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Rationale and design of the Lowlands Saves Lives trial: A randomized trial to compare CPR quality and long-term attitude towards CPR performance between face-to-face and virtual reality training with the Lifesaver VR-app

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Manuscripts

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3 **Rationale and design of the Lowlands Saves Lives trial:**
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5 **A randomized trial to compare CPR quality and long-term attitude**
6 **towards CPR performance between face-to-face and virtual reality**
7 **training with the Lifesaver VR-app**
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Abstract

Introduction: Layperson cardiopulmonary resuscitation (CPR) is a key aspect in the chain of survival after cardiac arrest. New, low cost, easily accessible training methods such as virtual reality (VR)-training with a smartphone application may reach broader populations but data on CPR performance are scarce.

Methods and analysis: The Lowlands Saves Lives trial is a national, prospective randomized open blinded end-point evaluation (PROBE) study, comparing two 20-min CPR training protocols: standardized, certified instructor led face-to-face training and VR-training, using the UK-Resuscitation Council endorsed Lifesaver VR app.

During VR-training, participants learn to resuscitate by completing a filmed CPR scenario while wearing VR-goggles and headphones. Eligible for inclusion are adult attendees of Lowlands Science, a specific section of the three-day Lowlands music festival (50.000 attendees), dedicated exclusively to science. Following the training, all participants will perform a CPR test on a certified CPR manikin. Primary outcome measures are depth and rate of chest compressions, measured using CPR manikins. The key secondary outcome is overall CPR performance, with real-time examination (blinded for study group) of all items of a European resuscitation-council endorsed checklist, and evaluation of a sample of video-taped CPR tests by a blinded event-committee.

Given the unique setting of a festival, the primary additional analysis will address the impact of alcohol-intake on CPR quality parameters and overall performance. Follow-up questionnaires will evaluate the attitude towards performing CPR. This unique study may provide important insights into innovative CPR training methods, factors that impact CPR performance, and the impact on long-term attitude towards resuscitation.

Ethics and dissemination: This study received approval from the research ethics committee of the Radboudumc. All participants will provide written informed. The results of

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2
3 this study will be published in peer-reviewed journals and presented at national and
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5 international conferences.
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8 **Registration:** The trial is registered at clinicaltrials.gov (NCT04013633, July 10th 2019).
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Article summary

Strengths and limitations of this study

- The Lowlands Saves Lives trial uses a unique real-world study setting of a Dutch music festival, and is the first randomized trial to compare cardiopulmonary resuscitation (CPR) quality between certified instructor led face-to-face training and Lifesaver virtual reality-training.
- We will assess clinically relevant CPR quality measures, obtained using objective measurements from CPR manikins and assessors blinded for the intervention, and follow-up will be collected on attitude towards CPR and influencing factors.
- Due to the nature of the intervention, participant blinding is not possible.
- The festival setting allows for a unique and relevant prespecified study question, and there will be stratification according to alcohol-intake to assess its impact on CPR quality and overall performance.
- The results of our study will provide important insights into the efficacy of innovative CPR training methods which may help to improve CPR skills of layperson rescuers, with the ultimate goal of improving outcomes after cardiac arrest.

Introduction

In Europe, about 300.000 out-of-hospital cardiac arrests (OHCA) occur annually, and despite the achieved improvements in treatment outcome is still dismal.¹⁻³ Early bystander cardiopulmonary resuscitation (CPR) is a key determinant of survival, but is not performed in about 40% of cases.^{1, 4-9} It is therefore essential to create awareness, willingness and capability of lay-volunteers to perform CPR.¹⁰ In this context, leading authorities have identified research on education as one of the top priorities for cardiac arrest research.^{11, 12}

Current guidelines state that high-level scientific evidence on the optimal CPR training method is scarce.¹³ Face-to-face CPR training has long been the gold standard, but new technologies have evolved that may hold potential to reach broader populations and provide quick, easily accessible CPR training that can be performed at home, at low costs.¹³⁻¹⁵

One of these novel training-methods is virtual reality (VR), a modality with promising potential according to a recent survey among resuscitation-experts.^{13, 16-18} The Lifesaver VR app provides an engaging learning experience, through participation in a filmed CPR scenario.¹⁵ This application is endorsed by the UK Resuscitation Council and can be installed for free on smartphones.

Apart from improving laypersons' skills, better insight into the attitude towards CPR and factors that may influence the decision to start may affect future bystander CPR rates.^{12, 19, 20} Aspects like fear to do harm, having no experience, or uncertainty about the impact of recent alcohol intake on CPR performance are everyday issues.^{13, 20}

The Lowlands Saves Lives trial is a randomized controlled trial comparing CPR quality and long-term attitude towards CPR between face-to-face and Lifesaver VR app CPR training. It will be conducted in the unique setting of a three-day Dutch music festival (50.000 attendees), which will provide a real-world sample of young and outgoing participants. Furthermore, this setting will allow for unique additional analyses, such as the impact of alcohol use and previous CPR training on CPR performance.

Methods and Analysis

We followed the SPIRIT guidelines in the design of our study protocol.²¹

Aim of the study

The primary aim of this study is to compare CPR quality between face-to-face CPR training and training using the Lifesaver VR app.

Hypothesis

Our hypothesis is that training with the Lifesaver VR app will result in CPR quality that is non-inferior to CPR quality achieved by face-to-face training.

Setting

The present study will be performed during the Lowlands-festival (August 16-18, 2019). This is an annual music-festival in the Netherlands with over 50.000 attendees. This project of the department of Cardiology, Radboudumc, Nijmegen, The Netherlands was selected by a jury to be conducted during Lowlands Science, a section of the festival dedicated exclusively to performing scientific research.²²

Overview of the study design

The Lowlands Saves Lives trial is a national, prospective randomized open blinded end-point evaluation (PROBE) study.^{23, 24} The study flowchart is depicted in [Figure 1](#).

Participants will be randomly allocated (1:1) to either certified instructor led, face-to-face training, or VR-training with the Lifesaver VR app.¹⁵ As the study will be performed during a musical festival where alcohol consumption is common, and alcohol consumption may impact CPR performance, we will perform an alcohol breathalyzer test in all participants. In case of an alcohol level >0.5‰ (the Dutch legal driving limit), participants will perform a

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3 tandem gait test. Participants not able to complete this test will not be randomized, and
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5 excluded from the study. Randomization will be stratified according to alcohol level.
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9 Directly following the training, all participants will complete a CPR skill test, which will take
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11 place in a separate room, with an assessor blinded for the study group. Participants will
12
13 demonstrate acquired BLS and AED skills during a specifically designed CPR scenario. We
14
15 will use a certified CPR training manikin to objectively measure chest compression depth,
16
17 rate and flow fraction. Furthermore, overall CPR performance will be scored with use of a
18
19 European Resuscitation Council endorsed checklist, with items that focus on the required
20
21 steps for performing adequate CPR and automated external defibrillator (AED) use
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23 ([Supplement 1](#)).¹⁵
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27 **Participants**

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29 Adult (≥ 18 years) attendees of the Lowlands Science, a specific section of the Lowlands
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31 music festival dedicated exclusively to scientific research. Further in- and exclusion criteria
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33 are shown in [Table 1](#). Inclusion of participants with previous CPR training (CPR course ≤ 2
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35 years) is capped at 20% of the total inclusions.¹⁷ Consent to participation includes an alcohol
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37 breathalyzer test in all participants (AlcoTrue P®, Bluepoint Medical, Selmsdorf, Germany).
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39 In addition, video-recording of the final CPR skill assessment will be performed on an
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41 individual basis, in the subset of participants that provide consent.
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44 The study will be performed during the entire duration of the festival, which is three full days
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46 and inclusion will continue until the end of the festival. Our estimated maximum educational
47
48 capacity is 480 participants.
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52 **Randomization and data management**

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54 Participants will be randomly allocated (1:1) to either of both training methods using the
55
56 online CASTOR Electronic Data Capture (CASTOR EDC) system.²⁵ We will use a random
57
58 block randomization algorithm and stratify randomization according to alcohol level, using a
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3 binary cut-off value of <0.5 versus $\geq 0.5\%$. CASTOR EDC will also be used for data
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5 management. CASTOR data will be exported for analysis.
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9 **Interventions**

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11 *Face-to-face training:* The training will comprise a 20-min CPR training by an instructor
12 certified by the Dutch Resuscitation Council, who is not part of the study team, and not an
13 employee of the Radboudumc, Nijmegen, The Netherlands. The training protocol is
14
15 standardized and was designed under supervision of our national BLS course director (HW).
16
17 The ratio of instructors to participants is 1 to 5. Chest compressions and ventilations will be
18
19 taught using certified CPR manikins (Little Anne, Laerdal Medical, Stavanger, Norway). AED
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21 use will be demonstrated and practiced with use of Zoll training AEDs (Zoll AED Trainer 3,
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23 Zoll Medical, Chelmsford, USA).
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31 In line with the recommendations of the European CPR education guidelines, we
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33 incorporated the following core-elements into the training: willingness to start CPR,
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35 recognition of unconsciousness, good quality chest compressions and feedback during the
36
37 training.¹³ We will also focus on creating awareness for AED use and benefit, and provide
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39 education on common myths on CPR (e.g. the belief that it may cause harm).
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44 *Lifesaver VR training:* All participants will complete the same CPR scenario using the
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46 Lifesaver VR app (<https://lifesavervr.org.uk/>). The completion of this scenario will take
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48 approximately 20 min. Lifesaver VR endorsed by the Resuscitation Council (UK), has been
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50 developed using charitable funds and does not generate financial revenues.¹⁵ Lifesaver is an
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52 innovative, immersive, and interactive game that can be installed for free on smartphones.
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54 The novel 'game-in-film' format provides an engaging learning experience with a real life
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56 CPR scenario. Users become actively involved with the resuscitation of a victim of cardiac
57
58 arrest and simulate cardiac compressions by performing compressions on a pillow. The app
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60 provides feedback on compression speed, and instructions on compression depth. It also

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3 teaches skills needed for adequate AED use. If a wrong decision is made, the user sees the
4 impact but is then able to rewind and make the correct decision. The recently added VR
5 feature allows the users to experience the resuscitation scenario in VR, using VR goggles,
6 further enhancing the experience. For this training, we will use Samsung S7 smartphones
7 (Samsung, Seoul, South Korea), in combination with Zeiss VR One Plus VR-goggles (Carl
8 Zeiss, Oberkochen, Germany) and headphones.

