BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033648
Article Type:	Protocol
Date Submitted by the Author:	21-Aug-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
Keywords:	Cardiac arrest, Education, Basic life support, Virtual reality, Cardiopulmonary resuscitation

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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Short title: Design of the Lowlands Saves Lives trial

Total word count: Abstract: 300; Paper: 3562 (excluding references)

Number of Figures: 2

Number of Tables: 1

Number of Data Supplements: 2

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Funding: None

Conflicts of interest: Prof. van Royen has conflicts of interest to declare, see page 14

Keywords: cardiac arrest, cardiopulmonary resuscitation, virtual reality, basic life support, education

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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

this study will be published in peer-reviewed journals and presented at national and international conferences.

Registration: The trial is registered at clinicaltrials.gov (NCT04013633, July 10th 2019).

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

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

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

Participants

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

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

Randomization and data management

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

binary cut-off value of <0.5 versus ≥0.5‰. CASTOR EDC will also be used for data management. CASTOR data will be exported for analysis.

Interventions

Face-to-face training: The training will comprise a 20-min CPR training by an instructor certified by the Dutch Resuscitation Council, who is not part of the study team, and not an employee of the Radboudumc, Nijmegen, The Netherlands. The training protocol is standardized and was designed under supervision of our national BLS course director (HW). The ratio of instructors to participants is 1 to 5. Chest compressions and ventilations will be taught using certified CPR manikins (Little Anne, Laerdal Medical, Stavanger, Norway). AED use will be demonstrated and practiced with use of Zoll training AEDs (Zoll AED Trainer 3, Zoll Medical, Chelmsford, USA).

In line with the recommendations of the European CPR education guidelines, we incorporated the following core-elements into the training: willingness to start CPR, recognition of unconsciousness, good quality chest compressions and feedback during the training.[13] We will also focus on creating awareness for AED use and benefit, and provide education on common myths on CPR (e.g. the belief that it may cause harm).

Lifesaver VR training: All participants will complete the same CPR scenario using the Lifesaver VR app (https://lifesavervr.org.uk/). The completion of this scenario will take approximately 20 min. Lifesaver VR endorsed by the Resuscitation Council (UK), has been developed using charitable funds and does not generate financial revenues.[15] Lifesaver is an innovative, immersive, and interactive game that can be installed for free on smartphones. The novel 'game-in-film' format provides an engaging learning experience with a real life CPR scenario. Users become actively involved with the resuscitation of a victim of cardiac arrest and simulate cardiac compressions by performing compressions on a pillow. The app provides feedback on compression speed, and instructions on compression depth. It also

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

A graphical impression of the Lifesaver VR set-up is provided in Figure 2.

Outcome measures and other parameters

Outcome measures in this study are based on a consensus document describing the preferred outcomes for reporting on CPR quality and on current CPR guidelines.[10, 26, 27]

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

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

Other study parameters: At baseline, all participants will complete a questionnaire after informed consent, with information on e.g. age, sex, weight, education level, previous CPR experience and previous CPR training (Supplement 2). Follow-up questionnaires after 1 year 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

considered statistically significant. Analyses will be performed using SPSS (IBM SPSS version 25, IBM Corp., USA).

Sample size calculation

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

Patient and public involvement

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

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

not only appeal to a larger target population, but it may also ensure a more sustained CPR quality. Several studies have shown that short booster trainings improve CPR performance and the guidelines place increasing emphasis on high-frequency, short, booster training for certified BLS-providers.[34, 35] This may facilitate improved skill-retainment, a major topic in current CPR (education) guidelines.[13, 14]

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

Training methods and outcome measures

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

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

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

The key secondary outcome measure is overall CPR performance. This is an integrative score, appointed real-time, by an assessor blinded for study groups. It reflects the entire CPR process, including alerting 112 and the ability to use the AED, and the score is

assessed with use of a checklist endorsed by the European Resuscitation Council. In addition, a blinded event committee will review a sample of the CPR skill tests registered on video in participants that provided additional consent.

In addition, we prespecified important additional analyses and incorporated specific elements in the design of our study to ensure that these questions could be adequately addressed. First, the goal of recruiting more laypersons to perform CPR may result in situations where CPR is required while someone has consumed alcohol in a restaurant or bar, which is often a controversial issue in case medical help is required.[36, 37] The unique setting of a music festival provides a setting to further explore this issue. In this context, randomization was stratified according to alcohol level, including a group with a level higher and lower than 0.5‰, the Dutch legal driving limit.

