PERSPECTIVE
TRIAL DESIGN

A trial like ALIC^{4}E: why design a platform, response-adaptive, open, randomised controlled trial of antivirals for influenza-like illness?

Christopher C. Butler[1], Samuel Coenen[2], Benjamin R. Saville[3,4], Johanna Cook[1], Alike van der Velden[5], Jane Homes[6], Menno de Jong[7], Paul Little[8], Herman Goossens[9], Philippe Beutels[10], Margareta Ieven[11], Nick Francis[12], Pieter Moons[9], Emily Bongard[1] and Theo Verheij[5]

Affiliations: [1]Primary Care and Vaccines Collaborative Clinical Trials Unit, Nuffield Dept of Primary Care Health Sciences, University of Oxford, Oxford, UK. [2]Dept of Epidemiology and Social Medicine (ESOC), University of Antwerpen, Antwerp, Belgium. [3]Berry Consultants, LLC, Austin, TX, USA. [4]Vanderbilt University School of Medicine, Nashville, TN, USA. [5]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (STR 6.103), Utrecht, The Netherlands. [6]Centre for Statistics in Medicine, University of Oxford, Oxford, UK. [7] Dept of Medical Microbiology at the Free University of Amsterdam Medical Centre, Amsterdam, The Netherlands. [8]University of Southampton, Southampton, UK. [9]Dept of Medical Microbiology, Antwerp University Hospital, Antwerp, Belgium. [10]Centre for Health Economics Research and Modelling Infectious Diseases (CHERMID), Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium. [11]Laboratory of Medical Microbiology, Vaccine and Infectious Diseases Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium. [12]Dept of Population Medicine, Cardiff University School of Medicine, Cardiff, UK.

Correspondence: Christopher C. Butler, Primary Care and Vaccines Collaborative Clinical Trials Unit, Nuffield Dept of Primary Care Health Sciences, University of Oxford, New Radcliffe House, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6NW, UK. E-mail: Christopher.butler@phc.ox.ac.uk

ABSTRACT ALIC^{4}E is the first publicly funded, multicountry, pragmatic study determining whether antivirals should be routinely prescribed for influenza-like illness in primary care. The trial aims to go beyond determining the average treatment effect in a population to determining effects in patients with combinations of participant characteristics (age, symptom duration, illness severity, and comorbidities). It is one of the first platform, response-adaptive, open trial designs implemented in primary care, and this article aims to provide an accessible description of key aspects of the study design. 1) The platform design allows the study to remain relevant to evolving circumstances, with the ability to add treatment arms. 2) 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 trial intervention that will be most effective for them. 3) Because the possibility of taking placebos influences participant expectations about their treatment, and determining effects of the interventions on patient help seeking and adherence behaviour in real-world care is critical to estimates of cost-effectiveness, ALIC^{4}E is an open-label trial.

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A platform, response-adaptive, open trial design allows for flexibility and may enhance efficiency in determining cost-effectiveness of interventions for acute infections http://ow.ly/NODY30jACb7

Cite this article as: Butler CC, Coenen S, Saville BR, *et al.* A trial like ALIC^{4}E: why design a platform, response-adaptive, open, randomised controlled trial of antivirals for influenza-like illness? *ERJ Open Res* 2018; 4: 00046-2018 [https://doi.org/10.1183/23120541.00046-2018].

Received: April 16 2018 | Accepted: April 16 2018

Introduction

ALIC^{4}E (Antivirals for influenza-Like Illness? An rCt of Clinical and Cost-effectiveness in primary CarE) is a publicly funded platform, response-adaptive, open, randomised controlled trial (RCT) of antiviral treatment for influenza-like illnesses (ILI) in primary care. There have been many industry-sponsored placebo-controlled RCTs of the efficacy of antivirals for ILI [1, 2], but no publically funded pragmatic trial that answers the question about whether treating people with these agents has a clinical and cost-effective meaningful advantage when added into routine primary care in terms of helping people return to their usual activities [3]. Clinicians are currently advised to prescribe oseltamivir under certain conditions, especially to those at higher risk of complications from ILI. The evidence that identifies those at higher risk is largely retrospective and of poor quality [4]. Furthermore, being at high risk of complications is not necessarily the same as having a good chance of benefiting from a particular treatment. Guidelines do not recommend treating otherwise healthy people, yet doing so may prevent spread and complications, or might help people in getting back to work/usual activities earlier. Thus, there is uncertainty about whether or not the drug should be prescribed at all. Is a reduction in time to first alleviation of symptoms of 17 h, for example, worthwhile for patients, given the associated costs and impact on primary care services? And if so, who might benefit most (children, older people, the sickest, only those treated early on in the illness, for example)? In so far as we know, ALIC^{4}E also is the first response-adaptive platform trial in primary care. Such trials are likely to become more common; recruiting into them and interpreting the results will require familiarity with key aspects of the design, and some aspects of the design may be controversial. So, what is a platform response-adaptive, open RCT and why did we choose to design ALIC^{4}E like that?