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11 A graphical impression of the Lifesaver VR set-up is provided in [Figure 2](#).

12 13 14 15 16 17 18 19 20 **Outcome measures and other parameters**

21 Outcome measures in this study are based on a consensus document describing the
22 preferred outcomes for reporting on CPR quality and on current CPR guidelines.^{10, 26, 27}

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27 The primary outcomes are the CPR quality parameters chest compression depth (mm) and
28 compression rate (compressions/min), assessed with the certified CPR manikins (Resusci
29 Anne QCPR, Laerdal Medical, Stavanger, Norway).

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34 The key secondary outcome measure is the overall CPR performance expressed as a real-
35 time appointed score by examiners blinded for study group, using the European
36 Resuscitation Council endorsed CPR checklist (Supplement 1). Video recordings of CPR skill
37 tests will be made of the subset of participants that provide consent for this additional study
38 feature. A random sample of all video-recordings will be reviewed by an external event
39 committee, blinded for study group. In addition, we report flow fraction (percentage of time
40 where compressions given) assessed with registrations of the certified CPR manikin. Finally,
41 we will calculate proportions of participants meeting guideline CPR quality criteria.^{10, 26, 27}

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52 *Other study parameters:* At baseline, all participants will complete a questionnaire after
53 informed consent, with information on e.g. age, sex, weight, education level, previous CPR
54 experience and previous CPR training ([Supplement 2](#)). Follow-up questionnaires after 1 year
55 will focus on attitude towards CPR and aspects that influence the decision to start CPR.^{19, 20}

Study organization

Diagram B.V. (Zwolle, The Netherlands) will be responsible for data monitoring and the coordination of the video-evaluations of a sample of CPR-skill tests. Baselines, outcome measures and follow-up data will be reviewed. The review of CPR-skill videos will be conducted by an event committee of two experienced CPR instructors, blinded for study group.

Pre-specified additional analyses

Our primary additional analysis concerns the impact of alcohol on CPR quality parameters and overall performance. In that context, randomization will be stratified according to alcohol levels.

The second additional analysis concerns the impact of previous CRP-training on CPR quality and overall performance. To ensure that this project provides sufficient information on the efficacy of the two training methods for laypersons without CPR training, the number of participants with previous CPR training is capped at 20% of the total of randomizations. Moreover, sample size calculations for the primary study aim were performed to assess the required number of laypersons without CPR training, after which this total was multiplied by 1.25 to calculate the total number of participants.

Exploratory analyses

The following sub-groups were pre-specified for analysis of the endpoints: male versus female, above versus below median age, above versus below median weight, with versus without previous CPR experience, above versus below median education level, and healthcare providers versus no health care providers.

Follow-up assessment

All participants will be asked to provide additional consent for a follow-up questionnaire to be conducted one year after finalization of the trial. This questionnaire will contain questions regarding attitude towards the trial and CPR in general, follow-up training and real-life resuscitation experience following participation in the trial.^{19, 20} Data will be analyzed in a similar way as the primary and secondary outcomes: between study groups, according to the pre-specified subgroups, and in exploratory analyses.

Statistical considerations

This study is designed to evaluate the hypothesis that VR-training is non-inferior to instructor-led training. A recent review reported that the expected effect on compression depth of instructor led training is about 5 mm, and that the average effect on compression rate is about 17/min.²⁸ Data on expected differences in CPR performance in relation to alcohol level are unavailable, but to optimally address this question randomization was stratified by alcohol level. To ensure sufficient data on the efficacy of both training methods for laypersons without CPR training we decided that sample size calculations for the primary endpoint should allow for meaningful conclusions in this group of specific interest.

Main outcomes of interest will be tested for non-inferiority. Other variables will be assessed for normal distribution and reported as means (standard deviation) or medians (interquartile range), whichever appropriate. Continuous data will be compared using a student's t-test or Mann-Whitney U test, whichever appropriate. Categorical variables will be reported as numbers (%) and compared using chi-squared or Pearson exact tests, whichever appropriate. All baseline variables (demographics, previous CPR experience) and outcome data (CPR rate and depth, CPR score, flow fraction) variables will also be compared between the two study groups using the abovementioned tests. In case of confounding variables, we will correct comparisons on the outcome measures between the study groups for these confounders using Analysis of Covariance (ANCOVA). A p-value of <0.05 will be

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3 considered statistically significant. Analyses will be performed using SPSS (IBM SPSS
4 version 25, IBM Corp., USA).
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9 **Sample size calculation**

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11 The present study is designed as non-inferiority trial, where the null hypothesis is that VR-
12 training is inferior to face-to-face training. The non-inferiority margin for depth is set at 5
13 mm²⁸, with an expected standard deviation of 10.^{29, 30} Based on these assumptions and an
14 alpha of 5% and a power of 90% we calculated that we need 69 participants per group.
15
16 As the inclusion of participants with previous CPR training is capped at 20%, at least 80% of
17 the participants will have no prior CPR training. As we prespecified that sample size
18 calculations should be based on this latter group, the total number per study group will
19 therefore need to be 1.25*69=86. Assuming a drop-out of 10%, we will aim to include 95
20 participants per group. This sample size will also provide sufficient power for a non-inferiority
21 hypothesis-testing for chest compression rate, given the standard deviation of 20 and
22 average increase in chest compression rate of 17/min found in previous studies.^{28, 30}
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37 **Patient and public involvement**

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39 No patients were involved in the design of this study protocol. However, we incorporated
40 several elements into our training that were identified by laypersons as important factors for
41 performing CPR and using an AED.²⁰
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Ethics and dissemination

The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects act. The research ethics committee of the Radboud University Medical Center has reviewed this study on the basis of the Dutch Code of conduct for health research, the Dutch Code of conduct for responsible use, the Dutch Personal Data Protection Act and the Medical Treatment Agreement Act. The ethics committee has passed a positive judgment on the study. All participants will provide written informed consent before participating in the trial. The results of this study will be published in peer-reviewed journals and presented at national and international conferences. The trial is registered at clinicaltrials.gov (NCT04013633, July 10th 2019).

Discussion

The Lowlands Saves Lives trial has been initiated as a project to reach a large group of citizens in a short period of time during a Dutch music festival and to stimulate awareness, willingness and capability of laypersons for CPR. Appreciating that in about 40% of the out-of-hospital cardiac arrests bystander CPR is not given, while early start of resuscitation is the key determinant of survival, we wanted to test the efficacy of two innovative training methods on CPR performance and attitude towards resuscitation. In the setting of a randomized trial with PROBE design, we will compare 20-min certified instructor led face-to-face training with 20-min virtual reality training using the Resuscitation Council endorsed Lifesaver VR app.

Layperson CPR

Appreciating that the vast majority of cardiac arrests occur at home, it is imperative to increase the rate of layperson initiated CPR as this is expected to markedly improve survival chances.^{8, 9, 31, 32} Several factors affect the decision to actually start CPR, varying from the fear to do harm, to perceived inability due to lack of training, or fear to be contaminated by providing mouth to mouth.^{19, 20} A previous American Heart Association consensus document on CPR education stated that layperson training should focus on overcoming barriers to initiating CPR.³³ It is therefore one of the key aspects during trainings, and the impact of both training methods on the attitude towards CPR will be subject of interest of the follow-up questionnaires.

Despite growing interest in CPR training, and the fact that several companies have appointed an in-house emergency service, the vast majority of citizens has not participated in CPR training. Current conventional certified training programs last about four hours, which poses a logistic and sometimes financial burden to partake in these programs.

