibility criteria

Inclusion	Exclusion

• Male or Female, aged at least one year • Presenting with ILI* in primary care during a period of increased influenza activity. * ILI=sudden onset of self-reported fever, with at least one respiratory symptom (cough, sore throat, running or congested nose) and one systemic symptom (headache, muscle ache, sweats or chills or tiredness), with symptom duration of 72 hours or less • Is able and willing to comply with all trial requirements • Participant or legal guardian(s) of a child is willing and able to give informed consent • Agrees not to take antiviral agents apart from study antiviral agents according to patient randomisation	• Chronic renal failure e.g. known or estimated creatinine glomerular filtration rate <60 ml/min (known = recorded in participant's clinical records) • Condition or treatment associated with significant impaired immunity (e.g. long-term oral steroids, chemotherapy, or immune disorder) (known=recorded in participant's clinical records) • Those who in the opinion of the responsible clinician should be prescribed immediate antiviral treatment • Allergic to oseltamivir or any other trial medication • Scheduled elective surgery or other procedures requiring general anaesthesia during the subsequent two weeks • Participant with life expectancy estimate by a clinician to be less than 6 months • Patient with severe hepatic impairment • Responsible clinician considers urgent hospital admission is required • Any other significant disease or disorder which, in the opinion of the responsible clinician, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or may affect the participant's ability to participate in the trial • Involvement, including completion of any follow up procedures, in another clinical trial of an investigational medicinal product in the last 90 days • Previous ALIC^{4}E trial participation • Patients unable to be randomised within 72 hours after onset of symptoms • Requirement for any live viral vaccine in the next 7 days • *Optional according to specific country legislation:* o Pregnant, lactating or breastfeeding women

The local implementation of the trial has built-in flexibility and local network recruitment processes vary. For example, medical students may assist with recruitment tasks in certain practices, while others will incorporate triage systems or additional trial specific clinics and/or research support staff in their recruitment processes.

Randomization and blinding

After obtaining informed, written consent, participants will be randomised at the point of care using a remote online electronic data capture (EDC) system (Research Online 2). Emergency randomisation procedures will be available should this web-based facility be temporarily unavailable. Randomisation will initially be a 1:1 ratio between the two arms, with stratification by subgroup according to ECDC definitions of those at higher risk of complications from influenza, namely their age (<12, 12-64, >64 years), severity of symptoms (low, medium, high), any relevant comorbidity[i] (yes/no), and duration of symptoms since onset (≤48hours/>48-72hours). The proportions randomised to study arms may be altered during the course of the trial following a pre-specified Bayesian, response adaptive approach[26].

ALIC^{4}E is an open trial. The participant, the recruiting clinician and the study personnel will be aware of the participant's allocation. An open pragmatic trial was chosen because this design is better for determining effects in routine care when patients are much less tightly supervised. Estimates of effect from placebo-controlled efficacy trials may not translate into similar effect sizes when interventions are taken up into routine clinical care. Knowledge of what medication one is taking influences help-seeking behaviour, and decisions to re-consult may substantially affect cost-effectiveness. In addition, efficacy estimates have already been repeatedly determined in efficacy trials with tightly controlled inclusion criteria, in which children, the elderly and people with co-morbidities have been under represented[27]. Clinicians do not prescribe placebos in routine care, and so the credible comparator is current best practice[28]. Therefore, no un-blinding or code breaking is required in the event of a relevant emergency. However, the trial team will be blind to treatment allocation at the aggregate level. The recruiter will promote equipoise for the participant about the two arms which will be carefully covered in trial specific training, and each arm of the trial will be supported as in routine practice; previous open pragmatic trials have been able to minimise placebo effects using this approach[29,30].

