RAndomized Cluster Evaluation of Cardiac ARrest Systems (RACE-CARS) trial: Study rationale and design

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ABSTRACT Out-of-hospital cardiac arrest (OHCA) occurs in nearly 350,000 people each year in the United States (US). Despite advances in pre and in-hospital care, OHCA survival remains low and is highly variable across systems and regions. The critical barrier to improving cardiac arrest outcomes is not a lack of knowledge about effective interventions, but rather the widespread lack of systems of care to deliver interventions known to be successful. The RAndomized Cluster Evaluation of Cardiac ARrest Systems (RACE-CARS) trial is a 7-year pragmatic, cluster-randomized trial of 62 counties (57 clusters) in North Carolina using an established registry and is testing whether implementation of a customized set of strategically targeted community-based interventions improves survival to hospital discharge with good neurologic function in OHCA relative to control/standard care. The multifaceted intervention comprises rapid cardiac arrest recognition and systematic bystander CPR instructions by 9-1-1 telecommunicators, comprehensive community CPR training and enhanced early automated external defibrillator (AED) use prior to emergency medical systems (EMS) arrival. Approximately 20,000 patients are expected to be enrolled in the RACE CARS Trial over 4 years of the assessment period. The primary endpoint is survival to hospital discharge with good neurologic outcome defined as a cerebral performance category (CPC) of 1 or 2. Secondary outcomes include the rate of bystander CPR, defibrillation prior to arrival of EMS, and quality of life. We aim to identify successful community- and systems-based strategies to improve outcomes of OHCA using a cluster randomized-controlled trial design that aims to provide a high level of evidence for future application. (Am Heart J 2024;277:125–137.)

Background and Rationale

Out-of-hospital cardiac arrest (OHCA) is a major public health challenge affecting approximately 350,000 adults in the United States (US) annually.[1] Despite advances in prehospital and in-hospital cardiac arrest care, overall survival of OHCA remains low.[2] Within the Cardiac Arrest Registry to Enhance Survival (CARES), representing a catchment area of over half of the U.S. population, survival to hospital discharge with good neurologic outcome was 7.3% in 2022, characterized by a strong regional variability.[3,4] As a clearly time-sensitive emergency, OHCA presents unique and formidable challenges to current health care systems.[5]

As with many current public health problems, the critical barrier preventing improvement in cardiac arrest care may not be lack of knowledge about effective measures, but rather lack of optimal systematic implementation of effective treatments in a timely manner. Measures known

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to increase survival after OHCA include early recognition that arrest has occurred, immediate initiation of bystander cardiopulmonary resuscitation (CPR) and early defibrillation, ideally before arrival of Emergency Medical Services (EMS).[2,6] In response to the clear public health imperative signaled by these statistics, the Institute of Medicine (IOM) in 2015, in their report "Strategies to Improve Cardiac Arrest Survival: A Time to Act," specifically called for studies on implementation of interventions for OHCA at the community, emergency medical services (EMS), and hospital levels.[5,7] A major gap in the current evidence on adult OHCA treatments concerns the effectiveness of community-level systems changes in the management of cardiac arrest. Moreover, current American Heart Association (AHA) resuscitation guidelines have a class IIb, level of evidence C-LD (limited data) recommendation for regional efforts to improve cardiac arrest care, highlighting the need for new, high-quality evidence in this area.

As part of the multistate HeartRescue Project,[8] statewide initiatives to improve bystander CPR rates and first responder systems were employed from 2010 to 2013 in North Carolina.[9] The multilayered intervention included training for laypeople, first responders and 9-1-1 dispatch centers, and was associated with an increase in bystander CPR and first responder defibrillation, which translated into a greater likelihood of survival, both at home and in public.[9,10] Notably, the study lacked a control group, and its results were based on data from only 11 counties covering approximately 30% of the population of NC.[9] Despite the progress, county-specific-statewide data suggest continued substantial variability in cardiac arrest care and outcomes. The RAndomized Cluster Evaluation of Cardiac ARrest Systems (RACE-CARS) trial (NCT04660526; clinicaltrials.gov) aims to test such a community-based multilayered intervention in a randomized-controlled manner. The basic premise of RACE-CARS, therefore, is that having guidelines and knowing what works based in those guidelines has been insufficient to improve the refractory national survival rates after OHCA.

This paper provides an overview of the design of the RACE-CARS trial.