Programs with a lower threshold to participate, preferably of shorter duration, may reach a broader population. Previous work has shown that a 30-min training yields similar results as a conventional training.²⁹ In addition, a modality that allows for easy, repetitive training may

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3 not only appeal to a larger target population, but it may also ensure a more sustained CPR
4 quality. Several studies have shown that short booster trainings improve CPR performance
5 and the guidelines place increasing emphasis on high-frequency, short, booster training for
6 certified BLS-providers.^{34, 35} This may facilitate improved skill-retainment, a major topic in
7 current CPR (education) guidelines.^{13, 14}
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13 The accessibility of Lifesaver VR, its low cost, and the possibility to perform it at convenient
14 moments, at home, could be advantageous and useful for laypersons that experience a
15 threshold to participate in face-to-face training. However, information on CPR quality data is
16 limited, and we are the first to assess the Lifesaver app in combination with a VR modality.
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23 **Training methods and outcome measures**

24 We will compare 20-min face-to-face training by a certified BLS-instructor with 20-min virtual
25 reality training with the Lifesaver app. The instructors will provide a standardized training,
26 developed with our national BLS coordinator. Outcomes achieved with the Lifesaver VR app
27 will be tested in the setting of a non-inferiority design.
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34 Our primary outcomes are in concordance with current international CPR guidelines. Both
35 chest compression depth and compression have repeatedly been associated with survival
36 after cardiac arrest.^{10, 26} Moreover, both outcome measures can be objectively assessed with
37 the output of the certified manikins.
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43 A recent review on the impact of training demonstrated that instructor-led training results in
44 about 5 mm additional chest compression depth.²⁸ This is what we defined as the non-
45 inferiority margin for this primary endpoint, with a required total of 190 participants. This total
46 is also sufficient to address non-inferiority for the number of chest compressions per minute.
47 As instructor-led training is reported to result in about an additional 17 compressions/minute,
48 this was set as non-inferiority margin for this primary endpoint.
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55 The key secondary outcome measure is overall CPR performance. This is an integrative
56 score, appointed real-time, by an assessor blinded for study groups. It reflects the entire
57 CPR process, including alerting 112 and the ability to use the AED, and the score is
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3 assessed with use of a checklist endorsed by the European Resuscitation Council. In
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5 addition, a blinded event committee will review a sample of the CPR skill tests registered on
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7 video in participants that provided additional consent.
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9 In addition, we prespecified important additional analyses and incorporated specific elements
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11 in the design of our study to ensure that these questions could be adequately addressed.
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13 First, the goal of recruiting more laypersons to perform CPR may result in situations where
14
15 CPR is required while someone has consumed alcohol in a restaurant or bar, which is often
16
17 a controversial issue in case medical help is required.^{36, 37} The unique setting of a music
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19 festival provides a setting to further explore this issue. In this context, randomization was
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21 stratified according to alcohol level, including a group with a level higher and lower than
22
23 0.5‰, the Dutch legal driving limit.
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26 Second, lack of CPR training is often mentioned as a reason not to perform CPR.²⁰ Data on
27
28 how much this affects CPR quality and overall CPR performance is limited, and we therefore
29
30 aim to objectify this issue. This may help to provide better quality evidence to address these
31
32 concerns.
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34 35 36 **Follow-up**

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38 With use of follow-up questionnaires we will gather and compare information on the attitude
39
40 towards CPR between both training methods. In addition, we will try and identify factors that
41
42 may influence the decision to initiate bystander CPR. The Lowlands Saves Lives trial not
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44 only focuses on the training itself, but on an entire experience: banners with links to the
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46 Dutch Heart Foundation (www.hartstichting.nl) providing additional information on
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48 resuscitation, and addresses for endorsed BLS-AED courses.
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51 52 53 **Implications**

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55 In a setting of a renowned Dutch music festival with about 50.000 attendees, our study is
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57 expected to contribute to increased awareness for resuscitation, and may result in about
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59 200-400 trained citizens. In addition, it will address a key topic in current resuscitation
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3 research, i.e. the search towards to optimal CPR training method, and it will be the first to
4
5 study the Lifesaver app with a virtual reality modality.
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8 Until now, the only data available for the Lifesaver app have been obtained in children, at
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10 that time without a VR feature. Results were promising, although compression depth seemed
11
12 suboptimal. Whether this is related to the low body weight of the children, or a consequence
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14 of the training method is uncertain. The VR modality may enhance the experience, and
15
16 mimicking a situation that is closer to the real-life setting may contribute to better results.

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18 Globally, increasing the rate of bystander CPR is anticipated to be one of the key factors to
19
20 improve survival after cardiac arrest. In the Netherlands, campaigns stress the importance to
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22 initiate CPR within 6 minutes of the arrest, given the much higher chances of survival within
23
24 this interval. All efforts are made to create a national network, that consists of citizens with an
25
26 official BLS-AED certificate that subscribe to a national text message based alert system
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28 combined with a registration system of AEDs.³⁸⁻⁴⁰ The goal is to achieve a coverage that
29
30 ensures a 6 minute response in all parts of the Netherlands.
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33 34 35 **Conclusion**

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37 The Lowlands Saves Lives trial will create awareness for the importance of bystander CPR,
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39 and aims to increase willingness and capability to participate in CPR. If an easily available,
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41 low cost app can result in similar CPR results as instructor-led training this may be an
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43 important step towards reaching this goal.
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Declarations

Competing interests

NVR received research grants from Abbott, Biotronik, AstraZeneca and Philips, and professional fees from Abbott, Microport, Amgen and Medtronic. The other authors have no conflicts of interest to declare.

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Author contributions

JN, JT, JLB and MAB conceived the idea. Study methodology was designed by JN, JLB, JT, RVG, NVR and MB. JN, PV and MAB designed the statistical analyses. JN, JLB, JT and MAB drafted the manuscript. PV, RVG and NVR provided critical revisions and substantial intellectual input. All authors agreed with the final version of the manuscript. JN takes full responsibility for integrity of the presented content.

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Tables

Table 1 – In- and exclusion criteria of the Lowlands Saves Lives trial

Inclusion criteria of the Lowlands Saves Lives trial	
1	Adult (≥ 18 years) Lowlands attendees
2	Provide informed consent
Exclusion criteria of the Lowlands Saves Lives trial	
1	Alcohol level $>0.5\%$ and not able to complete tandem gait test.
2	For any reason not being able to partake in the face-to-face or VR-app training (e.g. physical impairment).
3	For any reason not being able to perform the CPR test on the CPR manikin (e.g. physical impairment).

In- and exclusion criteria of the Lowlands Saves Lives trial. VR: Virtual reality; CPR:

Cardiopulmonary resuscitation

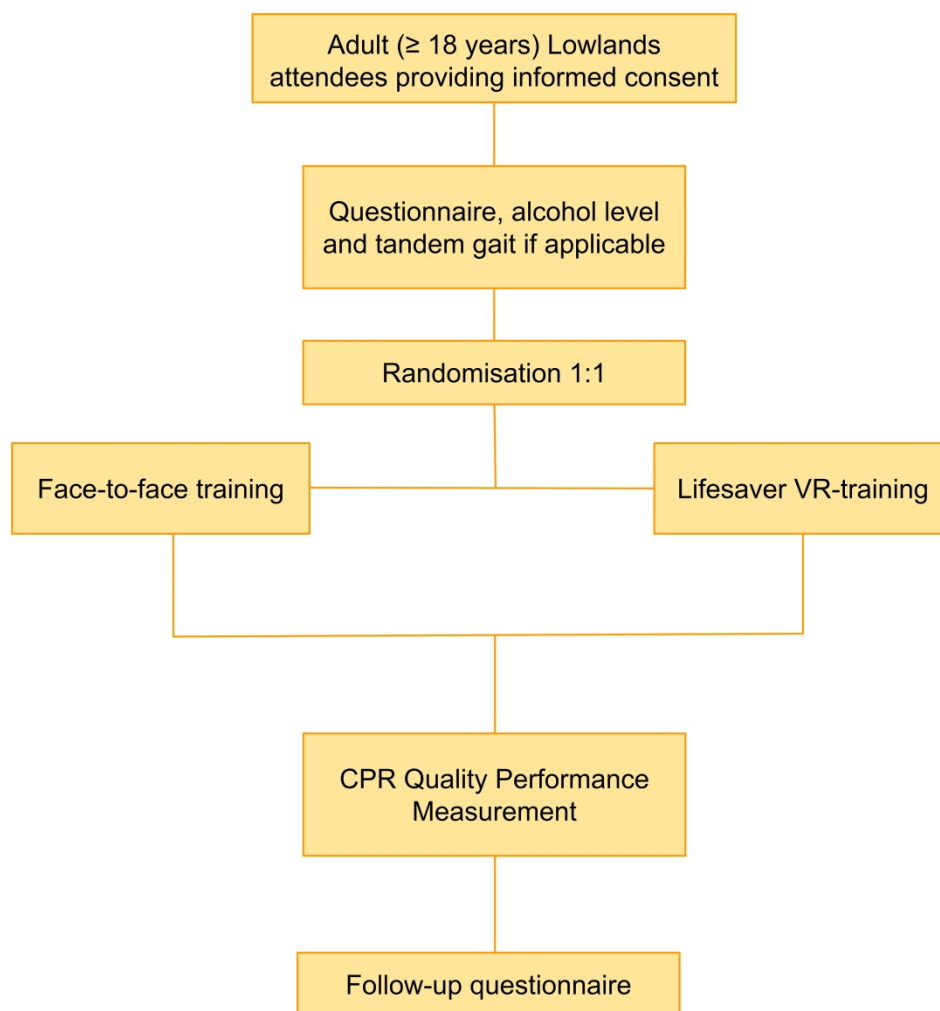
Figure Legends

Figure 1 – Study flowchart of the Lowlands Saves Lives trial

Study flowchart of the Lowlands Saves Lives trial. VR: Virtual reality; CPR: Cardiopulmonary resuscitation.

