PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a randomised controlled trial of Allen Carr's Easyway programme versus Lambeth and Southwark NHS service for smoking cessation.
AUTHORS	Wood, Kerry; Albery, Ian; Moss, Anthony; White, Sarah; Frings, Daniel

VERSION 1 – REVIEW

REVIEWER	Arie Dijkstra University of Groningen, the Netherlands
REVIEW RETURNED	07-Apr-2017

GENERAL COMMENTS	This is a great study, but I see no data reported. I read on state-of-the-art methodology to test the effects of two cessation courses, but I see no new knowledge.

REVIEWER	Ron Borland Cancer Council Victoria, Australia
REVIEW RETURNED	12-Apr-2017

GENERAL COMMENTS	First, the authors are to be congratulated for conducting an RCT of the Allen Carr method. Conducting trials where choosing to participate may be an important component of success is a challenge, and the approach taken is clever. However, there are several aspects of the design that are problematic, which should be addressed. It appears that the trial has commenced, but some changes, such as the extended follow-ups could be made. In particular, if the top-up reset component is included, then all what have started a quit attempt within the period where this is allowed, not just those who formally do so through the program should be followed up to ascertain 6 months outcomes (see below). Doing so would improve the study design considerably and may facilitate publication in top flight journals. There is also a lot of material in the paper that (to my mind) is not relevant to a protocol paper (but obviously is important to the actual implementation), and some key information that is missing. Methodological issues. Having the final follow-up at 24 rather than 26 weeks (ie 6 months) is a curious choice. The standard is at least 6 months and this falls just short. I realise this is unlikely to make a difference, but it may matter to some journals and to those doing meta-analyses.

	The primary outcome is prolonged abstinence. The allowance for "top-ups and resets" creates complexity in this respect. There are two main issues here. First it requires different follow-up intervals as a function of whether they have a reset, which is unusual, but potentially a useful approach, if some problems with it can be overcome. However, combining it with the use of the Russell Standard is not appropriate, as it effectively precludes self-generated recovery from slips as a means to success, while allowing full relapsers and any others who seek the top-up to have another go. The current protocol also fails to control for recovery from relapses that are either self-generated or which use some other intervention (than the focal ones). This could be solved by following-up all who are quit at the 6 months follow-up for 3 months (assuming all in the NHS condition would be past any organisationally provided top-ups), but less than 6, ie, do not meet the outcome criterion. These should all be followed-up for however long you need to establish the same outcome definition; ie 24 /26 weeks abstinence. This would requiring knowledge of all slips under the current proposal, which is far too cumbersome. I recommend the outcome be 3 months of abstinence without slips and no period of smoking daily for 7 or more days in the first 3 months. If such happens it would trigger a reset and the prolonged abstinence period would begin again from the start of this period. Resets beyond the 3 months (or whatever criterion is agreed to, would be treated as failures. More information is required as to what potential participants are told before randomization. If they are given details of both interventions (eg, completely unblinding them), then it might be useful to assess any pre-existing preferences for type of course. This will be useful if there is differential drop-out. If they are not given much information, this needs to be mentioned, and is likely to have the effect of more not completing the allocated program (but still needing to be include in the intention to treat analysis), and potentially differential drop-out. Finally, have the authors considered a fall-back of having sufficient power to claim non-inferiority at some point? Testing an untested (in RCTs) intervention against something close to the gold-standard of treatment is a high bar to overcome. I agree that the Dijkstra study suggests superiority, so agree with the basic framing, but think it wise to consider equivalence. Comments on specific subsections Abstract. Should make it clear whether participants have any notion of the alternative intervention Strengths and Limitations: I doubt this could be called a blinded trial (except for the researchers, which is pretty standard) Interventions. Please make it explicit that the facilitators will be people already delivering these programs (eg, ACE by an experienced ACE facilitator). For the NHS. Is varenicline a treatment option or just NRT? See above for comments re top-up Recruitment: See above comment on what told NB Typo on line 5 The material on randomisation and blinding is pretty standard stuff, so probably does not require this detail. Of more relevance is what the participant know of the alternative intervention. Withdrawal: similarly standard procedures. Inclusion in all analyses is standard and essential practice.