Intervention

Participants randomised to best usual primary care plus oseltamivir arm will be given a dose of 75 mg oseltamivir twice a day for five days by the oral route (capsules) for those ≥13 years. For those who are ≥1 year but <13 years the doses will be twice daily for 5 days in

suspension, administered orally, according to weight: 10-15 kg = 30 mg; >15-23 kg = 45 mg; >23-40 kg = 60 mg; >40 kg = 75 mg. Children weighing >40 kg and who are able to swallow capsules may receive treatment with the adult dosage of 75 mg capsules twice daily for five days as an alternative to the same dose of oseltamivir suspension. Route of administration, dosage and treatment periods follow the manufacturers Summary of Product Characteristics (SPC)[12]. Weight will be measured in children ≤12 years of age during the recruitment visit for medication dosing. All other participants will be asked about their weight at the baseline assessment and measured in case of uncertainty. A daily Symptom Diary and subsequent day 14-28 telephone call will be used to monitor intervention compliance, and together with a telephone call after day 28, will also ascertain a minimal data set for some other outcomes.

Endpoints

The primary outcome is patient reported time to having both returned to usual daily activity, and 'fever', 'headache' and 'muscle-ache' symptoms all rated as '≤minor problem'. For non-verbal children, 'clinginess' will replace 'headache' and 'muscle ache', when both are unanswered.

Secondary outcomes will include (collected up to day 28):

- Cost-effectiveness measures through health care resource use and health-related quality of life
- Effectiveness in subgroups of participants (based on age bands, initial illness severity, relevant co-morbidity, duration of symptoms, and laboratory confirmed influenza A/B positivity)
- Hospital admissions (overnight stay)
- (Re-) attendance at GP Practice, hospital emergency care, primary care OOH services or Paediatric Centres
- Complications related to ILI and/or potential relevant complications such as pneumonia
- Time to first reduction, time to alleviation of, and new/worsening ILI symptoms
- Use of prescription medications, including antibiotics
- Use of over-the-counter medications
- Participant reported self-management and usual daily activities

Procedures and assessments

Table 2 outlines the ALIC^{4}E Schedule of Procedures according to the SPIRIT guidelines.

Table 2. ALIC^{4}E Schedule of Procedures

	Screening	Baseline Day 1	Day 1-14	Day 14 - 28	Post day 28
Eligibility assessment[1]	✓				
Informed consent [1+2]		✓			
Baseline CRF[1]		✓			
Physical examination[1]		✓			
Swab(s)[1]		✓			
Randomisation[1]		✓			
Dispensing of trial drugs[1]		✓			
Symptom Diary[2]			✓		
Day 2-4 Phone Call[3]			✓		
Day 14 -28 Phone Call[3]				✓	
After day 28 Phone Call[3]					✓
Clinical notes Review*[3]					✓
Adverse event assessments [3]			✓		✓
SAE Follow-up[3]			✓		✓

*Country dependent
[1]Completed by recruiter
[2]Completed by participant, includes standardised written health–related quality of life assessment and documents resource use
[3]Completed by trial team (CI/PI/coordinator), Day 28 call includes standardised verbal health–related quality of life assessment

Baseline Assessment (Day 1)

After obtaining written, informed consent, recruiters will complete a baseline Case Report Form (CRF). This will include the required information for randomisation: age; relevant comorbidities; duration of symptoms; clinician's rating of severity of ILI as mild, moderate or severe. In addition, the CRF will ascertain participant's/parent's severity grading for:

fever, running or congested nose, sore throat, headache, cough, shortness of breath, muscle ache and pains, sweats/chills, diarrhoea, nausea and/or vomiting, abdominal pain, low energy/tired, not sleeping well, dizziness, feeling generally unwell (grading = no, minor, moderate, major problem); information about any usual care advice given to the participant; and type of health care coverage (e.g. public, private or mixed). The symptom questions will be supplemented with child-specific questions so that the Canadian Acute Respiratory Illness Flu Scale will be completed for children ≤12 years of age[31].

Additionally, clinical examination findings will be recorded including: temperature and the way it was measured (oral, ear or axilla); use of antipyretics in the last 4 hours; pulse rate; weight (≤12 years of age or in cases of uncertainty); height; smoking status; gender; and whether they have had flu vaccination within six months and pneumococcal vaccination within five years.

The recruiter will provide antiviral medication according to the participant's group allocation and standardised instructions on how to take the medication. The recruiter will also take an oropharyngeal and a nasal swab (COPAN®) from those <16 years of age and a nasopharyngeal swab (COPAN®) from those ≥16 years of age. All swabs will be placed in 3mL universal transport media (UTM) and transported to a local laboratory for storage. Finally, they will instruct participants how to complete the Symptom Diary and give information about telephone follow-up assessments.