Figure 2 – Lifesaver VR app

Demonstration of the Lifesaver VR set-up, using headphones, VR goggles and a pillow to perform chest compressions. VR: Virtual reality



Study flowchart of the Lowlands Saves Lives trial. VR: Virtual reality; CPR: Cardiopulmonary resuscitation.

299x310mm (300 x 300 DPI)

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Demonstration of the Lifesaver VR set-up, using headphones, VR goggles and a pillow to perform chest compressions. VR: Virtual reality

199x250mm (300 x 300 DPI)

Supplement 1 – CPR-skill assessment test

(European Resuscitation Council CPR/AED course assessment document)



2016.V2

BLS assessment record

Candidate Name:

Date:

Instructor:

Skill	The candidate	Achieved		Comments
		Yes	No	
Check response	Demonstrates gently shaking and shouting to establish responsiveness			
Assess breathing	Demonstrates head tilt and chin lift			
Assess breathing	Demonstrates look, listen and feel for normal breathing for no more than 10 sec (does not count aloud)			
Call emergency services (Get help)	Describes how to phone for emergency services: 112, unresponsive and non-breathing victim, AED			
Chest compressions	Demonstrates effective chest compressions; rate 100-120/min, depth 5-6 cm; hand position: centre of the chest. Minimises interruptions in chest compressions			
Rescue breaths	Demonstrates rescue breaths sufficient to cause the chest to rise and fall			
Compression : ventilation ratio	Demonstrates ratio of 30 compressions to 2 ventilations			
Activate AED	Switch the AED on or, if a helper is present, ask him/her to do it			
Attach pads	Demonstrates attaching pads in correct position			
Stand clear	Allows rhythm analysis whilst making sure that nobody touches the victim (including visual sweep and verbal instruction)			
Deliver shock	Demonstrates rapid and safe delivery of a shock (including visual sweep and verbal instruction to stand clear)			
Follow AED instructions	Demonstrates listening to and executing AED instructions			
CPR	Minimises interruptions in chest compressions and demonstrates correct sequence in ratio of 30 compressions to 2 ventilations			

CPR: Cardiopulmonary resuscitation; AED: Automated external defibrillator.

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3 **Supplement 2 – Questionnaire for study participants**
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5 Study number & instructor (to be completed by investigator)		
6 E-mail address*		
7 Sex	<input type="radio"/> Female <input type="radio"/> Male <input type="radio"/> Do not wish to disclose	
8 Age		
9 Weight		
10 Highest level of education	<input type="radio"/> Primary education <input type="radio"/> Secondary education <input type="radio"/> Short cycle tertiary education <input type="radio"/> Bachelor or equivalent <input type="radio"/> Master or equivalent	
11 Healthcare professional	<input type="radio"/> Yes <input type="radio"/> No	
12 Have you used any drugs/narcotics in the past 24 hours, besides alcohol?	<input type="radio"/> Yes, which: <input type="radio"/> No <input type="radio"/> Do not wish to disclose	
13 <i>Previous CPR experience</i>		
14 CPR course	<input type="radio"/> No <input type="radio"/> Yes, which level <input type="radio"/> BLS <input type="radio"/> BLS+AED <input type="radio"/> ALS <input type="radio"/> Other: Date last course:	
15 Witnessed a cardiac arrest	<input type="radio"/> No <input type="radio"/> Yes, ... times <input type="radio"/> Only as a witness <input type="radio"/> CPR performed as bystander/layperson <input type="radio"/> CPR performed as healthcare professional	
16 The victim was	<input type="radio"/> A stranger <input type="radio"/> A relative or other acquaintance	

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
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
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
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)

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
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)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	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)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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
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)
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

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
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2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how
13			
14			
15		17b	If blinded, circumstances under which unblinding is permissible, and
16			procedure for revealing a participant's allocated intervention during
17			the trial
18			

Methods: Data collection, management, and analysis

21			
22	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
23	methods		trial data, including any related processes to promote data quality (eg,
24			duplicate measurements, training of assessors) and a description of
25			study instruments (eg, questionnaires, laboratory tests) along with
26			their reliability and validity, if known. Reference to where data
27			collection forms can be found, if not in the protocol
28			
29			
30		18b	Plans to promote participant retention and complete follow-up,
31			including list of any outcome data to be collected for participants who
32			discontinue or deviate from intervention protocols
33			
34	Data	19	Plans for data entry, coding, security, and storage, including any
35	management		related processes to promote data quality (eg, double data entry;
36			range checks for data values). Reference to where details of data
37			management procedures can be found, if not in the protocol
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40	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
41	methods		Reference to where other details of the statistical analysis plan can be
42			found, if not in the protocol
43			
44			
45		20b	Methods for any additional analyses (eg, subgroup and adjusted
46			analyses)
47			
48		20c	Definition of analysis population relating to protocol non-adherence
49			(eg, as randomised analysis), and any statistical methods to handle
50			missing data (eg, multiple imputation)
51			

Methods: Monitoring

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54	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
55			and reporting structure; statement of whether it is independent from
56			the sponsor and competing interests; and reference to where further
57			details about its charter can be found, if not in the protocol.
58			Alternatively, an explanation of why a DMC is not needed
59			
60			

1		21b	Description of any interim analyses and stopping guidelines, including
2			who will have access to these interim results and make the final
3			decision to terminate the trial
4			
5			
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
7			spontaneously reported adverse events and other unintended effects
8			of trial interventions or trial conduct
9			
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11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
12			whether the process will be independent from investigators and the
13			sponsor
14			

15 Ethics and dissemination

16			
17	Research ethics	24	Plans for seeking research ethics committee/institutional review board
18	approval		(REC/IRB) approval
19			
20			
21	Protocol	25	Plans for communicating important protocol modifications (eg,
22	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
23			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
24			regulators)
25			
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
27			participants or authorised surrogates, and how (see Item 32)
28			
29		26b	Additional consent provisions for collection and use of participant data
30			and biological specimens in ancillary studies, if applicable
31			
32			
33	Confidentiality	27	How personal information about potential and enrolled participants will
34			be collected, shared, and maintained in order to protect confidentiality
35			before, during, and after the trial
36			
37	Declaration of	28	Financial and other competing interests for principal investigators for
38	interests		the overall trial and each study site
39			
40			
41	Access to data	29	Statement of who will have access to the final trial dataset, and
42			disclosure of contractual agreements that limit such access for
43			investigators
44			
45	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
46	post-trial care		compensation to those who suffer harm from trial participation
47			
48	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
49	policy		participants, healthcare professionals, the public, and other relevant
50			groups (eg, via publication, reporting in results databases, or other
51			data sharing arrangements), including any publication restrictions
52			
53			
54		31b	Authorship eligibility guidelines and any intended use of professional
55			writers
56			
57		31c	Plans, if any, for granting public access to the full protocol, participant-
58			level dataset, and statistical code
59			
60			

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
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

*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.

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BMJ Open

Rationale and design of the Lowlands Saves Lives trial: A randomised trial to compare CPR quality and long-term attitude towards CPR performance between face-to-face and virtual reality training with the Lifesaver VR-app

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-033648.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Sep-2019
Complete List of Authors:	Nas, Joris; Radboudumc, Cardiology Thannhauser, Jos; Radboudumc, Cardiology Vart, Priya; Radboudumc, Health Evidence van Geuns, Robert-Jan; Radboudumc, Cardiology van Royen, Niels; Radboudumc, Cardiology Bonnes, Judith; Radboudumc, Cardiology Brouwer, Marc; Radboudumc
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Medical education and training, Emergency medicine
Keywords:	Cardiac arrest, Education, Basic life support, Virtual reality, Cardiopulmonary resuscitation

SCHOLARONE™
Manuscripts

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3 1 **Rationale and design of the Lowlands Saves Lives trial:**
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8 3 **towards CPR performance between face-to-face and virtual reality**
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27
28 12 **Short title:** Design of the Lowlands Saves Lives trial

29
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34 15 **Number of Tables:** 1

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36 16 **Number of Data Supplements:** 2
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1
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7 3

8
9 4 **Keywords:** cardiac arrest, cardiopulmonary resuscitation, virtual reality, basic life support,
10 education
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12 5

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1 **Abstract**

2 **Introduction:** Layperson cardiopulmonary resuscitation (CPR) is a key aspect in the chain of
3 survival after cardiac arrest. New, low cost, easily accessible training methods such as virtual
4 reality (VR)-training with a smartphone application may reach broader populations but data
5 on CPR-performance are scarce.