Problems with traditional RCT designs

Although a traditional two arm or multi-arm trial clearly has its merits, it also has features in common with a horse race where all horses start at the same time, the distance over which the race is run is fixed, the number of horses entered can't change once the starting gun has been fired, and the ranking is made only when the horses have crossed the finish line (figure 1). But what if there is no obvious clear winner or one horse pulls a hamstring after the first furlong? Might it not be more efficient to let a study intervention (that rapidly became clear was really a donkey) retire as soon as its true colours are known? Might it not be better to be able to let horses run a bit further if there is no clear blue water between them at the apparent finish line before we call one the winner? And do we really have to arrange an entirely new race when another horse is available to compete?

Thus, a traditional trial can be inefficient and inflexible in that its design requires recruitment to a pre-set number of participants based on assumptions from previous studies that have usually been done in different places. Bruised trialists who have been disappointed by unclear results that have emerged from a trial that may have taken many years to complete have been known to mutter; "if only we had known that we had needed a slightly bigger sample size and could have carried on recruiting?". Other trialists have complained, "did we really need to carry on recruiting when, had we analysed the data regularly during study, it would already have been obvious that one intervention was far better?", and "damn, but just after we started the trial a new drug became available that required evaluation, which has already now become widely used so our trial is suddenly much less relevant. If only we could have included wondermycin in

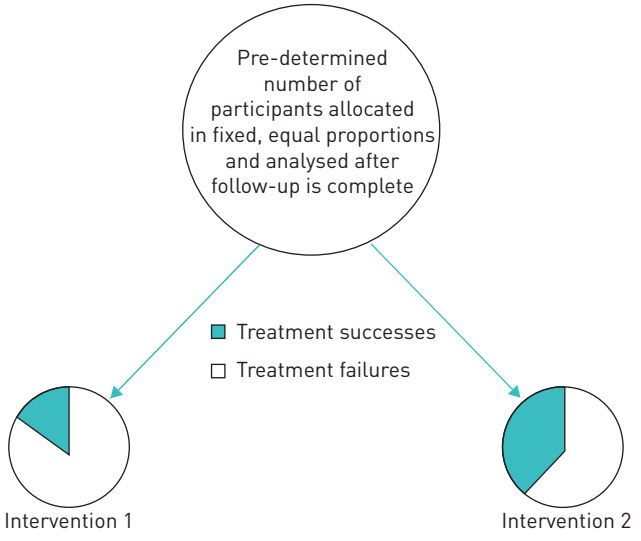

Figure 1 A conventional clinical trial typically enrols a homogenous set of patients as shown in the top circle. It then randomises patients equally between two groups (shown by circles "intervention 1" and "intervention 2") for the entire duration of the trial, and then measures outcomes (shown here as a proportion of responders to each treatment). The primary inference is then an average effect over the whole population.

our trial! Now we have to wait for our existing trial to finish and win funding for and set up a whole new trial with a whole new control group!".

Apart from being inefficient and inflexible, the traditional trial can also lack generalisability and applicability. Horses running in The Grand National may run differently back on the farm where they spend most of their lives, and indeed most horses back on the farm never get to run in The National. It is well known that effect sizes in placebo-controlled efficacy studies are seldom replicated in studies of real-world effectiveness.

What is a platform trial?