Diary (Day 1 – 14) and Follow-up

There is no requirement for participants to attend a face-to-face follow-up visit as part of their study participation, as all subsequent measurements will be ascertained by self-completed diary-based questionnaires and through telephone calls from the local trial team.

Participants (or their legal guardian or their carer) will be asked to complete a Symptom Diary from day 1 (baseline) through to day 14 after randomisation. The following data points will be collected once: expectations of treatment benefit; ethnicity; employment status; cohabitation; pregnancy and stage; and current long-term medication. The following data points are collected daily in the diary: severity of selected ILI symptom; quality of life (EQ Visual Analogue Scale (VAS)); return to usual daily activity; prescription medication use (including antibiotics); use of OTC medication or remedies; adherence to trial medication and

potential side-effects (up to day 7). The following data points will be collected weekly: quality of life (using EQ 5D 5L index (respondents >12 years) or EQ 5D 3Y (respondents ≤12 years)); effect of the participants' symptoms on usual daily activities; health care resource use; out-of-pocket expenditure; and ILI state of people in the same household.

Participants and legal guardians will be telephoned on day three (+/- one day) (with day one defined as the day they were recruited into the study) to offer support with Symptom Diary completion and to check for any urgent issues. They will also be telephoned on day 14 (up to day 28) and asked on what day they returned to their usual daily activity, if and when their fever, head- and muscle-ache symptoms reduced to minor severity or less to ensure the primary end point is collected for all participants, and to ascertain any Serious Adverse Events (SAEs) in the preceding two weeks. Participants will receive a final telephone call on or after day 28 to complete a verbal EQ-5D-5L/3Y and VAS, to answer remaining questions about symptom resolution if needed, and about their trial participation and consent process as part of a process evaluation (see below). The trial team will ask whether participants have had a recurrence of their symptoms during this time and whether they have been admitted into hospital as a result of their symptoms.

Participants who have visited the hospital with complications possibly related to ILI and who have had a chest X-ray will have their primary care clinical records examined by the trial team for confirmation of relevant diagnoses of complications, including pneumonia.

Laboratory testing and point of care test (POCT)

Once the swabs have been received at local laboratories, samples will be frozen and stored at -70°C (-20°C is acceptable if there is no deep-freezer). After each flu season, samples will be transported to the Laboratory of Medical Microbiology, University of Antwerp, Belgium for analysis. Each participant's swab(s) will be analysed using a Multiplex RT-PCR for detection of pathogen genes by TaqMan® technology to identify whether or not the participant is infected with influenza A or B, with other respiratory viruses[ii], or with bacteria[iii].

Interviews and Qualitative assessment

As part of the day 28 telephone call to the participants or legal guardians or carers, questions will be asked about motivation for participating in the ALIC^{4}E study, what influenced that decision, and questions related to research participation during a pandemic.

All participating clinicians will be asked to complete a brief questionnaire, and a sub-sample will be asked their perspectives on the trial process, their views of influenza management in primary care, and participation in pandemic research.

Safety and discontinuation or withdrawal of participants from trial treatment

Oseltamivir has a well-documented safety profile and is a commonly used medication in a primary care setting. As a result, no non-serious adverse events will be recorded in this study. All Serious Adverse Events (SAEs) occurring during the 28 days participants are enrolled on the trial will be recorded. It will be left to the Investigator's clinical judgment to decide whether or not a symptom or side effect is of sufficient severity to require the participant's removal from treatment. If the participant is withdrawn due to an adverse event (AE), the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised or until the end of their trial participation, whichever is later. If the participant is withdrawn due to an AE, follow up data will continue to be collected and their information will be included for the purpose of the intention to treat analysis. Participants have the right to withdraw from the study at any time without any prejudice to current and future health care.