6 **Methods and analysis:** The Lowlands Saves Lives trial is a prospective randomised open
7 blinded end-point evaluation (PROBE) study, comparing two 20-min CPR training protocols:
8 standardised, certified instructor led face-to-face training complying with current education-
9 guidelines (using Laerdal Little Anne manikins), and VR-training, using the UK-Resuscitation
10 Council endorsed Lifesaver VR app. In the latter, chest compressions are practiced on a
11 pillow.

12 During VR-training, participants learn to resuscitate by completing a filmed CPR-scenario
13 while wearing VR-goggles and headphones. Eligible for inclusion are adult attendees of
14 Lowlands Science, a specific section of the three-day Lowlands music festival (50.000
15 attendees), dedicated exclusively to science. Following the training, all participants will
16 perform a CPR-test on a Laerdal Resusci Anne Q CPR manikin. Primary outcome measures
17 are depth and rate of chest compressions, measured using CPR manikins. The key
18 secondary outcome is overall CPR-performance, with real-time examination (blinded for
19 study group) of all items of a European resuscitation-council endorsed checklist, and
20 evaluation of a sample of video-taped CPR-tests by a blinded event-committee.

21 Given the unique setting of a festival, the primary additional analysis will address the impact
22 of alcohol-levels on CPR-quality parameters and overall performance. Follow-up
23 questionnaires will evaluate the attitude towards performing CPR. This unique study may
24 provide important insights into innovative CPR-training methods, factors that impact CPR-
25 performance, and the impact on long-term attitude towards resuscitation.

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3 1 **Ethics and dissemination:** This study received approval from the research ethics
4
5 2 committee of the Radboudumc. All participants will provide written informed. The results of
6
7 3 this study will be published in peer-reviewed journals and presented at (inter)national
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9 4 conferences.

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12 5 **Registration:** The trial is registered at clinicaltrials.gov (NCT04013633, July 10th 2019).
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1 **Article summary**

2 **Strengths and limitations of this study**

- 4 • The Lowlands Saves Lives trial uses a unique real-world study setting of a Dutch
5 music festival, and is the first randomised trial to compare cardiopulmonary
6 resuscitation (CPR) quality between certified instructor led face-to-face training and
7 Lifesaver virtual reality-training.
- 8 • We will assess clinically relevant CPR quality and performance measures, obtained
9 using objective measurements from CPR manikins and assessors blinded for the
10 intervention, and follow-up will be collected on attitude towards CPR and influencing
11 factors.
- 12 • Due to the nature of the intervention, participant blinding is not possible.
- 13 • The festival setting allows for a unique and relevant prespecified study question, and
14 there will be stratification according to alcohol-levels to assess its impact on CPR
15 quality and overall performance.
- 16 • The results of our study will provide important insights into the efficacy of innovative
17 CPR training methods which may help to improve CPR skills of layperson rescuers,
18 with the ultimate goal of improving outcomes after cardiac arrest.

1 Introduction

2 In Europe, about 300.000 out-of-hospital cardiac arrests (OHCA) occur annually, and despite
3 the achieved improvements in treatment outcome is still dismal.¹⁻³ Early bystander
4 cardiopulmonary resuscitation (CPR) is a key determinant of survival, but is not performed in
5 about 40% of cases.^{1, 4-9} It is therefore essential to create awareness, willingness and
6 capability of lay-volunteers to perform CPR.¹⁰ In this context, leading authorities have
7 identified research on education as one of the top priorities for cardiac arrest research.^{11, 12}

8 Current guidelines state that high-level scientific evidence on the optimal CPR training
9 method is scarce.¹³ Face-to-face CPR training has long been the gold standard, but new
10 technologies have evolved that may hold potential to reach broader populations and provide
11 quick, easily accessible CPR training that can be performed at home, at low costs.¹³⁻¹⁵

12 One of these novel training-methods is virtual reality (VR), a modality with promising potential
13 according to a recent survey among resuscitation-experts.^{13, 16-18} The Lifesaver VR app
14 provides an engaging learning experience, through participation in a filmed CPR scenario.¹⁵
15 This application is endorsed by the UK Resuscitation Council and can be installed for free on
16 smartphones.

17 Apart from improving laypersons' skills, better insight into the attitude towards CPR and
18 factors that may influence the decision to start may affect future bystander CPR rates.^{12, 19, 20}
19 Aspects like fear to do harm, having no experience, or uncertainty about the impact of recent
20 alcohol-levels on CPR performance are everyday issues.^{13, 20}

21 The Lowlands Saves Lives trial is a randomised controlled trial comparing CPR quality and
22 long-term attitude towards CPR between face-to-face and Lifesaver VR app CPR training. It
23 will be conducted in the unique setting of a three-day Dutch music festival (50.000
24 attendees), which will provide a real-world sample of young and outgoing participants.
25 Furthermore, this setting will allow for unique additional analyses, such as the impact of
26 alcohol use and previous CPR training on CPR performance.

1 **Methods and Analysis**

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3 We followed the SPIRIT guidelines in the design of our study protocol.²¹

4

5 **Aim of the study**

6 The primary aim of this study is to compare CPR quality between face-to-face CPR training
7 and training using the Lifesaver VR app.

8

9 **Hypothesis**

10 Our hypothesis is that training with the Lifesaver VR app will result in CPR quality that is non-
11 inferior to CPR quality achieved by face-to-face training.

12

13 **Setting**

14 The present study will be performed during the Lowlands-festival (August 16-18, 2019). This
15 is an annual music-festival in the Netherlands with over 50.000 attendees. This project of the
16 department of Cardiology, Radboudumc, Nijmegen, The Netherlands was selected by a jury
17 to be conducted during Lowlands Science, a section of the festival dedicated exclusively to
18 performing scientific research.²²

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20 **Overview of the study design**

21 The Lowlands Saves Lives trial is a national, prospective randomised open blinded end-point
22 evaluation (PROBE) study.^{23, 24} The study flowchart is depicted in [Figure 1](#).

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24 Participants will be randomly allocated (1:1) to either certified instructor led, face-to-face
25 training, or VR-training with the Lifesaver VR app.¹⁵ As the study will be performed during a
26 musical festival where alcohol consumption is common, and alcohol consumption may
27 impact CPR performance, we will perform an alcohol breathalyzer test in all participants. In
28 case of an alcohol level >0.5‰ (the Dutch legal driving limit), participants will perform a

1 tandem gait test. Participants not able to complete this test will not be randomised, and
2 excluded from the study. Randomization will be stratified according to alcohol level.

3 Directly following the training, all participants will complete a CPR skill test, which will take
4 place in a separate room, with an assessor blinded for the study group. Participants will
5 demonstrate acquired BLS and AED skills during a specifically designed CPR scenario. We
6 will use a certified CPR training manikin to objectively measure chest compression depth and
7 rate (and other parameters, such as flow fraction, leaning etc.). Furthermore, overall CPR
8 performance will be scored with use of a European Resuscitation Council endorsed checklist,
9 with items that focus on the required steps for performing adequate CPR and automated
10 external defibrillator (AED) use ([Supplement 1](#)).¹⁵

11 12 **Participants**

13 Adult (≥ 18 years) attendees of Lowlands Science, a specific section of the Lowlands music
14 festival dedicated exclusively to scientific research. Further in- and exclusion criteria are
15 shown in [Table 1](#). Inclusion of participants with previous CPR training (CPR course ≤ 2 years)
16 is capped at 20% of the total inclusions.¹⁷ Consent to participation includes an alcohol
17 breathalyzer test in all participants (AlcoTrue P®, Bluepoint Medical, Selmsdorf, Germany).
18 In addition, video-recording of the final CPR skill assessment will be performed on an
19 individual basis, in the subset of participants that provide consent.

20 The study will be performed during the entire duration of the festival, which is three full days
21 and inclusion will continue until the end of the festival. Our estimated maximum educational
22 capacity is 480 participants.

23 24 **Randomization and data management**

25 Participants will be randomly allocated (1:1) to either of both training methods using the
26 online CASTOR Electronic Data Capture (CASTOR EDC) system.²⁵ We will use a random
27 block randomization algorithm and stratify randomization according to alcohol level, using a

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3 1 binary cut-off value of <0.5 versus $\geq 0.5\%$. CASTOR EDC will also be used for data
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5 2 management. CASTOR data will be exported for analysis.
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9 4 **Interventions**