Second, lack of CPR training is often mentioned as a reason not to perform CPR.[20] Data on how much this affects CPR quality and overall CPR performance is limited, and we therefore aim to objectify this issue. This may help to provide better quality evidence to address these concerns.

Follow-up

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

Implications

In a setting of a renowned Dutch music festival with about 50.000 attendees, our study is expected to contribute to increased awareness for resuscitation, and may result in about 200-400 trained citizens. In addition, it will address a key topic in current resuscitation

research, i.e. the search towards to optimal CPR training method, and it will be the first to study the Lifesaver app with a virtual reality modality.

Until now, the only data available for the Lifesaver app have been obtained in children, at that time without a VR feature. Results were promising, although compression depth seemed suboptimal. Whether this is related to the low body weight of the children, or a consequence of the training method is uncertain. The VR modality may enhance the experience, and mimicking a situation that is closer to the real-life setting may contribute to better results.

Globally, increasing the rate of bystander CPR is anticipated to be one of the key factors to improve survival after cardiac arrest. In the Netherlands, campaigns stress the importance to initiate CPR within 6 minutes of the arrest, given the much higher chances of survival within this interval. All efforts are made to create a national network, that consists of citizens with an official BLS-AED certificate that subscribe to a national text message based alert system combined with a registration system of AEDs.[38-40] The goal is to achieve a coverage that ensures a 6 minute response in all parts of the Netherlands.

Conclusion

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

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.

Funding

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

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.

Acknowledgements

We would like to thank Lowlands Science for providing the opportunity to perform this study at their event. We would like to thank Helma Weijenberg for her help with designing the training protocol. We would like to thanks Laerdal, Zoll, Zeiss and Samsung for providing the study materials. These parties were not in any way involved in the design of the trial.

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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