	Data collection. Much of this is pretty standard stuff and not necessary Data verification: Not clear what “source documentation” refers to. If it just refers to checking the data, then not needed here, this would be assumed. Statistical analysis.Again should be shortened. See also initial comments. It would be easier to read if all the sensitivity analyses around the primary outcome were listed, then the secondary cessation outcomes, then, as done, the non-cessation outcome, or process measures listed. Plan of presentation: Simply say a consort diagram will be used to describe the sampling, drop-outs and randomisation. Indeed a Consort diagram with planned sample size and spaces for all the numbers that will eventually be determined would be useful. Dissemination: Not really informative, could drop Funding: It must be made clear what rights ACE has over publication. Can they veto, do they get advanced notice, do they have an opportunity to comment? Contributors: Normally a footnote re authorship. Competing interests: Please make it clear any relationships with either NHS SSS or ACE. Roles and responsibilities: Not needed Table 1. Not needed It is not clear to me how the material from the renumbering on relates to the protocol paper. From p10 of this it looks like an alternative version of the protocol. I have not evaluated this. Clarity is required as to what is to be published and what is supplementary material.

REVIEWER	Agurtzane Mujika Faculty of Nursing. University of Navarra. Spain
REVIEW RETURNED	04-May-2017

GENERAL COMMENTS	The manuscript presents a study protocol on an interesting and novel RCT. Thank you for the opportunity to review it. There are only a number of minor observations I would like to make: 1. The last paragraph in the introduction seems redundant as it deals with information that is presented in detail in the methods section. Probably the last 2-3 sentences in the paragraph would be enough. 2. Please revise footnote on p.4 is correct. 3. In the description of the NHS cessation interventions the setting of the quit date (p.5) raises questions in terms of the implications it may have for follow up period. The information in the protocol (supplementary file) makes this very clear, specifying it should be within 2 weeks so this information should be added in the main text. In fact the process diagram is very helpful, I would consider using it as a figure within the paper.

	4. Recruitment & Randomisation, allocation concealment and sequence generation P.7, Do participants receive written information on the study (other than the leaflet) before they undergo screening? And is there any inclusion criteria for participants in terms of time from screening to sending the consent? The first couple of sentences in the paragraph 3 might be moved to paragraph 2. 5. Statistical analyses p. 9, paragraph 1, list the covariates. In the protocol it is acknowledged that participants will be paid. How was considered including (or not) this information in the manuscript?

VERSION 1 – AUTHOR RESPONSE

Response to reviewer 1

Comment: This is a great study, but I see no data reported. I read on state-of-the-art methodology to test the effects of two cessation courses, but I see no new knowledge.

Response: This is the protocol for our study, data is currently being collected. Therefore, no data available to share at present.

Response to reviewer 2

Comment: Methodological issues. Having the final follow-up at 24 rather than 26 weeks (i.e. 6 months) is a curious choice. The standard is at least 6 months and this falls just short. I realise this is unlikely to make a difference, but it may matter to some journals and to those doing meta-analyses.

Response: We have not yet carried out any 24 week follow-ups, therefore we have changed the follow-up to 26 weeks. The protocol paper has been amended accordingly.

Comment: The primary outcome is prolonged abstinence. The allowance for “top-ups and resets” creates complexity in this respect. There are two main issues here. First it requires different follow-up intervals as a function of whether they have a reset, which is unusual, but potentially a useful approach, if some problems with it can be overcome. However, combining it with the use of the Russell Standard is not appropriate, as it effectively precludes self-generated recovery from slips as a means to success, while allowing full relapsers and any others who seek the top-up to have another go. The current protocol also fails to control for recovery from relapses that are either self-generated or which use some other intervention (than the focal ones). This could be solved by following-up all who are quit at the 6 months follow-up for 3 months (assuming all in the NHS condition would be past any organisationally provided top-ups), but less than 6, ie, do not meet the outcome criterion. These should all be followed-up for however long you need to establish the same outcome definition; ie 24 /26 weeks abstinence. This would require knowledge of all slips under the current proposal, which is far too cumbersome. I recommend the outcome be 3 months of abstinence without slips and no period of smoking daily for 7 or more days in the first 3 months. If such happens it would trigger a reset and the prolonged abstinence period would begin again from the start of this period. Resets beyond the 3 months (or whatever criterion is agreed to, would be treated as failures.