Traditional trials usually compare, say, treatment A with treatment B, and then another traditional trial compares treatment B with treatment C. So it is hard to know how A would fare head-to-head with C. A platform trial design allows for such comparisons in the same trial, head-to-head under a master protocol (figure 2). Arms can thus be added or dropped during platform trials, without having to set up a whole new trial [5]. This is done according to pre-specified criteria. Control participants, both current and those who have previously contributed data, can be used for assessing the effect of newly added interventions, and appropriate modelling can adjust for possible drifts or changes in the population over time. The sharing of a common control arm dramatically decreases the overall sample size needed to evaluate each of the interventions. Thus, this design is suited to conditions where multiple interventions are available or emerging, and where head-to-head comparisons of multiple interventions are useful [6].

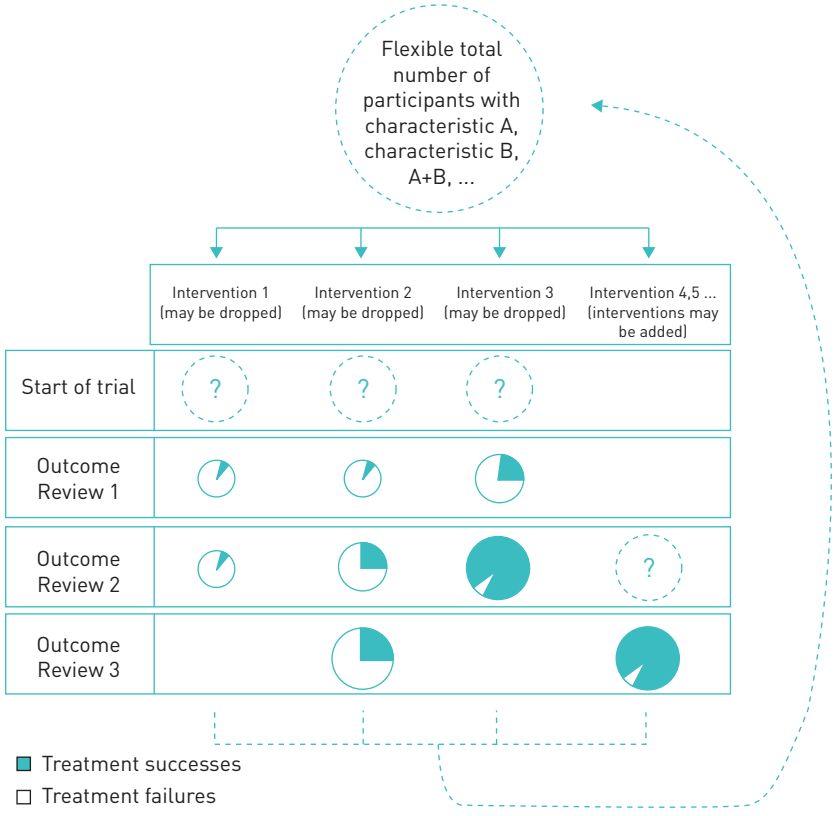

Figure 2 A response-adaptive platform trial may start by enrolling a broad patient population and randomise patients equally across a range of treatments, shown here as interventions 1, 2 and 3. Interim analyses produce estimates of which patients are responding better to which treatments. The figure shows an interim analysis as "outcome review 1". Intervention 3 has the highest proportion of treatment success; therefore, according to pre-specified rules, more patients are randomised to that therapy in the next stage and fewer to intervention 1. At outcome review 2 the efficacy of intervention 1 is still small and that treatment arm is terminated. Intervention 3 is so effective it may be changed to be the control. Intervention 4 represents a new treatment that the trial committee has decided to add to the platform trial. Outcome review 3 shows the results when just two treatments, intervention 2 and 4, remain with treatment 4 offering higher efficacy. Additional treatments may be considered at this review. Analyses are performed at *a priori* described intervals, randomisation rates are constantly updated and decision rules for arm termination tested. Interventions may be terminated within a particular patient characteristic group or overall according to predetermined rules. Finally, unlike conventional trials, additional interventions (shown here as 4 and 5) may be added during the course of the trial.