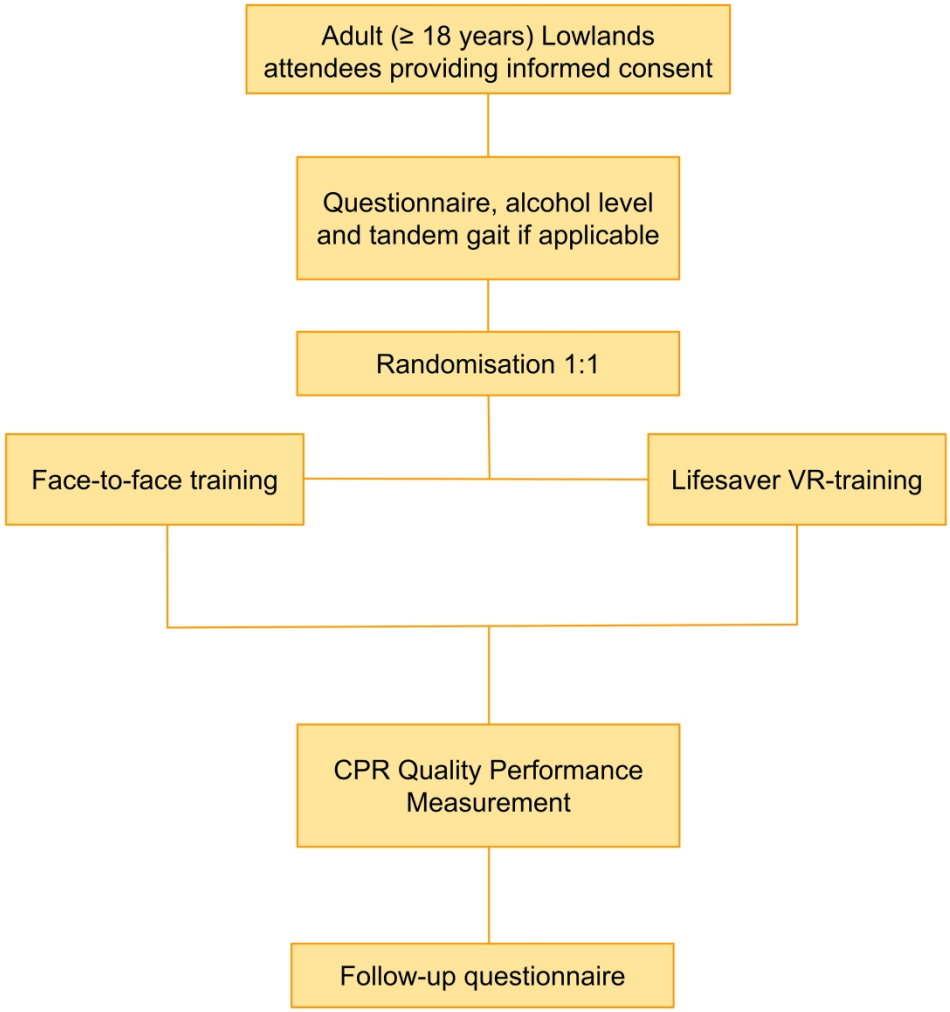
Figure Legends

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.

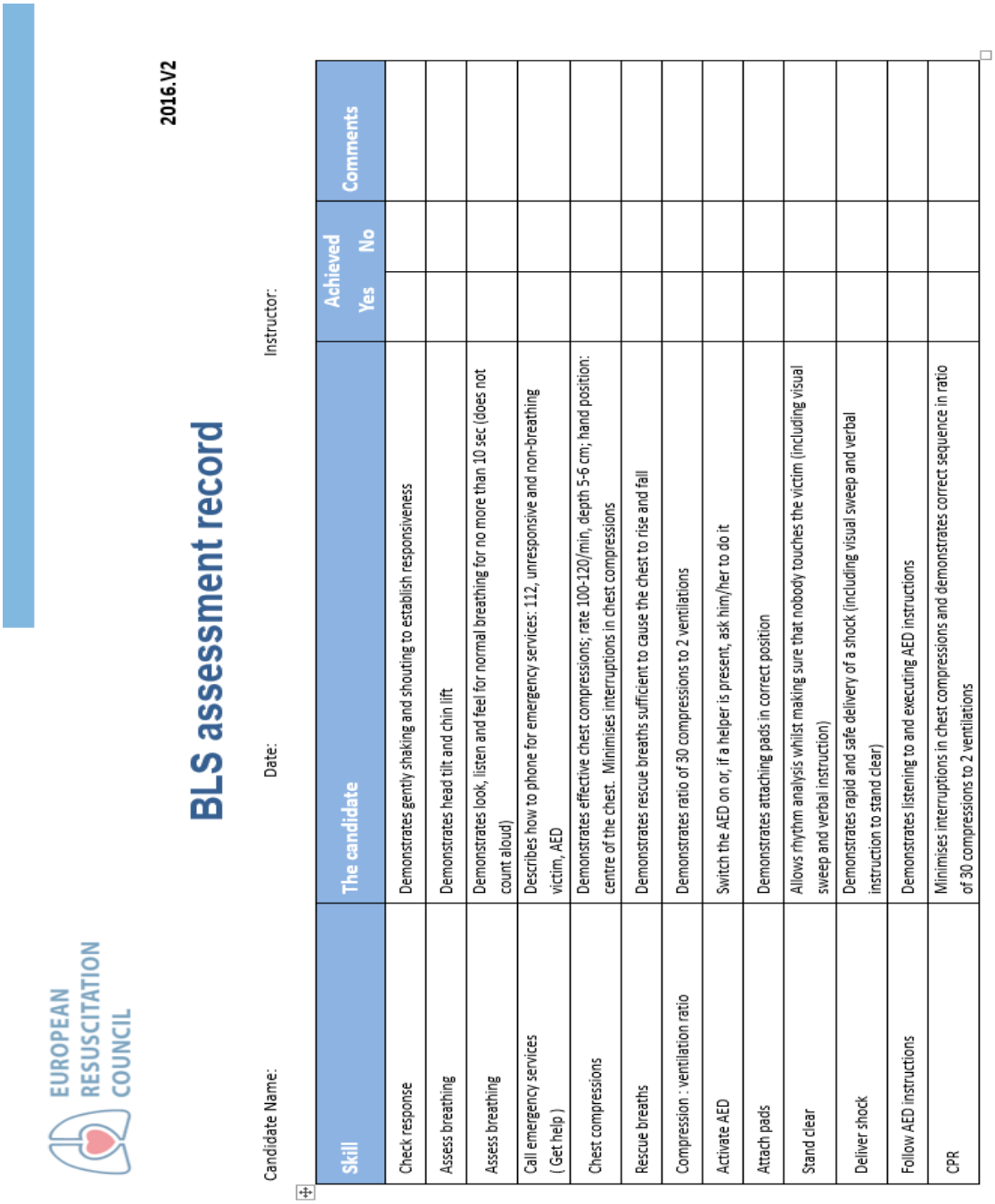
299x310mm (300 x 300 DPI)