11 5 *Face-to-face training:* The training will comprise a 20-min CPR training by an instructor
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13 6 certified by the Dutch Resuscitation Council, who is not part of the study team, and not an
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15 7 employee of the Radboudumc, Nijmegen, The Netherlands. The training protocol is
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17 8 standardised and was designed under supervision of our national BLS course director (HW).
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19 9 The ratio of instructors to participants is 1 to 5. Chest compressions and ventilations will be
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21 10 taught using certified CPR manikins (Little Anne, Laerdal Medical, Stavanger, Norway).
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23 11 These manikins will provide auditory feedback on compression depth. There will be enough
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25 12 manikins for each participant to have their own, but practicing CPR-skills will be done in pairs
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27 13 of two participants. AED use will be demonstrated and practiced with use of Zoll training
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29 14 AEDs (Zoll AED Trainer 3, Zoll Medical, Chelmsford, USA).
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34 16 In line with the recommendations of the European CPR education guidelines, we
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36 17 incorporated the following core-elements into the training: willingness to start CPR,
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38 18 recognition of unconsciousness, good quality chest compressions and feedback during the
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40 19 training.¹³ We will also focus on creating awareness for AED use and benefit, and provide
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42 20 education on common myths on CPR (e.g. the belief that it may cause harm).
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47 22 *Lifesaver VR training:* Lifesaver is an innovative, immersive, and interactive game that can
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49 23 be installed for free on smartphones (<https://lifesavervr.org.uk/>). During VR-training,
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51 24 participants learn to resuscitate by completing a filmed CPR-scenario while wearing VR-
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53 25 goggles and headphones. The completion of this scenario will take approximately 20 min.
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55 26 The novel 'game-in-film' format provides an engaging learning experience with a real life
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57 27 CPR scenario. Users become actively involved with the resuscitation of a victim of cardiac
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59 28 arrest and simulate cardiac compressions by performing compressions on a pillow. The app

1 provides feedback on compression speed, and instructions on compression depth. It also
2 teaches skills needed for adequate AED use. If a wrong decision is made, the user sees the
3 impact but is then able to rewind and make the correct decision. The recently added VR
4 feature allows the users to experience the resuscitation scenario in VR, using VR goggles,
5 further enhancing the experience. For this training, we will use Samsung S7 smartphones
6 (Samsung, Seoul, South Korea), in combination with Zeiss VR One Plus VR-goggles (Carl
7 Zeiss, Oberkochen, Germany) and headphones. . Lifesaver VR endorsed by the
8 Resuscitation Council (UK), has been developed using charitable funds and does not
9 generate financial revenues.¹⁵

10 A graphical impression of the Lifesaver VR set-up is provided in [Figure 2](#).

11

12 **Outcome measures and other parameters**

13 Outcome measures in this study are based on a consensus document describing the
14 preferred outcomes for reporting on CPR quality and on current CPR guidelines.^{10, 26, 27}

15 The primary outcomes are the CPR quality parameters chest compression depth (mm) and
16 compression rate (compressions/min), assessed with the certified CPR manikins (Resusci
17 Anne QCPR, Laerdal Medical, Stavanger, Norway).

18 The key secondary outcome measure is the overall CPR performance expressed as a real-
19 time appointed score by examiners blinded for study group, using the European
20 Resuscitation Council endorsed CPR checklist (Supplement 1). Video recordings of CPR skill
21 tests will be made of the subset of participants that provide consent for this additional study
22 feature. A random sample of all video-recordings will be reviewed by an external event
23 committee, blinded for study group. In addition, we will report on other, secondary CPR-
24 quality parameters such as flow fraction (percentage of time where compressions given) and
25 proportions of chest compressions with full release (as a measure for leaning), assessed with
26 registrations of the certified CPR manikin. Finally, we will calculate proportions of participants
27 meeting guideline CPR quality criteria.^{10, 26, 27}

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3 1 *Other study parameters:* At baseline, all participants will complete a questionnaire after
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5 2 informed consent, with information on e.g. age, sex, weight, education level, previous CPR
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7 3 experience and previous CPR training ([Supplement 2](#)).²⁸ All relevant baseline variables will
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9 4 be reported and compared between both study groups. Follow-up questionnaires after 6
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11 5 months will focus on attitude towards CPR and aspects that influence the decision to start
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13 6 CPR.^{19, 20}

7 **Study organization**

8 Diagram B.V. (Zwolle, The Netherlands) will be responsible for data monitoring and the
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10 9 coordination of the video-evaluations of a sample of CPR-skill tests. All primary outcome
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12 10 measures will be monitored. Baselines and follow-up data will be monitored as well. The
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14 11 review of CPR-skill videos will be conducted by an event committee of two experienced CPR
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16 12 instructors, blinded for study group.

14 **Pre-specified additional analyses**

15 Our primary additional analysis concerns the impact of alcohol on CPR quality parameters
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17 16 and overall performance. In that context, randomization will be stratified according to alcohol
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19 17 levels.

20 The second additional analysis concerns the impact of previous CRP-training on CPR quality
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22 18 and overall performance. To ensure that this project provides sufficient information on the
23
24 19 efficacy of the two training methods for laypersons without CPR training, the number of
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26 20 participants with previous CPR training is capped at 20% of the total of randomizations.
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28 21 Moreover, sample size calculations for the primary study aim were performed to assess the
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30 22 required number of laypersons without CPR training, after which this total was multiplied by
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32 23 1.25 to calculate the total number of participants.

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1 **Exploratory analyses**

2 The following sub-groups were pre-specified for analysis of the respective outcome
3 measures: male versus female, above versus below median age, above versus below
4 median weight, with versus without previous CPR experience, above versus below median
5 education level, and healthcare providers versus no health care providers.

7 **Follow-up assessment**

8 All participants will be asked to provide additional consent for a follow-up questionnaire to be
9 conducted 6 months after finalization of the trial. This questionnaire will contain questions
10 regarding attitude towards the trial and CPR in general, follow-up training and real-life
11 resuscitation experience following participation in the trial.^{19, 20} Data will be analyzed in a
12 similar way as the primary and secondary outcomes: between study groups, according to the
13 pre-specified subgroups, and in exploratory analyses.

15 **Statistical considerations**

16 This study is designed to evaluate the hypothesis that VR-training is non-inferior to instructor-
17 led training. A recent review reported that the expected effect on compression depth of
18 instructor led training is about 5 mm, and that the average effect on compression rate is
19 about 17/min.²⁹ Data on expected differences in CPR performance in relation to alcohol level
20 are unavailable, but to optimally address this question randomization was stratified by
21 alcohol level. To ensure sufficient data on the efficacy of both training methods for
22 laypersons without CPR training we decided that sample size calculations for the primary
23 outcome measure should allow for meaningful conclusions in this group of specific interest.
24 Main outcomes of interest will be tested for non-inferiority. Other variables will be assessed
25 for normal distribution and reported as means (standard deviation) or medians (interquartile
26 range), whichever appropriate. Continuous data will be compared using a student's t-test or
27 Mann-Whitney U test, whichever appropriate. Categorical variables will be reported as
28 numbers (%) and compared using chi-squared or Pearson exact tests, whichever

1 appropriate. All baseline variables (demographics, previous CPR experience) and outcome
2 data (CPR rate and depth, CPR score, flow fraction, leaning etc.) variables will also be
3 compared between the two study groups using the abovementioned tests. In case of
4 confounding variables, we will correct comparisons on the outcome measures between the
5 study groups for these confounders using Analysis of Covariance (ANCOVA). A p-value of
6 <0.05 will be considered statistically significant. Analyses will be performed using SPSS (IBM
7 SPSS version 25, IBM Corp., USA).

9 **Sample size calculation**

10 The present study is designed as non-inferiority trial, where the null hypothesis is that VR-
11 training is inferior to face-to-face training. The non-inferiority margin for depth is set at 5
12 mm²⁹, with an expected standard deviation of 10.^{30, 31} Based on these assumptions and an
13 alpha of 5% and a power of 90% we calculated that we need 69 participants per group.
14 As the inclusion of participants with previous CPR training is capped at 20%, at least 80% of
15 the participants will have no prior CPR training. As we prespecified that sample size
16 calculations should be based on this latter group, the total number per study group will
17 therefore need to be $1.25 \times 69 = 86$. Assuming a drop-out of 10%, we will aim to include 95
18 participants per group, i.e. a total of 190 participants. This sample size will also provide
19 sufficient power for a non-inferiority hypothesis-testing for chest compression rate, given the
20 standard deviation of 20 and average increase in chest compression rate of 17/min found in
21 previous studies.^{29, 31}

23 **Patient and public involvement**

24 No patients were involved in the design of this study protocol. However, we incorporated
25 several elements into our training that were identified by laypersons as important factors for
26 performing CPR and using an AED.²⁰

1 **Ethics and dissemination**

2 The study will be conducted according to the principles of the Declaration of Helsinki and in
3 accordance with the Medical Research Involving Human Subjects act. The research ethics
4 committee of the Radboud University Medical Center has reviewed this study on the basis of
5 the Dutch Code of conduct for health research, the Dutch Code of conduct for responsible
6 use, the Dutch Personal Data Protection Act and the Medical Treatment Agreement Act. The
7 ethics committee has passed a positive judgment on the study. All participants will provide
8 written informed consent before participating in the trial. The results of this study will be
9 published in peer-reviewed journals and presented at national and international conferences.
10 The trial is registered at clinicaltrials.gov (NCT04013633, July 10th 2019).

1 Discussion

2 The Lowlands Saves Lives trial has been initiated as a project to reach a large group of
3 citizens in a short period of time during a Dutch music festival and to stimulate awareness,
4 willingness and capability of laypersons for CPR. Appreciating that in about 40% of the out-
5 of-hospital cardiac arrests bystander CPR is not given, while early start of resuscitation is the
6 key determinant of survival, we wanted to test the efficacy of two innovative training methods
7 on CPR performance and attitude towards resuscitation. In the setting of a randomised trial
8 with PROBE design, we will compare 20-min certified instructor led face-to-face training with
9 20-min virtual reality training using the Resuscitation Council endorsed Lifesaver VR app.