Response Adaptive-Platform Trial Design

An "adaptive platform trial" enables multiple interventions for the same indication to be tested simultaneously within a master protocol, and often includes the capacity to add, or drop, study arms while the study is in progress[32,33]. Platform trials provide an effective framework to study patient heterogeneity in outcomes, with the goal of determining the best treatment for various subgroups of patients. In addition, platform trial designs can incorporate response adaptive randomization in order to randomize more participants to the best performing interventions during the course of the trial. This can increase statistical power and efficiency of the trial, as well as lead to better patient outcomes over the course of the study[34].

We chose an adaptive platform trial design because it provided flexibility to evaluate additional interventions in the trial, should interventions emerge that are suitable to pragmatic evaluation in primary care. Additionally, the design provides the ability to prospectively identify particular subgroups of interest that may receive benefit from antiviral agents, as opposed to estimating a single overall effect. This is done by incorporating a Bayesian modelling approach, combined with response adaptive randomization based on pre-specified

participant characteristics. There will be multiple interim analyses during recruitment; planned after every 750 patients and/or between flu seasons.

In ALIC^{4}E, participants will be initially randomised in a 1:1 ratio to the two arms, with stratification by subgroup and random blocks. Each arm will maintain at least a 10% probability of randomisation within each subgroup throughout the course of the trial. Arm superiority will be assessed by subgroup and may be declared superior in some subgroups, but not within others. If, at an interim analysis, an arm meets the superiority criterion for one of the treatments, randomization probabilities may be modified for those subgroups such that a minimum of 10% of participants are allocated to the inferior arm, with the remaining allocation to the superior arm (a maximum of 90%, if two arms). In this event, stratification and blocking will no longer occur within these subgroups. This will ensure the majority of participants receive the best-known therapy, yet the trial design will still allow the assessment of seasonal variation and population changes in the study population over time. In addition, we will still be able to collect data about costs and health related behaviours (including health care seeking) associated with a poorly performing arm.

New comparator arms may enter the trial as determined by the Trial Steering Committee. Eligible therapies will include newly approved treatments for ILI or therapies recommended by public health agencies during an influenza pandemic. If an arm is added to the trial, there is a pre-specified algorithm determining randomization ratios, and for activating response adaptive randomization within subgroups to the respective treatment arms. The operating characteristics of the trial will be updated via simulation; however, the general structure of the trial does not change. Response adaptive randomization may be activated in subgroups without satisfying superiority criterion only if the number of interventions is greater than two.

Justification of sample size

A sample size calculation for the planned design is not available using traditional formulas. Instead, simulations must be used to estimate the operating characteristics of the adaptive algorithm, including estimates of how many participants with particular characteristics are required in order to detect differences in treatments. In these simulations, the pre-specified algorithm will be applied such that the randomization of participants with particular pre-specified characteristics will depend on the number of arms and the collected outcome data. In addition, the algorithm will determine when arms are dropped for futility, when an

intervention is declared superior, and will have a process for adding a new intervention to the platform trial.

Between 2500 and 4500 participants will be recruited during three consecutive winters. This range has been chosen to ensure sufficient power for comparisons in the overall population, as well as within the pre-specified subgroups. Given the nature of the study's adaptive design and the desire to ensure sufficient power for multiple hypotheses across several subgroups, the number of participants needed to be recruited is a complex multi-dimensional calculation. Hence, numerous simulations were conducted to calculate power under various plausible scenarios. The maximum target of 4500 participants was chosen from these simulations because it gave over 80% power for many of the subgroup analyses with a one day benefit in terms of symptoms relief from oseltamivir. 2500 participants will provide over 99% power for comparing the primary end point in the overall study population where there is at least one day benefit of oseltamivir for participants with confirmed influenza. This number will also provide >80% power for all subgroups if there is a 2-day benefit of oseltamivir in participants with confirmed influenza. We based these simulations on the assumption that 50% of patients will have confirmed influenza and 50% of patients will have ILI originating from another viral infection.

Statistical Analysis

The primary analysis will be intention to treat (ITT) and will include all randomised participants in the treatment arm they were assigned regardless of treatment taken. Secondary analyses will include the subset of the ITT population with confirmed influenza. There will be at least one interim analysis when accrual and data collection for each season is complete and before recruitment opens in the subsequent flu season. If accrual is rapid and large numbers of patients are enrolled, for example in the case of flu pandemic, more than one interim analysis may be conducted during a flu season, each occurring after approximately an additional 750 patients have been enrolled. The adaptive randomisation probabilities may be updated and arms assessed for superiority after each interim analysis.