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)



EUROPEAN RESUSCITATION COUNCIL

2016.V2

BLS assessment record

Candidate Name: Date: Instructor:

Skill	The candidate	Achieved Yes	Achieved No	Comments
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	O Female O Male O Do not wish to disclose	
Age		
Weight		
Highest level of education	O Primary education O Secondary education O Short cycle tertiary education O Bachelor or equivalent O Master or equivalent	
Healthcare professional	O Yes O No	
Have you used any drugs/narcotics in the past 24 hours, besides alcohol?	O Yes, which: O No O Do not wish to disclose	
Previous CPR experience		
CPR course	O No O Yes, which level O BLS O BLS+AED O ALS O Other: Date last course:	
Witnessed a cardiac arrest	O No O Yes, ... times O Only as a witness O CPR performed as bystander/layperson O CPR performed as healthcare professional	
The victim was	O A stranger O A relative or other acquaintance	

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

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

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
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)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

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.

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:	*BMJ Open*
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

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

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Short title: Design of the Lowlands Saves Lives trial

Total word count: Abstract: 300; Paper: 3562 (excluding references)

Number of Figures: 2

Number of Tables: 1

Number of Data Supplements: 2

Scientific committee: Lars Wik MD PhD (Oslo University Hospital, Oslo, Norway) and Giuseppe Ristagno MD PhD (Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy)

Event committee: Reinier Waalewijn MD PhD (National course director advanced life support, Gelre Hospital, Apeldoorn, the Netherlands) and Wiebe de Vries PhD (University of Applied Sciences Leiden, Leiden, The Netherlands,, The Netherlands)

Funding: None

Conflicts of interest: Prof. van Royen has conflicts of interest to declare, see page 14

Keywords: cardiac arrest, cardiopulmonary resuscitation, virtual reality, basic life support, education

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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 prospective randomised open blinded end-point evaluation (PROBE) study, comparing two 20-min CPR training protocols: standardised, certified instructor led face-to-face training complying with current education-guidelines (using Laerdal Little Anne manikins), and VR-training, using the UK-Resuscitation Council endorsed Lifesaver VR app. In the latter, chest compressions are practiced on a pillow.

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 Laerdal Resusci Anne QCPR 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-levels 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 this study will be published in peer-reviewed journals and presented at (inter)national conferences.

Registration: The trial is registered at clinicaltrials.gov (NCT04013633, July 10th 2019).

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 randomised 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 and performance 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-levels 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-levels on CPR performance are everyday issues.[13, 20]

The Lowlands Saves Lives trial is a randomised 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 randomised 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

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

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

Participants

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

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

Randomization and data management

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

binary cut-off value of <0.5 versus ≥0.5‰. CASTOR EDC will also be used for data management. CASTOR data will be exported for analysis.

Interventions

Face-to-face training: The training will comprise a 20-min CPR training by an instructor certified by the Dutch Resuscitation Council, who is not part of the study team, and not an employee of the Radboudumc, Nijmegen, The Netherlands. The training protocol is standardised and was designed under supervision of our national BLS course director (HW). The ratio of instructors to participants is 1 to 5. Chest compressions and ventilations will be taught using certified CPR manikins (Little Anne, Laerdal Medical, Stavanger, Norway). These manikins will provide auditory feedback on compression depth. There will be enough manikins for each participant to have their own, but practicing CPR-skills will be done in pairs of two participants. AED use will be demonstrated and practiced with use of Zoll training AEDs (Zoll AED Trainer 3, Zoll Medical, Chelmsford, USA).

In line with the recommendations of the European CPR education guidelines, we incorporated the following core-elements into the training: willingness to start CPR, recognition of unconsciousness, good quality chest compressions and feedback during the training.[13] We will also focus on creating awareness for AED use and benefit, and provide education on common myths on CPR (e.g. the belief that it may cause harm).