Response: This is indeed a tricky issue which we sought advice from our advisory panel. The basic principle we followed was that we would follow ITT, and that participants should be smoke-free for 6 months from the point the treatment is administered. In the ACE method, the top-ups are part of treatment as usual, so it is reasonable that the smoke-free period starts from the date of the top-up – the top-up is essentially part of the normal 'dosage' of the method. To establish equivalence we also account for the fact some NHS patients are also given a reset, as part of their treatment as usual. In sum, all participants will have to be smoke-free for six months, in line with RS6, from the point that they receive the treatment. People who do not slip more than the defined number of times, do not attend top-ups, and still maintain from the end of treatment to the final outcome point can of course self-recover. Where participants engage in a subsequent data collection point (i.e. 4 weeks) before top-up, this data will be held, but a new set of data collected and used in subsequent analysis.

We are recording, and may undertake secondary analysis on those who use top-up sessions, as well as looking at the effects of use of non-treatment arm stop smoking aids.

Comment: More information is required as to what potential participants are told before randomization. If they are given details of both interventions (eg., completely unblinding them), then it might be useful to assess any pre-existing preferences for type of course. This will be useful if there is differential drop-out. If they are not given much information, this needs to be mentioned, and is likely to have the effect of more not completing the allocated program (but still needing to be include in the intention to treat analysis), and potentially differential drop-out.

Response: Sections added throughout paper to reflect this. Specifically:

• Abstract 'Before being randomised the research team will not inform participants which two treatments are being compared. Once randomised researchers will be blind to participant condition, and participants blind to the condition they are not assigned to'.

• Recruitment 'At this point they will not be informed which two interventions are being compared in the study'.

• Blinding 'Participants will be blind to both interventions until randomised and once allocated will continue to be blind to the alternative intervention'.

Comment: Finally, have the authors considered a fall-back of having sufficient power to claim non-inferiority at some point? Testing an untested (in RCTs) intervention against something close to the gold-standard of treatment is a high bar to overcome. I agree that the Dijkstra study suggests superiority, so agree with the basic framing, but think it wise to consider equivalence.

Response: A non-inferiority hypothesis has also been considered. If there is truly no difference between the treatment groups, assuming success rates of 50%, then 382 patients are required to be 90% sure that the upper limit of a 90% two-sided confidence interval will exclude a difference in favour of the NHS 1-1 counselling service group of more than 15%. Adjusting for a loss to follow-up rate of 25% gives a target sample size of 510.

Comment: Abstract. Should make it clear whether participants have any notion of the alternative intervention

Response: Added 'Before being randomised the research team will not inform participants which two treatments are being compared. Once randomised, researchers will be blind to participant condition, and participants blind to the condition they are not assigned to'.

Comment: Strengths and Limitations: I doubt this could be called a blinded trial (except for the researchers, which is pretty standard) Interventions. Please make it explicit that the facilitators will be people already delivering these programs (eg., ACE by an experienced ACE facilitator).

Response: Under Limitations added 'Although researchers are blinded, therapists delivering the interventions are not blinded i.e. each intervention is delivered by experienced facilitators for NHS and ACE separately'.

Comment: For the NHS. Is varenicline a treatment option or just NRT?

Response: Varenicline is a treatment option. However, participants requesting Varenicline must visit their GP to obtain a prescription. This has been added to the description of the NHS intervention: 'This treatment is combined with prescribed NRT of the patients' choice (including Varenicline)'.

Comment: Recruitment: See above comment on what told. NB Typo on line 5

Response:
• Typo on Line 5 corrected.
• Sentence added '…they will not be informed which two interventions are being compared in the study'.

Comment: The material on randomisation and blinding is pretty standard stuff, so probably does not require this detail. Of more relevance is what the participants know of the alternative intervention.

