PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Antivirals for influenza-Like Illness? A randomized Controlled trial of Clinical and Cost effectiveness in primary CarE (ALIC4E): The ALIC4E Protocol
AUTHORS	Bongard, Emily; van der Velden, AW; Cook, Johanna; Saville, Ben; Beutels, Philippe; Munck Aabenhus, Rune; Brugman, Curt; Chlabicz, Slawomir; Coenen, Samuel; Colliers, Annelies; Davies, Melanie; De Paor, Muireann; De Sutter, An; Francis, Nick A.; Glinz, Dominik; Godycki-Cwirko, Maciek; Goossens, Herman; Holmes, Jane; Ieven, Margareta; de Jong, Menno; Lindbaek, Morten; Little, Paul; Martinon Torres, Frederico; Moragas, Ana; Pauer, József; Pfeiferová, Markéta; Radzeviciene-Jurgute, Ruta; Sundvall, Pär-Daniel; Torres, Antoni; Touboul, Pia; Varthalis, Dionyssios; Verheij, Theo; Butler, C

VERSION 1 – REVIEW

REVIEWER	Dr. Tengbin Xiong IQVIA™, 12/F, Garden Square, No.968 West Beijing Road Shanghai, 200041, China
REVIEW RETURNED	07-Jan-2018

GENERAL COMMENTS	This is a well written protocol for a multi-center, phase IV, and open-labelled RCT, which was designed to investigate whether adding antiviral treatment to best usual primary care for ILI is effective in reducing time taken to return to usual daily activity, and to explore whether antiviral treatment is cost-effective. The background and general information is comprehensive, the objectives are clear, and the trial design is sound. I only have the following questions and it would be better if they can be further clarified. 1. Page 12 line 48: Intervention: please justify the route of administration, dosage, and treatment periods. 2. It would be better to have a literature review for published CEA studies of oseltamivir (non-trial based). 3. The open label design has well been justified, but are there any potential bias or limitations? 4. Are there any discontinuation criteria for participants in best usual primary care plus oseltamivir arm? 5. How to monitor subject compliance? 6. How the safety has been assessed? 7. More details could be added for the Statistical Analysis section? Currently the protocol only identifies the populations for primary and secondary analyses. 'Frequent interim analyses' could also be better defined. Details may include the types of variables, statistical measures, and outputs that will be generated for this study.

REVIEWER	Alexander Doroshenko MD MPH FFPH FRCPC

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	Assistant Professor, Division of Preventive Medicine, Faculty of Medicine and Dentistry, University of Alberta; Adjunct Professor, School of Public Health, University of Alberta; Medical Officer of Health, Edmonton Zone, Alberta Health Services, Canada
REVIEW RETURNED	22-Jan-2018

GENERAL COMMENTS	In this study authors propose to address an important question about whether adding Oseltamivir to routine management of influenza-like illness during influenza season confer clinical benefits to patients and public health benefits to society. This is a well-written and comprehensive protocol. Pragmatic trial methodology offers "real-life" evaluation of the effect of antivirals in the primary care settings and adaptive platform trial design offers flexibility. Including cost-effectiveness is important consideration. Authors should clarify the following points: 1. How was abbreviation of the trial (ALIC4E) derived? 2. Background section should include explanation that oseltamivir may be used for the management of ILI on assumption that many cases of ILI may be caused by influenza and that probability of this is higher during influenza season (which is presumably based on determination by public health authorities which include laboratory confirmation for some cases). Or is there any other rationale? 3. Page 7, Line 15: Reference 1 is meant to support the statement that "Annual influenza epidemics account for considerable morbidity and mortality…", however it only refers to burden of pediatric influenza. 4. Page 11, lines 11-21: Authors should reference the agency/authority they base their definition of ILI on. For example, in children under 5, gastrointestinal symptoms may also be present. In patients under 5 or 65 and older, fever may not be prominent. 5. Page 11, exclusion criteria: Three exclusion criteria are rather subjective and based on clinical judgement of responsible clinicians. Their judgement can differ by country, level of training, intensity of influenza season. How can author ensure that individuals for whom intervention may work are not systematically excluded? 6. Authors propose to collect data on influenza vaccination among participants. Will it be adjusted to how well vaccine strains are matched to a given season predominant strains? 7. Would authors propose to collect data on whether individuals presenting with ILI could be part of an outbreak (e.g. family members, living in congregate settings). Could this be a sub-group of participants identified one of the secondary outcomes? 8. Page 16, line 33: Authors state that after flu season collected laboratory specimens will be transported to lab in the University of Antwerp. What is the rationale for this to be done after flu season, rather than in real time? 9. How would author propose to handle/adjust differences in costs between countries? 10. Can intensity (determined by the magnitude by which incidence exceeds thresholds determined by public health agencies) and severity (may be determined by strain associated with greater morbidity) of the influenza season impact how effective tested intervention (oseltamivir in addition to routine care) can be?