10

11 Layperson CPR

12 Appreciating that the vast majority of cardiac arrests occur at home, it is imperative to
13 increase the rate of layperson initiated CPR as this is expected to markedly improve survival
14 chances.^{8, 9, 32, 33} Several factors affect the decision to actually start CPR, varying from the
15 fear to do harm, to perceived inability due to lack of training, or fear to be contaminated by
16 providing mouth to mouth ventilations.^{19, 20} A previous American Heart Association
17 consensus document on CPR education stated that layperson training should focus on
18 overcoming barriers to initiating CPR.³⁴ It is therefore one of the key aspects during trainings,
19 and the impact of both training methods on the attitude towards CPR will be subject of
20 interest of the follow-up questionnaires.

21 Despite growing interest in CPR training, and the fact that several companies have appointed
22 an in-house emergency service, the vast majority of citizens is not currently trained in CPR.³⁵
23 European documentation on BLS-training for instructors (Cosy) states that BLS-courses
24 should be at least two hours. In the Dutch setting, current conventional certified training
25 programs last about four hours, which may pose a logistic and sometimes financial burden to
26 partake in these programs.

27 Programs with a lower threshold to participate, preferably of shorter duration, may reach a

1 broader population. Previous work has shown that a 30-min training yields similar results as
2 a conventional training.³⁰ In addition, a modality that allows for easy, repetitive training may
3 not only appeal to a larger target population, but it may also facilitate a more sustained CPR
4 quality. Several studies have shown that short booster trainings improve CPR performance
5 and the guidelines place increasing emphasis on high-frequency, short, booster training for
6 certified BLS-providers.^{36, 37} This may facilitate improved skill-retainment, a major topic in
7 current CPR (education) guidelines.^{13, 14}

8 The accessibility of Lifesaver VR, its low cost, and the possibility to perform it at convenient
9 moments, at home, could be advantageous and useful for laypersons that experience a
10 threshold to participate in face-to-face training. However, information on CPR quality data is
11 limited, and we are the first to assess the Lifesaver app in combination with a VR modality.

13 **Training methods and outcome measures**

14 We will compare 20-min face-to-face training by a certified BLS-instructor with 20-min virtual
15 reality training with the Lifesaver app. The instructors will provide a standardised training,
16 developed with our national course director BLS. Outcomes achieved with the Lifesaver VR
17 app will be tested in the setting of a non-inferiority design.

18 Our primary outcomes are in concordance with current international CPR guidelines. Both
19 chest compression depth and compression rate have repeatedly been associated with
20 survival after cardiac arrest.^{10, 26} Moreover, both outcome measures can be objectively
21 assessed with the output of the certified manikins.

22 A recent review on the impact of training demonstrated that instructor-led training results in
23 about 5 mm additional chest compression depth.²⁹ This is what we defined as the non-
24 inferiority margin for this primary outcome measure, with a required total of 190 participants.
25 This total is also sufficient to address non-inferiority for the number of chest compressions
26 per minute. As instructor-led training is reported to result in about an additional 17
27 compressions/minute, this was set as non-inferiority margin for this primary outcome
28 measure.

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3 1 The key secondary outcome measure is overall CPR performance. This is an integrative
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5 2 score, appointed real-time, by an assessor blinded for study groups. It reflects the entire
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7 3 CPR process, including alerting 112 and the ability to use the AED, and the score is
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9 4 assessed with use of a checklist endorsed by the European Resuscitation Council. In
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11 5 addition, a blinded event committee will review a sample of the CPR skill tests registered on
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13 6 video in participants that provided additional consent.

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15 7 In addition, we prespecified important additional analyses and incorporated specific elements
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17 8 in the design of our study to ensure that these questions could be adequately addressed.

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19 9 First, the goal of recruiting more laypersons to perform CPR may result in situations where
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21 10 CPR is required while someone has consumed alcohol in a restaurant or bar, which is often
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23 11 a controversial issue in case medical help is required.^{38, 39} The unique setting of a music
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25 12 festival provides a setting to further explore this issue. In this context, randomization was
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27 13 stratified according to alcohol level, including a group with a level higher and lower than
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29 14 0.5‰, the Dutch legal driving limit.

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31 15 Second, lack of CPR training is often mentioned as a reason not to perform CPR.²⁰ Data on
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33 16 how much previous CPR-training affects CPR quality and overall CPR performance is
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35 17 limited, and we therefore aim to objectify this issue. This may help to provide better quality
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37 18 evidence to address these concerns.

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42 43 20 **Follow-up**

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45 21 With use of follow-up questionnaires we will gather and compare information on the attitude
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47 22 towards CPR between both training methods. In addition, we will try and identify factors that
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49 23 may influence the decision to initiate bystander CPR. The Lowlands Saves Lives trial not
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51 24 only focuses on the training itself, but on an entire experience: banners with links to the
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53 25 Dutch Heart Foundation (www.hartstichting.nl) providing additional information on
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55 26 resuscitation, and addresses for endorsed BLS-AED courses.

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59 60 28 **Implications**

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3 1 In a setting of a renowned Dutch music festival with about 50.000 attendees, our study is
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5 2 expected to contribute to increased awareness for resuscitation, and may result in about
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7 3 200-400 trained citizens. In addition, it will address a key topic in current resuscitation
8
9 4 research, i.e. the search towards to optimal CPR training method, and it will be the first to
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11 5 study the Lifesaver app with a virtual reality modality.
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13 6 Until now, the only data available for the Lifesaver app have been obtained in children, at
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15 7 that time without a VR feature. Results were promising, although compression depth seemed
16
17 8 suboptimal. Whether this is related to the low body weight of the children, or a consequence
18
19 9 of the training method is uncertain. The VR modality may enhance the experience, and
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21 10 mimicking a situation that is closer to the real-life setting may contribute to better results.
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23 11 Globally, increasing the rate of bystander CPR is anticipated to be one of the key factors to
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25 12 improve survival after cardiac arrest. In the Netherlands, campaigns stress the importance to
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27 13 initiate CPR within 6 minutes of the arrest, given the much higher chances of survival within
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29 14 this interval. All efforts are made to create a national network, that consists of citizens with an
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31 15 official BLS-AED certificate that subscribe to a national text message based alert system
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33 16 combined with a registration system of AEDs.⁴⁰⁻⁴² The goal is to achieve a coverage that
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35 17 ensures a 6 minute response in all parts of the Netherlands. European guidelines also stress
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37 18 the importance of early bystander response.¹⁰
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43 **Potential limitations**

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45 21 In the present study, no data will be available on CPR-performance prior to the training.
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47 22 Second, due to the lack of follow-up skill testing no data are available on CPR skill retention.
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49 23 We will include a maximum of 20% of participants with previous CPR experience, which may
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51 24 impact the overall skill-performance in both study groups. However, the group of participants
52
53 25 without previous CPR-training comprises a subgroup of special interest, and our target
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55 26 sample size allows for adequate statistical power to perform analyses on the primary
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57 27 outcome measure in these participants. Due to the specific study setting, our study sample
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59 28 may be unique when compared to other studies on this topic, which may limit generalizability
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1 of our results to for example elderly civilians.

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3 **Conclusion**

4 The Lowlands Saves Lives trial will create awareness for the importance of bystander CPR,
5 and aims to increase willingness and capability to participate in CPR. If an easily available,
6 low cost app can result in similar CPR results as instructor-led training this may be an
7 important step towards reaching this goal.

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For peer review only

1 **Declarations**

2

3 **Competing interests**

4 NVR received research grants from Abbott, Biotronik, AstraZeneca and Philips, and
5 professional fees from Abbott, Microport, Amgen and Medtronic. The other authors have no
6 conflicts of interest to declare.

7

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9 This research received no specific grant from any funding agency in the public, commercial
10 or not-for-profit sectors

11

12 **Author contributions**

13 JN, JT, JLB and MAB conceived the idea. Study methodology was designed by JN, JLB, JT,
14 RVG, NVR and MB. JN, PV and MAB designed the statistical analyses. JN, JLB, JT and
15 MAB drafted the manuscript. PV, RVG and NVR provided critical revisions and substantial
16 intellectual input. All authors agreed with the final version of the manuscript. JN takes full
17 responsibility for integrity of the presented content.

18

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24

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3 **1 Tables**
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5 **2 Table 1 – In- and exclusion criteria of the Lowlands Saves Lives trial**
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Inclusion criteria of the Lowlands Saves Lives trial	
1	Adult (≥ 18 years) Lowlands attendees
2	Provide informed consent
Exclusion criteria of the Lowlands Saves Lives trial	
1	Alcohol level $>0.5\%$ and not able to complete tandem gait test.
2	For any reason not being able to partake in the face-to-face or VR-app training (e.g. physical impairment).
3	For any reason not being able to perform the CPR test on the CPR manikin (e.g. physical impairment).