Response: Standard information re: randomisation deleted. This section now reads:
Randomisation, allocation concealment and sequence generation
Participants will be randomised to condition by Sarah White (study statistician) using the Kang and Park (11) 'Covariate Adaptive Randomization Program' (Version 1.0) software package. Four stratification factors, each at two levels, will be used: nicotine dependence (determined by the Fagerstrom Test for Nicotine Dependence [FTND] questionnaire (12)), number of prior quit attempts, age and gender. Participants will be assigned to the ACE and NHS 1-1 intervention groups in a ratio of 1.1 (310 in each).

Comment: Blinding
Participants will be blind to both interventions until randomised and once allocated will be blind to the alternative intervention. Members of the trial steering committee, management committee, and other team members (with the exception of the statistician/randomiser), will remain blind to treatment allocation until the last follow-up is completed and the data recorded, and the clinical team is not authorised to reveal it.
Comment: Withdrawal: similarly standard procedures. Inclusion in all analyses is standard and essential practice.

Response: This section has been deleted.

Comment: Data collection. Much of this is pretty standard stuff and not necessary

Response: Standard information here has been deleted. This section now reads:

Data collection, management and analysis
All data will be collected via paper questionnaires, apart from carbon monoxide readings where a Smokerlyzer piCO analyser will be used.

Participant data will only be linked directly with their participant ID code. Personal data (e.g. identifiable data) will be accessible to the research team (as part of the screening process), the statistician and the direct care team. Hard copies of data will be destroyed via confidential waste disposal five years after the research findings have been published. Electronic copies of data will be stored in two archives. In both cases, only anonymous data will be archived. They will be archived at London South Bank Data Archive and a national data repository such as the UK Data Archive.

Comment: Data verification: Not clear what “source documentation” refers to. If it just refers to checking the data, then not needed here, this would be assumed.

Response: This section has been deleted.

Comment: Statistical analysis. Again should be shortened. See also initial comments.
It would be easier to read if all the sensitivity analyses around the primary outcome were listed, then the secondary cessation outcomes, then, as done, the non-cessation outcome, or process measures listed.

Response: This has been amended and now reads ‘A senior statistician determined the sample size and wrote the statistical analysis plan which was subsequently agreed by the Steering committee. All statistical analyses will be performed using SPSS version 24 software. Participants will be analysed on an intention to treat basis at the point of randomisation. 95% confidence intervals will be presented for all analyses. Missing data will be replaced by the mean within condition score. The following stratification variables will be included as covariates in all regression models: baseline quit efficacy (at inclusion), age (at inclusion), gender and baseline nicotine dependency. These covariates have been selected as they have been shown to influence treatment success, and we wish to investigate the unique effects of treatment across a demographically heterogeneous sample.

Primary outcome analysis. Participants for whom smoking cessation cannot be confirmed (i.e. are lost to follow-up) will be included in the analysis as failed quits, in line with the Russell 6 Standard. Logistic regression will be used to estimate the effectiveness of the treatment condition upon smoking cessation at six months.

A series of sensitivity analyses will be conducted to assess the robustness of primary results with regards to definition of the primary outcome. To investigate if the differential effects of interventions are present at each time point (4 and 12 weeks), the primary analysis will be repeated twice, the dependent variable being smoking cessation confirmed at 4 and 12 weeks. The primary analysis will be repeated on smoking cessation outcomes at both 12 and 26 weeks using only participants who did not ‘reset’ their quit dates (NHS arm) or attended a top-up session (ACE arm). This is preferable to including them as failed quits, as many may in fact be successful cessations, whilst also attending a top-up.

Secondary smoking outcomes. Use of NRT in each treatment arm will be tested by conducting a logistic regression. Treatment arm and treatment success will be included as the independent variables.
Secondary non-smoking outcomes analyses. To analyse the take up of treatment between conditions, a logistic regression will be undertaken on treatment completion (operationalised as attendance at the ACE session and attendance at all five weeks of the NHS sessions). Multi-level regression models with time of measurement (4 weeks, 12 weeks and 26 weeks) will be undertaken with perceived value of being nicotine free, readiness to change, intentions to reengage, life satisfaction as the dependent variables, treatment arm as independent variable. Planned comparisons between treatment arms at each time point will be undertaken.