The composite primary endpoint of return to usual activities with resolution of any fever, muscle- and headache to a minor problem or less will be modelled according to a Bayesian piece-wise exponential model. This is a survival time model that allows the baseline hazard to vary across follow-up. The hazard for reaching the primary endpoint will be modelled

during four time intervals – 0-2 day, 3-5 days, 6-10 days, and 11 or more days. Participants not reaching the primary endpoint by 28 days (including participants that die) will be considered censored at 28 days. Participants who withdraw, are lost to follow-up, or not evaluated for the primary endpoint for any reason will be considered censored at their last contact date or 28 days, whichever is earlier.

Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) will compare the direct medical costs and health outcomes (in terms of number of days where ILI limits usual activities and in terms of Quality Adjusted Life Years gained) between the different arms. The analysis will use data from the trial (resource use, EQ-5D-5L, EQ-5D-3Y and VAS scores), and other relevant data from the countries in which the trial is set (e.g., unit costs, and type of health care provided within each country). Potential differences in repeated measures (EQ-5D-5L, EQ-5D-3Y and VAS) between arms will be investigated on a per-participant basis using mixed effects models. Valuation of quality of life (using a standardized instrument for measuring generic health status) will be done in accordance with the guidelines of the Euroqol group[35], using the 'EQ-5D-5L Crosswalk Index Value Calculator'.

Uncertainty will be explored using bootstrapping to represent clouds of Incremental Cost-effectiveness Ratios (ICERs) on the cost-effectiveness plane, as well as cost-effectiveness acceptability curves. Subgroup analyses will be performed to acknowledge heterogeneity within each arm of the trial (e.g., age, severity, country). Value of perfect information analysis may also be performed to identify which sources of uncertainty should be reduced through additional research to efficiently improve decision making.

Discussion

The ALIC^{4}E Trial will be the first large-scale, international, non-industry sponsored, pragmatic, randomised trial of (cost-)effectiveness of adding oseltamivir to best usual primary care for people suffering from ILI.

ALIC^{4}E will be an open trial in order to approximate effects in conditions close to those of usual care in order to determine real-world estimates of (cost-) effectiveness. Open trials have been criticised because, should a treatment appear beneficial, it may not be clear if the effect resulted from biological mechanism or because of a placebo effect. When considering the

possible outcomes of ALIC^{4}E, if no benefit is found in the antiviral arm, despite the comparator usual care arm not being enhanced by the possible effects of a placebo, then prescribing the antiviral agent should not be recommended. On the other hand, if a benefit from an antiviral agent is identified in the pragmatic trial, given that the drug's efficacy will have already been demonstrated in many placebo-controlled trials and that the drug's mechanisms of action is known and is specific to the condition under study, then it would be obtuse to suggest that any benefit ALIC^{4}E may identify derives from the placebo effect, and not from the antiviral's effect on influenza.

The lack of cost-effectiveness analyses alongside clinical trials, and given that children, older people and people with co-morbidities are underrepresented in studies that have been done, has once again been highlighted after the WHO's decision to downgrade the status of oseltamivir[9,36]. Despite the lack of trial evidence, the 2017 WHO Model List of Essential Medicines states that the use of oseltamivir should be restricted to severe illness due to confirmed, or suspected influenza virus infection in critically ill hospitalised patients[10]. Another report quoting the WHO states: "unless new information supporting the use in seasonal and pandemic outbreaks is provided, the next Expert Committee might consider oseltamivir for deletion"[9]. The current UK and US guidelines recommend treatment of defined subgroups of frail patients and patients with increased risk for complications[6,37]. Because the evidence base for these recommendations is incomplete, withholding treatment from these or other patients may possibly deny them benefit. By including a 'best usual primary care' arm, our study will determine the added benefit of antiviral agents over and above current practice for seasonal and potentially pandemic influenza. This information will be of great importance to the delivery of primary care for ILI, as well as enhance the evidence base around advocating self-care. In many countries, patients with ILI symptoms are advised not to consult but to self-manage, and patients with additional risk factors are seldom routinely treated with an antiviral agent. This is largely because of an absence of evidence about the cost-effectiveness overall and in sub-groups of interest.