Trial design overview and objectives

The RACE-CARS trial is being conducted to test the effectiveness of a multifaceted community and health systems intervention aimed to improve outcomes after OHCA in a pragmatic, registry-based, cluster-randomized trial. For the trial, 62 counties (assigned to 57 clusters based on local EMS agencies) in NC were recruited from the 100 total counties in the state, in which more than 20,000 OHCA cases meeting the inclusion and exclusion criteria of the trial are projected to occur during the planned 4-year intervention period (Figure 1). The clusters were randomized 1:1 to intervention or usual care using a covariate-constrained randomization scheme based on cluster characteristics, to minimize variation between intervention and control counties. The overall trial timeline is 7-years, with a 6-month start-up period and a 12-month intervention training phase, followed by a 4-year intervention and data collection period and a 12-month close-out and data analysis period. Consecutive cardiac arrest metrics and outcomes are being collected using CARES, a prospective, nation-wide clinical registry of patients with OHCA in the United States.[11] Because CARES has already been in place for most of the state, and all patient and outcomes information is entered into this registry, the RACE-CARS is a "registry-based trial" with important advantages including existing capture of data and inclusion of the entire population of patients with OHCA resuscitated by EMS in participating counties.

The primary objective of the RACE-CARS trial is to test whether the implementation of a system-based set of interventions (Figure 2) to improve OHCA treatment results in increased survival to hospital discharge with good neurologic function defined as a cerebral performance category (CPC) of 1 or 2 (Table 1).[12] Secondary objectives include an improvement in bystander CPR rates and an increase in defibrillation performed prior to EMS arrival by either bystanders or first responders. Improving the rates of cardiac arrest recognition by 9-1-1 telecommunicators and timely CPR instructions by telecommunicators is an important tertiary objective, as are the results from the ancillary studies investigating functional status and quality of life at 3 and 12-months after cardiac arrest and qualitative analyses into the success of the implementation.

Trial population

Inclusion criteria

The trial's main inclusion criteria are congruent with the inclusion criteria of the CARES registry[11]: 1) OHCA of nontraumatic etiology with attempted resuscitation, and 2) patients who are pulseless on arrival of a first responder or patients who become pulseless in the presence of a first responder with an attempted resuscitation; or patients who have a pulse on arrival of EMS, where defibrillation was previously administered by a bystander or first responder (Table 2).

Exclusion criteria

As per CARES standards, untreated cardiac arrests, as well as cardiac arrests managed by non-911 EMS transport providers, those of obvious traumatic etiology as well as bystander suspected cardiac arrests where return of spontaneous circulation (ROSC) was achieved without the need for defibrillation prior to 911 responder arrival. Additional exclusion criteria applied specifically in RACE-CARS include patients age <18 years as well as pa-

Table 1. Study objectives and endpoints

	Objectives	Endpoints
Primary Endpoint		
	To improve survival to hospital discharge with good neurologic function (CPC 1-2) by 33% (from 9.0% to 12.0%)	Survival with good neurologic outcomes as measured by a CPC score of 1 or 2 at hospital discharge
Secondary Endpoints		
	To increase bystander rates of CPR in intervention counties by 33% compared with control counties	Rate of bystander CPR (percent of patients who receive CPR from a bystander)
	To increase rates of bystander or first responder defibrillation prior to EMS arrival in intervention counties by 50% compared to control counties.	Percent of cardiac arrest patients who are defibrillated before EMS arrival, by either a bystander or first responder.
Tertiary Endpoints		
	To improve rates of cardiac arrest recognition by 9-1-1 telecommunicators	Percent of cardiac arrest patients whose cardiac arrests are recognized by 9-1-1-telecommunicators through telephone call, and the timing of that recognition.
	To increase rates of 9-1-1 dispatch assisted CPR instructions	Percent of cardiac arrest patients with responders who receive CPR instructions by 9-1-1-telecommunicators through telephone call, as well as time to first instruction and time to first chest compression.
	To compare rates of overall hospital survival	Survival to hospital discharge
	To compare functional status at 3 and 12-mo for cardiac arrest survivors	Modified Rankin score at 3 and 12-mo
	To compare quality of life (QOL) at 3 and 12-mo for cardiac arrest survivors	Quality of life (SF-36, EQ-5D-5L) at 3 and 12-mo for cardiac arrest survivors
	To assess intermediate measures of implementation in the intervention counties	RE-AIM framework (reach, effectiveness, adoption, implementation, maintenance metrics under development)

CPC, cerebral performance category; *CPR*, cardiopulmonary resuscitation.

Table 2. Inclusion and exclusion criteria

Inclusion Criteria	**Out-of-hospital cardiac arrest of nontraumatic etiology defined per CARES standards as:** Patients who are pulseless on arrival of a first responder or EMS; OR Patients who become pulseless in the presence of a first responder; OR Patients who have a pulse on arrival of EMS, where defibrillation was previously administered by a bystander or first responder. Age $\geq$ 18 y
Exclusion Criteria	**As per CARES standards:** Untreated cardiac arrests, including arrests in which resuscitation efforts are not initiated or terminated immediately upon arrival of EMS because the patient is not a viable candidate for resuscitation due to: a. Injuries incompatible with life, b. The presence of rigor mortis or lividity, c. Signs of decomposition, or d. The presence of a valid DNR. Patients who become pulseless in the presence of EMS. Cardiac arrest of obvious traumatic etiology Bystander suspected cardiac arrest, where ROSC was achieved without the need for defibrillation or first responder CPR **Additional exclusion criteria in RACE CARS:** Age $<$ 18 y Cardiac arrests occurring in nursing homes and healthcare facilities Patients who become pulseless in the presence of a first responder

Figure 1. RACE CARS trial participation at baseline. Participating counties in North Carolina; the total population included consists of 8.52 million people representing 79.7% of the entire population of North Carolina.