Comment: Plan of presentation: Simply say a consort diagram will be used to describe the sampling, drop-outs and randomisation. Indeed a Consort diagram with planned sample size and spaces for all the numbers that will eventually be determined would be useful.

Response: Standard information has been deleted and this section now reads:

A CONSORT diagram will be used to describe the sampling, drop-outs and randomisation.

Comment: Dissemination: Not really informative, could drop

Response: This section has been deleted.

Comment: Funding: It must be made clear what rights ACE has over publication. Can they veto, do they get advanced notice, do they have an opportunity to comment?

Response: This has been addressed and the following added 'The research team are contractually free to publish whatever findings the study produces, ACE has no veto over publication, but will be given advanced notice of the findings prior to publication'.

Comment: Contributors: Normally a footnote re authorship.

Response: Amended

Comment: Competing interests: Please make it clear any relationships with either NHS SSS or ACE.

Response: 'No Authors have any conflicts of interest with NHS stop smoking services, or Allen Carr's Easyway to declare. The authors have no financial relationship or interest with the funding organisation.'
Comment: Roles and responsibilities: Not needed

Response: This section has been deleted.

Comment: Table 1. Not needed

Response: Table. 1 has been deleted

Reviewer 3

Comment: 1. The last paragraph in the introduction seems redundant as it deals with information that is presented in detail in the methods section. Probably the last 2-3 sentences in the paragraph would be enough.

Response: This paragraph has been shortened to read 'To test the efficacy of the ACE programs against existing provision, this study will compare the efficacy of two stop smoking interventions. Specifically, Allen Carr's Easyway to stop smoking programme and a 1-1 counselling service available via the NHS will be compared. By comparing the ACE programme to a NHS delivered treatment program, an estimate of the relative effectiveness of ACE in comparison to the NHS service can be made. This will potentially inform future judgements about the use of this method by private and public health care providers. The findings will add to the evidence base around the use of the NHS stop smoking service and the Allen Carr's Easyway method'.

Comment: 2. Please revise footnote on p.4 is correct.

Response: This footnote is correct.

Comment: 3. In the description of the NHS cessation interventions the setting of the quit date (p.5) raises questions in terms of the implications it may have for follow up period. The information in the protocol (supplementary file) makes this very clear, specifying it should be within 2 weeks so this information should be added in the main text. In fact the process diagram is very helpful, I would consider using it as a figure within the paper.

Response: Revised sentence to read 'A quit date is set (within two weeks of receiving the intervention) and the importance of complete abstinence discussed'. Process diagram added as figure in paper.

Comment: 4. Recruitment & Randomisation, allocation concealment and sequence generation P.7, Do participants receive written information on the study (other than the leaflet) before they undergo screening? And is there any inclusion criteria for participants in terms of time from screening to sending the consent?
The first couple of sentences in the paragraph 3 might be moved to paragraph 2.

Response: Sections amended to read:
'Recruitment. People will be informed of the trial through local placement of posters, leaflets to residential properties, booklets to major employers, employment networks and councils, webpages at LSBU and social media campaigns. People interested in enrolling will be invited to contact London South Bank University to provide contact details and will be sent (via email or post) an information sheet containing written information about the study. Within two days, potential participants will be contacted by phone and undergo eligibility pre-screening. At this point they will not be informed which two interventions are being compared in the study. If eligible, participants will be asked about demographics, nicotine dependence and prior quit attempts to allow for stratified randomisation into the trial. Within two days of being screened the research team will send eligible participants a consent form (via post or email). As this stage is before intention to treat or condition allocation, no restrictions on contact attempts are placed on this stage. On gaining written consent, participant's details will be sent to the independent randomiser for allocation.
Randomisation, allocation concealment and sequence generation
Participants will be randomised to condition by Sarah White (study statistician) using the Kang and Park (11) 'Covariate Adaptive Randomization Program' (Version 1.0) software package. Four stratification factors, each at two levels, will be used: nicotine dependence (determined by the Fagerstrom Test for Nicotine Dependence [FTND] questionnaire (12)), number of prior quit attempts, age and gender. Participants will be assigned to the ACE and NHS 1-1 intervention groups in a ratio of 1.1 (310 in each).'