The virulence, spread and type of circulating influenza strains varies from season to season. ALIC^{4}E aims to recruit over three winter/influenza seasons in 15 countries, thereby obtaining widely applicable data allowing us to determine whether any benefit or otherwise of antiviral agents is influenced by season. Furthermore, the aim is to include a wide age-range of participants from many different settings, as well as those with co-morbidities. Additionally,

in the event of an influenza pandemic, or should additional intervention arms be included, a decision could be made to increase the maximum sample size.

The adaptive design offers several advantages over a traditional study design. Recruitment into a particular arm can be stopped once a pre-determined level of certainty about the effectiveness or non-effectiveness of treatment in that arm has reached a pre-defined estimated precision. Adaptive randomisation could increase the chances of participants being allocated to arms where their information will be most useful and to the intervention that is most effective for them. This can lead to better patient care and better patient outcomes as the trial progresses. Secondly, the platform design allows new intervention arms to be added to the trial, benefiting from comparisons with existing treatment arms in a head to head way. This flexibility extends to a potential pandemic situation where additional or alternative interventions may be added according to governmental or public health recommendations. In this way, the study will remain current and relevant to clinical practice and evolving circumstances throughout.

ALIC^{4}E will be novel in many ways. It will provide critical information about the clinical and cost-effectiveness of adding oseltamivir to best current ILI management in conditions that approximate usual care, both overall, as well as in important, pre-specified subgroups. ALIC^{4}E is likely therefore to enhance the evidence base supporting and important and common area of clinical practice.

Declarations

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CCB and TV are co-chief investigators of this trial and act as guarantors of the study in its entirety. CCB and TV led the development of the research question, study design and obtaining the funding along with AV, JC, PB, HG, MJ and PL. EB, JC and AV manage the trial and coordinate the operational delivery of the study protocol to the networks co-ordinating centres. BS and JH are the trial statisticians. PB provides health economics input. MI provides support with sampling and analysis. RMA, CBr, SCh, SC, AC, MD, MDP, ADS, NF, DG, MGC, ML, FMT, AM, JP, MP, RRJ, PDS, AT, PTL, DV are representatives of the collaborating co-ordinating centres responsible for their networks participation in the trial. EB and AV drafted the manuscript, supervised by CCB. All other authors provided critical review and final approval of the manuscript.

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Trial Status

Recruitment started in January 2016 and is expected to be completed by May 2018. The first two seasons assessed only oseltamivir as an antiviral. There are currently no other suitable antivirals available to evaluate within this trial. The current protocol is version 4.1 02-DEC-2017.