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27 **3**

28 *In- and exclusion criteria of the Lowlands Saves Lives trial. VR: Virtual reality; CPR:*

29 *Cardiopulmonary resuscitation*
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3 **1 Figure Legends**
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7 **3 Figure 1 – Study flowchart of the Lowlands Saves Lives trial**
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11 *Study flowchart of the Lowlands Saves Lives trial. VR: Virtual reality; CPR: Cardiopulmonary*
12 *resuscitation.*
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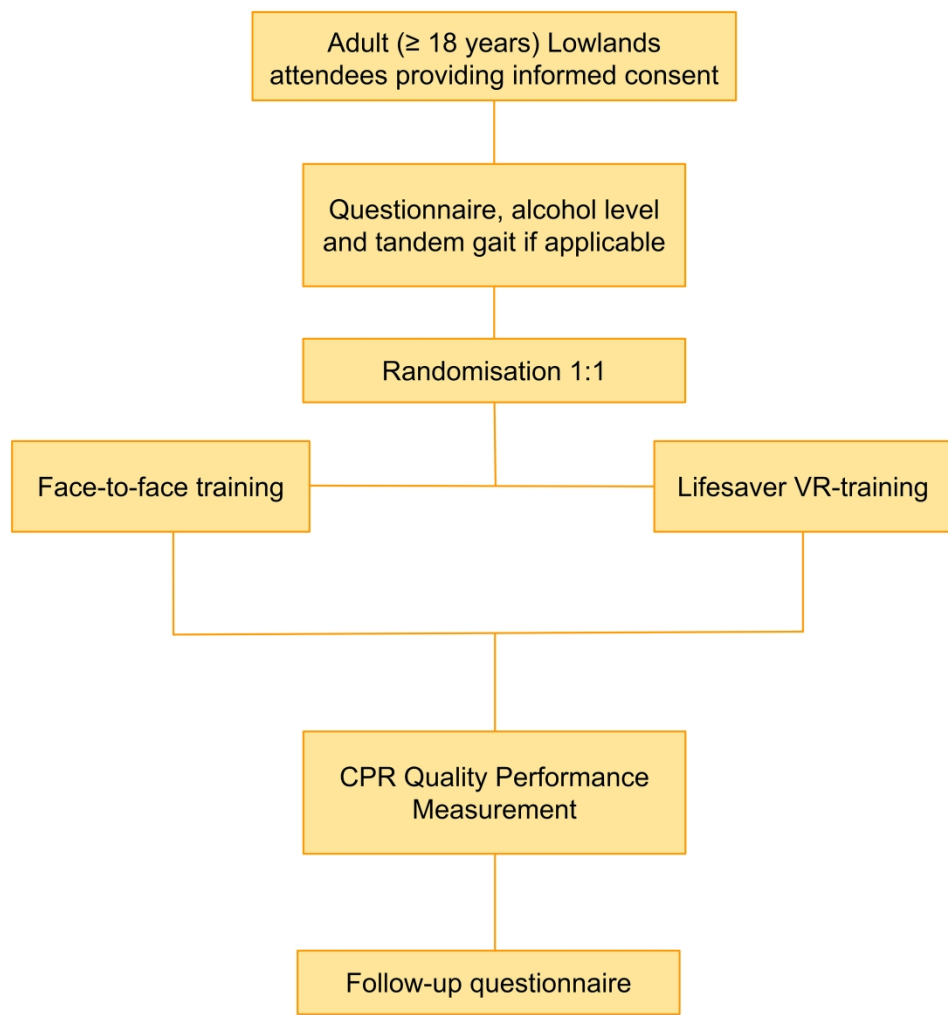
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20 **9 Figure 2 – Lifesaver VR app**
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24 *Demonstration of the Lifesaver VR set-up, using headphones, VR goggles and a pillow to*
25 *perform chest compressions. VR: Virtual reality*
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Study flowchart of the Lowlands Saves Lives trial. VR: Virtual reality; CPR: Cardiopulmonary resuscitation.

299x310mm (300 x 300 DPI)



Demonstration of the Lifesaver VR set-up, using headphones, VR goggles and a pillow to perform chest compressions. VR: Virtual reality

199x250mm (300 x 300 DPI)

Supplement 1 – CPR-skill assessment test

(European Resuscitation Council CPR/AED course assessment document)



2016.V2

BLS assessment record

Candidate Name:

Date:

Instructor:

Skill	The candidate	Achieved		Comments
		Yes	No	
Check response	Demonstrates gently shaking and shouting to establish responsiveness			
Assess breathing	Demonstrates head tilt and chin lift			
Assess breathing	Demonstrates look, listen and feel for normal breathing for no more than 10 sec (does not count aloud)			
Call emergency services (Get help)	Describes how to phone for emergency services: 112, unresponsive and non-breathing victim, AED			
Chest compressions	Demonstrates effective chest compressions; rate 100-120/min, depth 5-6 cm; hand position: centre of the chest. Minimises interruptions in chest compressions			
Rescue breaths	Demonstrates rescue breaths sufficient to cause the chest to rise and fall			
Compression : ventilation ratio	Demonstrates ratio of 30 compressions to 2 ventilations			
Activate AED	Switch the AED on or, if a helper is present, ask him/her to do it			
Attach pads	Demonstrates attaching pads in correct position			
Stand clear	Allows rhythm analysis whilst making sure that nobody touches the victim (including visual sweep and verbal instruction)			
Deliver shock	Demonstrates rapid and safe delivery of a shock (including visual sweep and verbal instruction to stand clear)			
Follow AED instructions	Demonstrates listening to and executing AED instructions			
CPR	Minimises interruptions in chest compressions and demonstrates correct sequence in ratio of 30 compressions to 2 ventilations			

CPR: Cardiopulmonary resuscitation; AED: Automated external defibrillator.

Supplement 2 – Questionnaire for study participants

Study number & instructor (to be completed by investigator)		
E-mail address*		
Sex	<input type="radio"/> Female <input type="radio"/> Male <input type="radio"/> Do not wish to disclose	
Age		
Weight		
Highest level of education	<input type="radio"/> Primary education <input type="radio"/> Secondary education <input type="radio"/> Short cycle tertiary education <input type="radio"/> Bachelor or equivalent <input type="radio"/> Master or equivalent	
Healthcare professional	<input type="radio"/> Yes <input type="radio"/> No	
Have you used any drugs/narcotics in the past 24 hours, besides alcohol?	<input type="radio"/> Yes, which: <input type="radio"/> No <input type="radio"/> Do not wish to disclose	
<i>Previous CPR experience</i>		
CPR course	<input type="radio"/> No <input type="radio"/> Yes, which level <input type="radio"/> BLS <input type="radio"/> BLS+AED <input type="radio"/> ALS <input type="radio"/> Other: Date last course:	
Witnessed a cardiac arrest	<input type="radio"/> No <input type="radio"/> Yes, ... times <input type="radio"/> Only as a witness <input type="radio"/> CPR performed as bystander/layperson <input type="radio"/> CPR performed as healthcare professional	
The victim was	<input type="radio"/> A stranger <input type="radio"/> A relative or other acquaintance	

* If you want to be approached for a follow-up study or receive the information digitally

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For peer review only



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

Section/item	Item No	Description	Page
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	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	N/A
	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)	1
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	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7
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)	7

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	7
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	10
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)	Figure 1 12
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	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8

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	8
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1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	N/A
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	8
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	7
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
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15		17b	If blinded, circumstances under which unblinding is permissible, and	N/A
16			procedure for revealing a participant's allocated intervention during	
17			the trial	
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Methods: Data collection, management, and analysis

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22	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	10
23	methods		trial data, including any related processes to promote data quality (eg,	
24			duplicate measurements, training of assessors) and a description of	
25			study instruments (eg, questionnaires, laboratory tests) along with	
26			their reliability and validity, if known. Reference to where data	
27			collection forms can be found, if not in the protocol	
28				
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30		18b	Plans to promote participant retention and complete follow-up,	N/A
31			including list of any outcome data to be collected for participants who	
32			discontinue or deviate from intervention protocols	
33				
34	Data	19	Plans for data entry, coding, security, and storage, including any	11
35	management		related processes to promote data quality (eg, double data entry;	
36			range checks for data values). Reference to where details of data	
37			management procedures can be found, if not in the protocol	
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40	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	12
41	methods		Reference to where other details of the statistical analysis plan can be	
42			found, if not in the protocol	
43				
44		20b	Methods for any additional analyses (eg, subgroup and adjusted	12
45			analyses)	
46				
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48		20c	Definition of analysis population relating to protocol non-adherence	N/A
49			(eg, as randomised analysis), and any statistical methods to handle	
50			missing data (eg, multiple imputation)	
51				

Methods: Monitoring

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54	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	1
55			and reporting structure; statement of whether it is independent from	11
56			the sponsor and competing interests; and reference to where further	
57			details about its charter can be found, if not in the protocol.	
58			Alternatively, an explanation of why a DMC is not needed	
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2		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	N/A
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6	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	N/A
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11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
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Ethics and dissemination

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17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
18				
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20				
21	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)	N/A
22				
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25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
27				
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30		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10 12
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33	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	14
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37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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41	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	N/A
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45	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	N/A
46				
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48	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	14
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54		31b	Authorship eligibility guidelines and any intended use of professional writers	20
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57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	N/A

*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.

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