Comment: 5. Statistical analyses p. 9, paragraph 1, list the covariates.

Response: Added "The following stratification variables will be included as covariates: baseline quit efficacy (at inclusion), age (at inclusion), gender and baseline nicotine dependency."

Comment: In the protocol it is acknowledged that participants will be paid. How was considered including (or not) this information in the manuscript?

Response: Under the recruitment section the following has been added “Once randomised, participants will see the research team four times (baseline, 4 weeks, 12 weeks and 26 weeks). They will be paid £15 cash for attending each measurement point and regardless of quit outcome, they will be entered into a prize draw to win a Caribbean holiday for two, iPad and gym membership.”

VERSION 2 – REVIEW

REVIEWER	Ron Borland Cancer Council Victoria, Australlia
REVIEW RETURNED	16-Jul-2017

GENERAL COMMENTS	This is a greatly improved and easier to read protocol. I also appreciate the changes to the design made as a result of the earlier reviews. I have only one significant outstanding issue. I think there needs to be some discussion of the use of the reset strategy. First, because this is a novel approach and thus readers will be interested in how it is designed to work. Second, there should be some discussion of the implications of the strategy used as compared with the alternative of setting the outcome to be 6 months sustained abstinence after the end of any reset period. This would allow spontaneous resets as well as ones generated via the formal interventions. Minor note. It is not entirely clear to me which of the supplementary materials are to be included in the published version. I leave that to the editors to work out with the authors.

REVIEWER	Agurtzane Mujika School of Nursing. University of Navarra. Spain
REVIEW RETURNED	10-Jul-2017

GENERAL COMMENTS	The authors have responded to the suggestions made

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Ron Borland
Institution and Country: Cancer Council Victoria, Australia

Comment: I have only one significant outstanding issue. I think there needs to be some discussion of the use of the reset strategy. First, because this is a novel approach and thus readers will be interested in how it is designed to work. Second, there should be some discussion of the implications of the strategy used as compared with the alternative of setting the outcome to be 6 months sustained abstinence after the end of any reset period. This would allow spontaneous resets as well as ones generated via the formal interventions.

Response: The following section has been added to the main document:

Both NHS and ACE treatments offer top-ups are part of treatment as usual, so it is reasonable that the smoke-free period starts from the date of the top-up (the top-up is part of the normal 'dosage' of the method). Therefore, all participants will have to be smoke-free for six months (primary outcome), in line with RS6, from the point they receive the treatment. People who do not slip more than the defined number of times, do not attend top-ups, and still maintain from the end of treatment to the final outcome point can of course self-recover. Where participants engage in a subsequent data collection point (i.e. 4 weeks) before top-up, this data will be held, but a new set of data will be collected and used in subsequent analysis.

An alternative approach would be to track all participants from the end of a pre-specified 'grace period' which would allow for spontaneous resets. However, such a response would effectively mean that the actual smoke free period between end of treatment and the primary outcome measure point could vary considerably. If there are differences in the number of resets/top-ups used between treatment arms, this would introduce non-trivial systematic bias into the final analysis. In order to explore how the use of top-ups/resets affects outcomes, we will undertake secondary analysis looking only at those who did not use resets/top-ups (and, if appropriate in terms of statistical power, comparing rates between those that do and do not between arms).

Reviewer: 3
Reviewer Name: Agurtzane Mujika
Institution and Country: School of Nursing. University of Navarra. Spain
Please state any competing interests: None declared

Comment: The authors have responded to the suggestions made

Response: The Data sharing statement in the main document now matches the scholar One statement and the image has been changed from pdf as requested.

VERSION 3 – REVIEW

REVIEWER	Ron Borland Cancer Council Victoria, Australia No Competing Interest
REVIEW RETURNED	24-Sep-2017

GENERAL COMMENTS	Thankyou for responding to the comments. I have no more concerns. This will be a very important study and some of the methods are of interest of themselves.