Lifesaver VR training: Lifesaver is an innovative, immersive, and interactive game that can be installed for free on smartphones (https://lifesavervr.org.uk/). During VR-training, participants learn to resuscitate by completing a filmed CPR-scenario while wearing VR-goggles and headphones. The completion of this scenario will take approximately 20 min. The novel 'game-in-film' format provides an engaging learning experience with a real life CPR scenario. Users become actively involved with the resuscitation of a victim of cardiac arrest and simulate cardiac compressions by performing compressions on a pillow. The app

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

A graphical impression of the Lifesaver VR set-up is provided in Figure 2.

Outcome measures and other parameters

Outcome measures in this study are based on a consensus document describing the preferred outcomes for reporting on CPR quality and on current CPR guidelines.[10, 26, 27]

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

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

Other study parameters: At baseline, all participants will complete a questionnaire after informed consent, with information on e.g. age, sex, weight, education level, previous CPR experience and previous CPR training (Supplement 2).[28] All relevant baseline variables will be reported and compared between both study groups. Follow-up questionnaires after 6 months 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. All primary outcome measures will be monitored. Baselines and follow-up data will be monitored as well. 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 respective outcome measures: 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 6 months 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.[29] 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 outcome measure 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, leaning etc.) 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 considered statistically significant. Analyses will be performed using SPSS (IBM SPSS version 25, IBM Corp., USA).

Sample size calculation

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

Patient and public involvement

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

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 randomised 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, 32, 33] 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 ventilations.[19, 20] A previous American Heart Association consensus document on CPR education stated that layperson training should focus on overcoming barriers to initiating CPR.[34] 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 is not currently trained in CPR.[35] European documentation on BLS-training for instructors (Cosy) states that BLS-courses should be at least two hours. In the Dutch setting, current conventional certified training programs last about four hours, which may pose 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.[30] In addition, a modality that allows for easy, repetitive training may not only appeal to a larger target population, but it may also facilitate a more sustained CPR quality. Several studies have shown that short booster trainings improve CPR performance and the guidelines place increasing emphasis on high-frequency, short, booster training for certified BLS-providers.[36, 37] This may facilitate improved skill-retainment, a major topic in current CPR (education) guidelines.[13, 14]

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

Training methods and outcome measures

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

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

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

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

In addition, we prespecified important additional analyses and incorporated specific elements in the design of our study to ensure that these questions could be adequately addressed. First, the goal of recruiting more laypersons to perform CPR may result in situations where CPR is required while someone has consumed alcohol in a restaurant or bar, which is often a controversial issue in case medical help is required.[38, 39] The unique setting of a music festival provides a setting to further explore this issue. In this context, randomization was stratified according to alcohol level, including a group with a level higher and lower than 0.5‰, the Dutch legal driving limit.

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

Follow-up

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

Implications

In a setting of a renowned Dutch music festival with about 50.000 attendees, our study is expected to contribute to increased awareness for resuscitation, and may result in about 200-400 trained citizens. In addition, it will address a key topic in current resuscitation research, i.e. the search towards to optimal CPR training method, and it will be the first to study the Lifesaver app with a virtual reality modality.

Until now, the only data available for the Lifesaver app have been obtained in children, at that time without a VR feature. Results were promising, although compression depth seemed suboptimal. Whether this is related to the low body weight of the children, or a consequence of the training method is uncertain. The VR modality may enhance the experience, and mimicking a situation that is closer to the real-life setting may contribute to better results.

Globally, increasing the rate of bystander CPR is anticipated to be one of the key factors to improve survival after cardiac arrest. In the Netherlands, campaigns stress the importance to initiate CPR within 6 minutes of the arrest, given the much higher chances of survival within this interval. All efforts are made to create a national network, that consists of citizens with an official BLS-AED certificate that subscribe to a national text message based alert system combined with a registration system of AEDs.[40-42] The goal is to achieve a coverage that ensures a 6 minute response in all parts of the Netherlands. European guidelines also stress the importance of early bystander response.[10]

Potential limitations

In the present study, no data will be available on CPR-performance prior to the training. Second, due to the lack of follow-up skill testing no data are available on CPR skill retention. We will include a maximum of 20% of participants with previous CPR experience, which may impact the overall skill-performance in both study groups. However, the group of participants without previous CPR-training comprises a subgroup of special interest, and our target sample size allows for adequate statistical power to perform analyses on the primary outcome measure in these participants. Due to the specific study setting, our study sample may be unique when compared to other studies on this topic, which may limit generalizability

of our results to for example elderly civilians.