VERSION 1 – AUTHOR RESPONSE

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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

Authors Response to Reviewers:

Reviewer 1:

No.	Reviewers Comment	Authors Response	Change to paper
1	Page 12 line 48: Intervention: please justify the route of administration, dosage, and treatment periods	Ok - Updated in intervention section	Added: *Route of administration, dosage and treatment periods follow the manufacturers Summary of Product Characteristics (SPC).*
2	It would be better to have a literature review for published CEA studies of oseltamivir (non-trial based).	We searched for randomised open studies but did not find any. Placebo controlled studies have been described in the background section.	None
3	The open label design has well been justified, but are there any potential bias or limitations?	Further comments added to the discussion	Added: *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 ALIC4E, 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 ALIC4E may identify derives from the placebo effect, and not from the antiviral's effect on*

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			influenza.
4	Are there any discontinuation criteria for participants in best usual primary care plus oseltamivir arm?	Added a new section: *Safety and discontinuation or withdrawal of participants from trial treatment*	Added: *Oseltamivir has a well-documented safety profile and is a commonly used medication in a primary care setting. As a result of this 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.*
5	How to monitor subject compliance?	Updated Intervention section	Added: *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.*

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6	How the safety has been assessed?	SAEs are being reported and monitored. Self-reported safety incidents and side effects reported through diary and telephone questionnaires	Described in 'Diary (Day 1 – 14) and Follow-up' and further clarification in 'Safety and discontinuation or withdrawal of participants from trial treatment'.
7	More details could be added for the Statistical Analysis section? Currently the protocol only identifies the populations for primary and secondary analyses. 'Frequent interim analyses' could also be better defined. Details may include the types of variables, statistical measures, and outputs that will be generated for this study.	Statistical section updated to include better definition of 'frequent interim analyses'. A separate statistical analysis manuscript is being prepared for peer reviewed publication which describes further the statistical aspects of the trial.	Added: *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.*

Reviewer 2:

No.	Reviewers Comment	Authors Response	Change to paper
1	How was abbreviation of the trial (ALIC4E) derived?	Paper title updated to reflect this	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
2	Background section should include explanation that oseltamivir may be used for the management of ILI on assumption that many cases of ILI may be caused by influenza and that probability of this is higher during influenza season (which is	Rational is correct, background updated	Added: *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*

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	presumably based on determination by public health authorities which include laboratory confirmation for some cases). Or is there any other rationale?		*confirmed influenza cases.*
3	Page 7, Line 15: Reference 1 is meant to support the statement that "Annual influenza epidemics account for considerable morbidity and mortality…", however it only refers to burden of pediatric influenza.	Additional references have been included	Refs: 1. Antonova EN, Rycroft CE, Ambrose CS, et al. Burden of paediatric influenza in Western Europe: a systematic review. *BMC Public Health* 2012;12(1 %@ 1471-2458):968. doi: 10.1186/1471-2458-12-968 %U https://doi.org/10.1186/1471-2458-12-968 2. World Health Organisation. Factsheet [Available from: http://www.who.int/mediacentre/factsheets/fs211/en/. (accessed 10 Aug 2017). 3. Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. *MMWR Morb Mortal Wkly Rep* 2010;59(33):1057-62. [published Online First: 2010/08/28] 4. Schanzer DL, Langley JM, Tam TW. Co-morbidities associated with influenza-attributed mortality, 1994-2000, Canada. *Vaccine* 2008;26(36):4697-703. doi: 10.1016/j.vaccine.2008.06.087 [published Online First: 2008/07/16]
4	Page 11, lines 11-21: Authors should reference the agency/authority they base their definition of ILI	Background for ILI definition included	Added: *The definition of ILI used in ALIC4E was based on the European Centre for Disease Prevention and Control*

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	on. For example, in children under 5, gastrointestinal symptoms may also be present. In patients under 5 or 65 and older, fever may not be prominent.		*(ECDC) definition with flexibility to maximise recruitment of children and the elderly.* Refs: 23. Official Journal of European Union. Commission implementing decision of 8 August 2012 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council (notified under document C(2012) 5538). , 2012:16. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32012D0506&qid=1428573336660&from=EN#page=16 (accessed 08 Feb 2018). 24. Casalegno JS, Eibach D, Valette M, et al. Performance of influenza case definitions for influenza community surveillance: based on the French influenza surveillance network GROG, 2009-2014. Euro Surveill2017. 25. Aguilera JF, Paget WJ, Mosnier A, et al. Heterogeneous case definitions used for the surveillance of influenza in Europe. *Eur J Epidemiol* 2003;18(8):751-4. [published Online First: 2003/09/17]
5	Page 11, exclusion criteria: Three exclusion	We agree that some subjectivity is inevitable but we can't expect	None