When designing ALIC^{4}E, we were informed that a new agent for ILI would soon become available for pragmatic evaluation, but only once our trial was due to begin. We were concerned about going to all the trouble of doing a trial that would inevitably take several years to complete, that might provide an answer only about our original drug, but by the time we reported our findings other drugs could have come to market that needed similar evaluation. In addition, trial context can change, so while oseltamivir, our initial drug, might be effective now it may not work so well or, alternatively, it could work especially well in subsequent seasons as the virus changes, resistance develops or different influenza sub-types predominate. Thus, in a way, ALIC^{4}E should ideally be a perpetual trial without end, and it is an enticing possibility to embed ALIC^{4}E style "platforms" into routine primary care so that all clinicians, when in equipoise about a management decision, can enter the patient into a trial fairly seamlessly.

What is response-adaptive randomisation?

Put simply, response-adaptive randomisation is a way of adapting the randomisation of participants to the study arms based on analyses of the observed data during the recruitment phase of the study. The purpose is to ensure maximal study efficiency and also to give study participants the maximum chance of benefiting from the best performing study intervention. This approach is best suited to evaluating effects of treatment for conditions that have a shorter natural history, such as acute infections, or when robust proximal outcomes are readily available. Thus, outcomes are analysed at several pre-specified time-points during the trial and as soon as a signal begins to emerge that a particular intervention might be performing better, then proportionally more people can be randomised to that intervention. This ensures that if thresholds for estimates of effectiveness, or otherwise, are reached before what would have happened in a traditional trial, results could inform the care of people outside the trial sooner, but this also ensures that trial participants become more likely to receive the most effective approach as the trial progresses. This cannot happen when the proportions randomised to each arm are fixed.

Patient characteristics that may be relevant to treatment outcomes can be pre-specified in advance, and the randomisation plans ensure that treatment effects can be properly assessed prospectively within subgroups defined by several characteristics. In the ALIC^{4}E trial, we were keen to know not only if oseltamivir was clinically and cost-effective for ILI in primary care, but also to identify if the drug might work better according to age, duration of symptoms before initiation of treatment, comorbidity and illness severity. Thus, we pre-specified these groups, and, based on extensive prospective simulations, calibrated the decision rules and adaptive randomisation so that ALIC^{4}E would be prospectively powered to provide an estimate of effectiveness for each subgroup, as well as determining average effects in the overall study population. In essence, we would not only ask of the study what the average effect of oseltamivir is in people presenting in primary care with ILI, but does it work perhaps better or less well in an individual who is say young, sicker, without comorbidity and who receives early treatment. Although such interactions are often underpowered in traditional studies, the efficient use of response-adaptive randomisation and statistical modelling can provide sufficient power to address these important questions. There are the normal caveats that to truly determine whether a subgroup behaves differently from others requires powering on interactions, but again that can be more flexible in an adaptive trial than the power implications of using a fixed design in assessing interactions.

Why an "open" (pragmatic) trial?

ALIC^{4}E deliberately does not have a placebo-control arm. Instead, the comparator arm is current best care according to the judgment of the responsible clinicians, but without the addition of an antiviral agent. This often invites criticism; some have suggested that trials which are not placebo controlled may give an answer that favours a drug, while in actual fact, the drug's advantage could simply be a placebo effect from expectations about feeling better that arise from the act of being prescribed and taking a pill. However, there have been many placebo-controlled efficacy trials of oseltamivir which have been systematically reviewed many times; every time the conclusion is that oseltamivir reduces symptom burden in those with ILI for around a day plus or minus a few hours, and that this reduction in symptom burden is greater in those who have true flu (rather than another virus). So, the efficacy question, *i.e.* whether oseltamivir works better than placebo in reducing symptom burden (or whether the intervention is causally related to the outcome), is not novel. Moreover, knowledge from such so-called explanatory trials is relevant for drug developers and health insurers rather than for patients or clinicians who needs knowledge from pragmatic trials. In addition, the uncertainty in the minds of patients in a placebo-blinded study may bias the perceptions of symptoms and of symptomatic benefit. Furthermore, the variation in patient behaviour and concordance with taking medicines is much more tightly controlled in efficacy studies and unlikely to reflect what actually happens in daily practice. Clinicians also don't prescribe placebos in routine care, and placebos may influence patients' adherence and healthcare seeking. The uncertainty associated with knowing that there is a 50% chance that the drug you are taking is something that can never work, may