Conclusion

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

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.

Funding

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

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.

Acknowledgements

We would like to thank Lowlands Science for providing the opportunity to perform this study at their event. We would like to thank Helma Weijenberg for her help with designing the training protocol. We would like to thanks Laerdal, Zoll, Zeiss and Samsung for providing the study materials. These parties were not in any way involved in the design of the trial.

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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

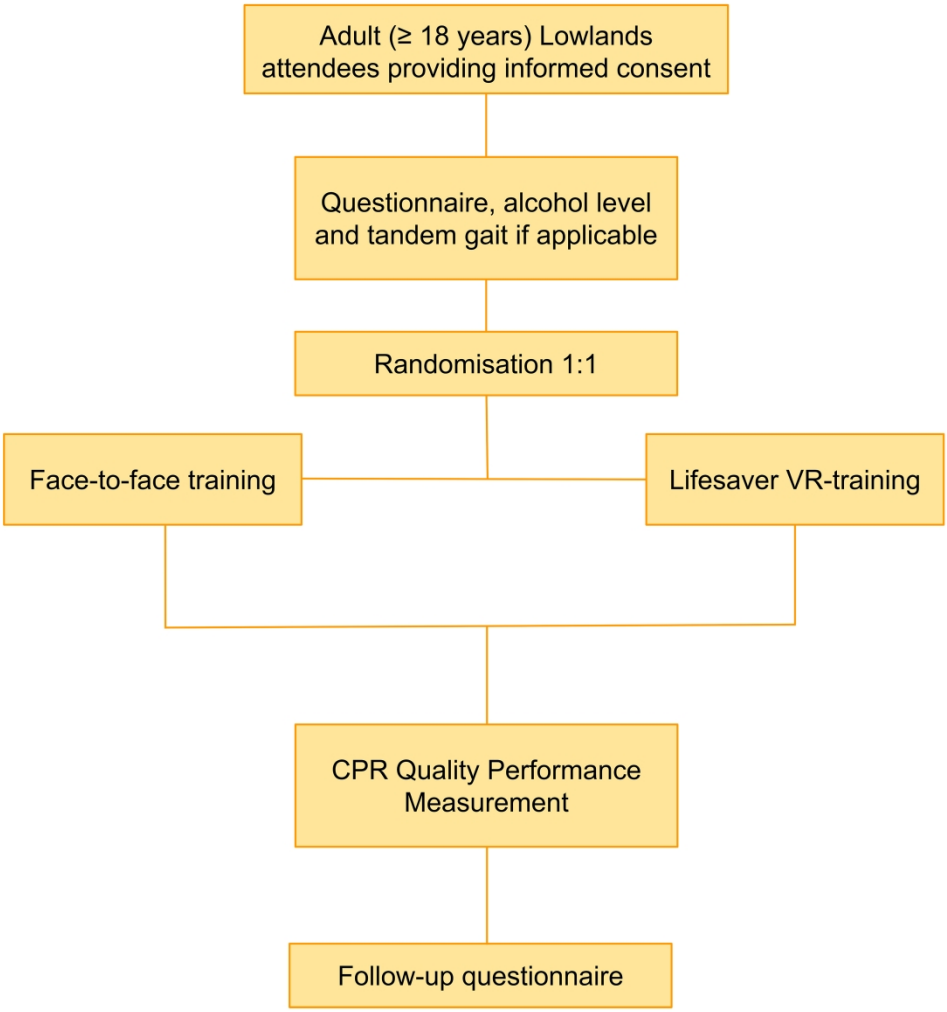
Figure Legends

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.