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	criteria are rather subjective and based on clinical judgement of responsible clinicians. Their judgement can differ by country, level of training, intensity of influenza season. How can author ensure that individuals for whom intervention may work are not systematically excluded?	to require clinicians to randomise patients whom they feel should not be randomised. We will make these exclusions clear in the report to aid judgement of applicability of findings.	
6	Authors propose to collect data on influenza vaccination among participants. Will it be adjusted to how well vaccine strains are matched to a given season predominant strains?	This is not a study of ILI incidence but of the effectiveness of antiviral agents for ILI and we will do an analysis of those who are found to have virological evidence of influenza	None
7	Would authors propose to collect data on whether individuals presenting with ILI could be part of an outbreak (e.g. family members, living in congregate settings). Could this be a sub-group of participants identified one of the secondary outcomes?	We will not be able to link those randomised to other participants who were randomised by living proximity	None
8	Page 16, line 33: Authors state that after flu season collected laboratory specimens will be transported to lab in the University of Antwerp. What is the rationale for this to be done after flu season, rather than in real time?	The swab results will not influence care but simply allow us to do a subgroup analysis of the effect of antivirals in those found to have virological evidence of influenza	None
9	How would author propose to handle/adjust differences in costs	These will be reported separately	None

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	between countries?		
10	Can intensity (determined by the magnitude by which incidence exceeds thresholds determined by public health agencies) and severity (may be determined by strain associated with greater morbidity) of the influenza season impact how effective tested intervention (oseltamivir in addition to routine care) can be?	One of the strengths of this study, unlike many influenza studies is that our study will cover three influenza seasons so we will be able to determine whether benefit or otherwise of oseltamivir is influenced by season. This has been updated in the discussion.	Added: The virulence, spread and type of circulating influenza strains varies from season to season. ALIC4E 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*.

VERSION 2 – REVIEW

REVIEWER	Tengbin Xiong IQVIA, China
REVIEW RETURNED	02-Mar-2018

GENERAL COMMENTS	The comments have been well addressed and the revised version can be recommended for publication.

REVIEWER	Alexander Doroshenko University of Alberta, Canada
REVIEW RETURNED	21-Mar-2018

GENERAL COMMENTS	The proposed study is of great clinical and public health importance. Authors have adequately addressed most of my comments. I have one further comment/clarification pertaining to my original comment 6 regarding the collection of vaccination data (for this protocol it is optional to address). I appreciate that the proposed trial is the study of the effectiveness of antiviral agents for ILI, however authors state that they would record whether participants received influenza vaccination within last six months. What is the rationale for collecting influenza vaccination data? Is there a plan to do sub-group analysis based on vaccination status (i.e. whether effect of antivirals differ among those vaccinated versus not)? If there is rationale to collect vaccination data, then knowing whether influenza vaccine had a good match to a given season's circulating strains and how effective vaccine was for a given season would also be helpful. This latter information will be availa

VERSION 2 – AUTHOR RESPONSE

I am pleased to submit a revised protocol paper entitled ‘Antivirals for influenza-like illness? Protocol for a randomized controlled trial of clinical and cost effectiveness in primary care (ALIC4E)’ for

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publication in the BMJ Open. This study forms a primary care work package (WP4) in the Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE: www.prepare-europe.org) consortium. PREPARE is a European Commission funded network for the rapid and efficient delivery of harmonised, large-scale clinical research studies on infectious diseases.

ALIC4E is a randomised controlled trial of investigational medicinal products (CTIMP) in primary care that will determine the clinical- and cost-effectiveness of adding antiviral agents (currently oseltamivir) to best usual primary care for patients with specific characteristics suffering from influenza like illness (ILI), and thus enable clinicians to better individualise prescribing decisions.

We feel that the publication of this trial protocol in the BMJ Open is pertinent due to the WHO decision to downgrade oseltamivir in the 2017 list of essential medicines from a “core” drug to one that is “complimentary” (a category of drugs considered less cost-effective) and the associated comments and questions surrounding the stockpiling and use of oseltamivir based on available evidence. The ALIC4E 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 trial has a novel adaptive-platform design and been implemented in 15 European countries with 21 active networks and we are currently in the participant follow up stage of the third recruiting season.

We have made revisions to the re-submitted manuscript based on comments from the editors. We have not changed the protocol with regard to the second reviewer’s additional comments as these were optional but instead have included a response in the ‘response to reviewers’ section.

On behalf of the ALIC4E trial team and networks we thank you for your consideration!

VERSION 3 – REVIEW

REVIEWER	Alexander Doroshenko University of Alberta, Canada
REVIEW RETURNED	23-May-2018

GENERAL COMMENTS	Authors adequately addressed my comments. Specifically with respect to my comment about the reasons for collecting influenza vaccination data, authors suggested approach to explore the interaction between vaccination status and treatment effect once they collected data is reasonable.

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