lead to increased subsequent consulting or alternatively, for some individuals, a placebo effect in lowering re-consulting. What is clear is that it cannot be assumed that patient or clinician perceptions and behaviour will correspond to the real-world situation, and measuring perceived self-reported health (quality of life) and measuring subsequent healthcare utilisation is critical in estimating clinical and cost-effectiveness. Thus, provided that equipoise is properly explained to trial participants, an open (non-placebo-controlled) trial will provide important and potentially more realistic estimates of overall clinical and cost-effectiveness in routine care, and will take future healthcare utilisation into account [7]. Consider the possible main result of ALIC^{4}E: we might find no advantage in the antiviral agent arm when compared to usual care. This would lead to the clear conclusion that prescribing the antiviral agent should not be recommended. However, we might identify a benefit for some or all participants. Given that the drug's efficacy is not in question, that the drug's mechanisms of action are known from explanatory trials and are specific to the condition under study, then it would be obtuse to suggest that the benefits ALIC^{4}E may identify derive entirely from the placebo effect of oseltamivir and not from its effect on influenza. In a pragmatic trial, however, a part of this benefit may indeed derive from the placebo effect of taking an influenza-specific medicine, but that is what would have happened if it were to be used in usual practice and so the effect on help seeking can then be properly estimated.

Thus, under both scenarios we answer the question that is of interest to clinicians and patients. Instead of whether oseltamivir is better than placebo (already a "done deal"!), we address whether or not patients experience meaningful benefit in practice, whether clinicians should prescribe the drug in routine care and, if so, which particular set of patients are most likely to receive benefit in terms of feeling better earlier and/or cost-effectiveness.

Conclusion

Although there have been no additional arms added to the ALIC^{4}E trial since commencement, we needed the prospective flexibility to add arms should a new agent have become available for evaluation after ALIC^{4}E had started. The Data Monitoring and Trial Steering Committee evaluated data from each of the first two study influenza seasons according to the pre-specified analysis plan. Should things change, like a new pandemic emerging this winter, we would be able to randomise patients to treatment with oseltamivir, best usual practice alone or a new intervention seamlessly within the existing master protocol. This approach, therefore, is well suited to trials performed: where the context is dynamic in ways that are relevant to possible treatment effects; where patient characteristics and characteristic combinations might be particularly important in deciding which subgroups to treat; when new interventions might become available during the trial; and where one needs answers rapidly to guide care, such as during a pandemic in which the trial is being conducted. The benefit to study participants includes the increasing chance of being allocated to the intervention that would be best for them.

Key points

1) There have been many placebo-controlled, efficacy trials of oseltamivir for influenza-like illness, and systematic reviews of these trials have generated precise estimates for reductions in time to first alleviation of symptoms. These trials have almost always been funded by the pharmaceutical industry for regulatory and licensing purposes. Further placebo-controlled studies that determine the efficacy of oseltamivir in terms of number of hours with fewer symptoms would be repetitive and probably uninformative for guiding routine care. A critical outstanding question is not whether oseltamivir alleviates symptoms, but whether prescribing the drug in routine primary care is worth it in terms of helping people return to their usual activities and, if so, which patient characteristics are associated with greatest benefit?
2) ALIC^{4}E will be the first publically funded, multi-country, open trial determining whether antivirals should be routinely prescribed for influenza-like illness in primary care by assessing their clinical and cost-effectiveness.
3) 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 (*e.g.* age, symptom duration, illness severity and comorbidities).
4) The platform design allows the study to remain relevant to evolving circumstances, with the ability to add and drop treatments arms.
5) 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, increasing their chances of receiving the intervention that will be most effective for them.
6) Because the possibility of taking a placebo also 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.

Conflict of interest: M. de Jong reports advisory board, travel and fees from Janssen, MedImmune and Shionogi. He also reports Independent Data and Safety Monitoring Board (IDSMB) and fees from Janssen, and IDSMB, travel and fees from GSK and Vertex, outside the submitted work. P. Beutels reports grants from European Commission project "PREPARE" during the conduct of the study, and an unrestricted gift for part-time research from Pfizer and GSK, outside the submitted work.

Support statement: The ALIC^{4}E trial is being delivered as work package 4 of the Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) consortium grant. Funding has been received from the European Commission FP7 (grant number 602525). Funding information for this article has been deposited with the Crossref Funder Registry.

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