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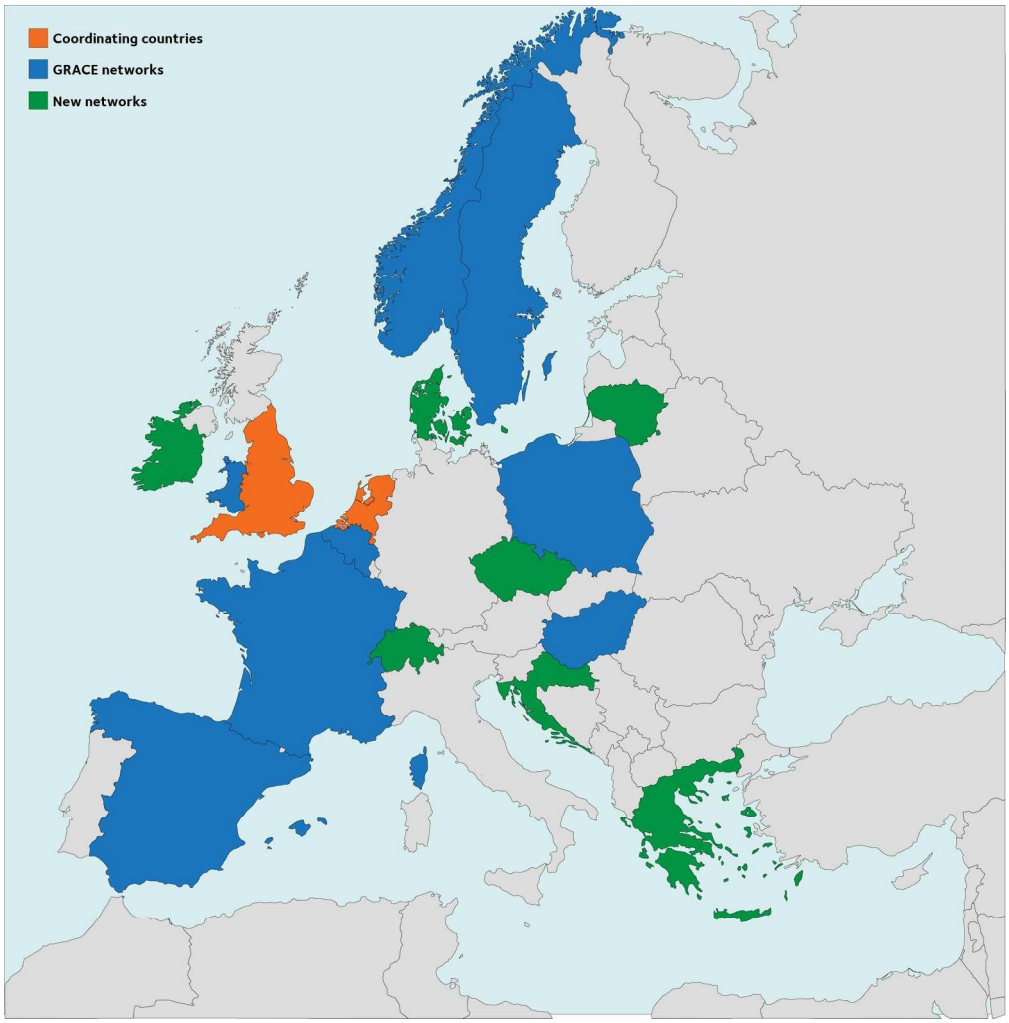
Figure 1. ALIC^{4}E European Networks. Coordinating centres are in Oxford, UK and Utrecht, The Netherlands. The ALIC^{4}E recruiting networks include: Belgium (Antwerp, Ghent); Czech Republic; Denmark; France; Greece; Hungary; Ireland; Lithuania; Netherlands, Norway; Poland (Bialystok, Lodz); Spain (Barcelona, Catalonia, Santiago de Compostela); Sweden; Switzerland; and the UK (Oxford, Southampton and Cardiff).

Endnotes

[i] Heart Disease/ Diabetes/Chronic respiratory condition (e.g. asthma, COPD)/Hepatic, hematologic, neurologic or neurodevelopmental condition/Stroke or Transient Ischemic Attack/Overnight hospital admission in the last year.

[ii] Rhinovirus, Coronavirus (NL63/229E/OC43/HKU1), Parainfluenza (1, 2, 3, 4), Human Metapneumovirus A/B, Bocavirus, Respiratory Syncytial Viruses A/B, Adenovirus, Enterovirus, Parechovirus.

[iii] *Mycoplasma pneumoniae, Chlamydia pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae type B, Staphylococcus aureus*.



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171x173mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	1, 3, 8, 18, 23, 30, 34, 38
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	3, 35
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	3, 7
	5b	Name and contact information for the trial sponsor	7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	33

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	10
	6b	Explanation for choice of comparators	11-14
Objectives	7	Specific objectives or hypotheses	16
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	13
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	19, 32, 38
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	18-24
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	23, 26
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	24
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	24
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	37, 39

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	30
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	30
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	20
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	20
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	20
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	20
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	20
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	20 - 23
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	23, 29

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	32-33
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	27-32
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	27-32
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	30
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	27, 33
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	28, 33
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	25-27
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	33
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	34
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	34

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	34
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	32
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	35
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	35
	31b	Authorship eligibility guidelines and any intended use of professional writers	35
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	separate
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	41

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.