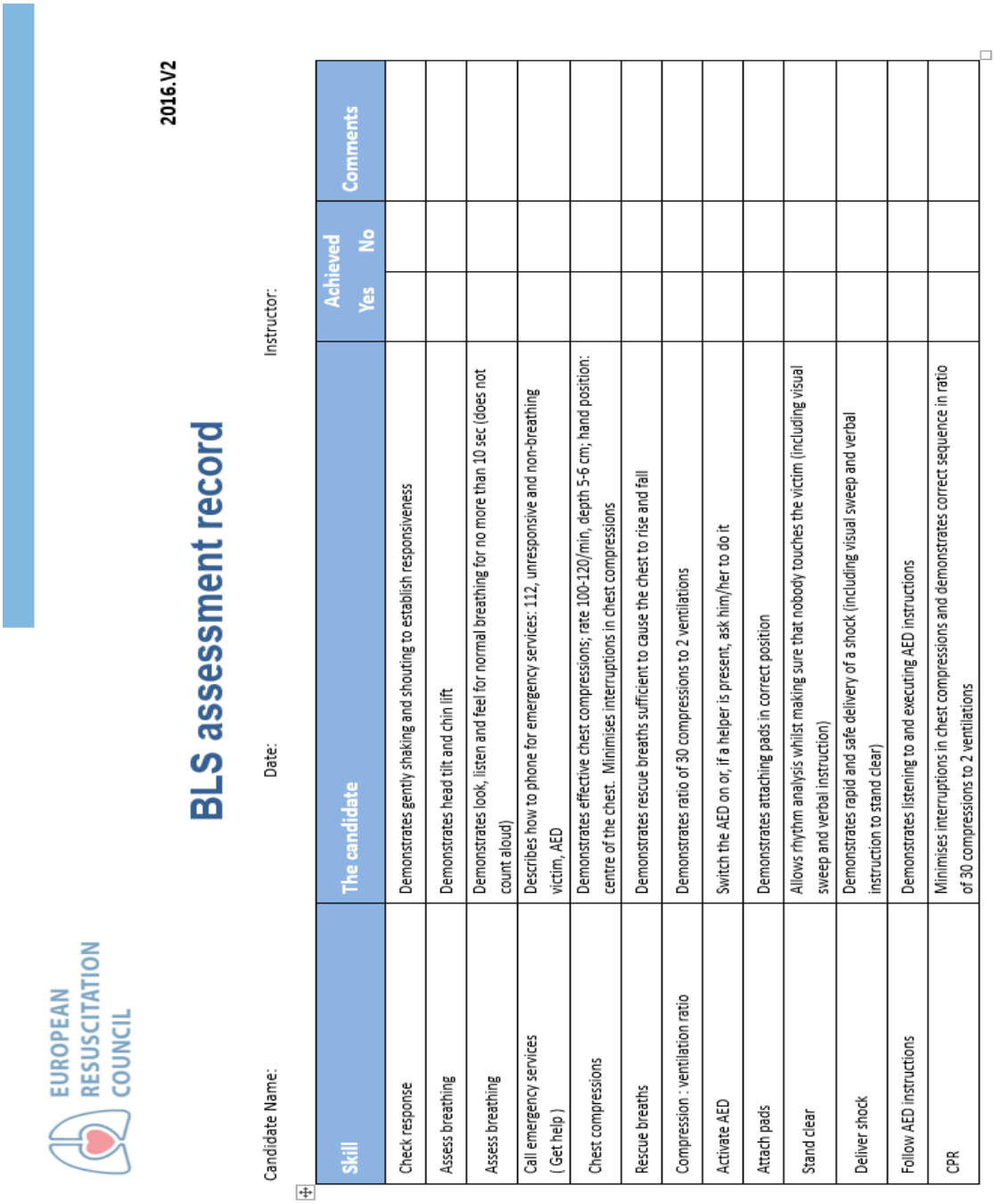
299x310mm (300 x 300 DPI)

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)



EUROPEAN RESUSCITATION COUNCIL

2016.V2

BLS assessment record

Candidate Name: Date: Instructor:

Skill	The candidate	Achieved Yes	Achieved No	Comments
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	O Female O Male O Do not wish to disclose	
Age		
Weight		
Highest level of education	O Primary education O Secondary education O Short cycle tertiary education O Bachelor or equivalent O Master or equivalent	
Healthcare professional	O Yes O No	
Have you used any drugs/narcotics in the past 24 hours, besides alcohol?	O Yes, which: O No O Do not wish to disclose	
Previous CPR experience		
CPR course	O No O Yes, which level O BLS O BLS+AED O ALS O Other: Date last course:	
Witnessed a cardiac arrest	O No O Yes, ... times O Only as a witness O CPR performed as bystander/layperson O CPR performed as healthcare professional	
The victim was	O A stranger O A relative or other acquaintance	

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

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

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	1 11

	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
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
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10 12
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Appendices

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