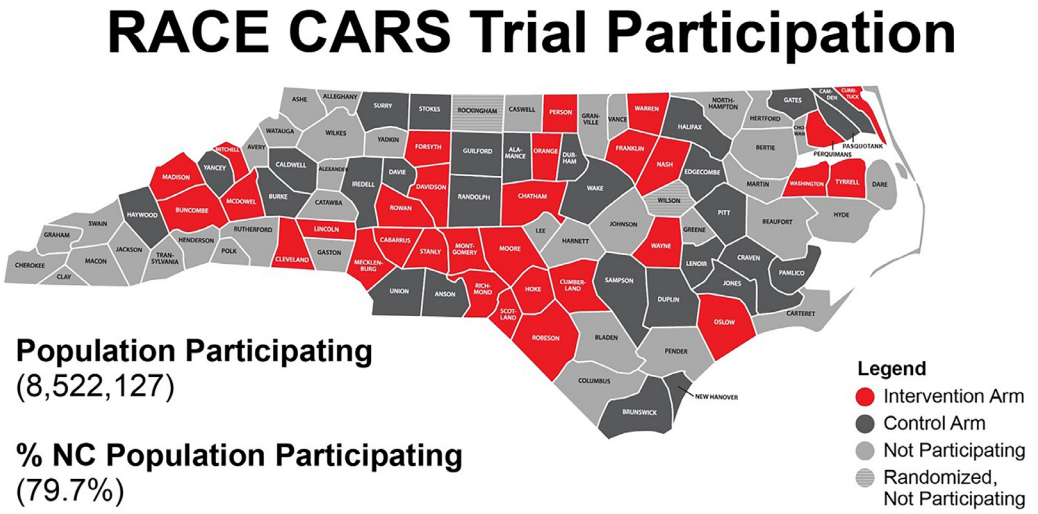
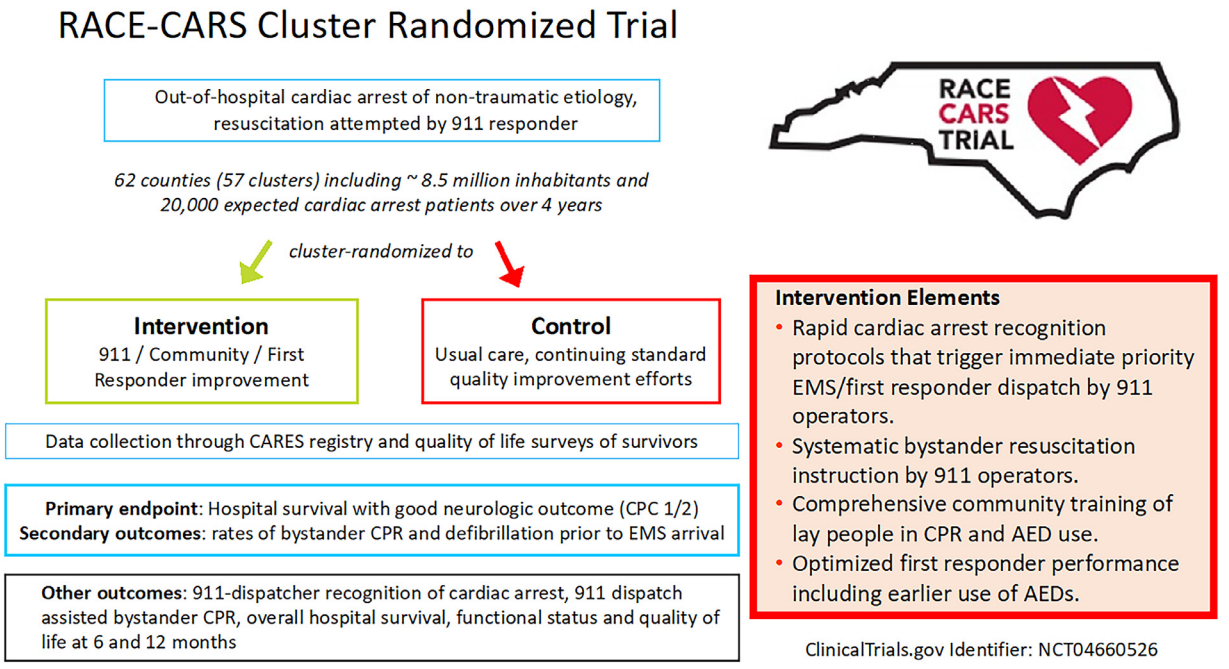
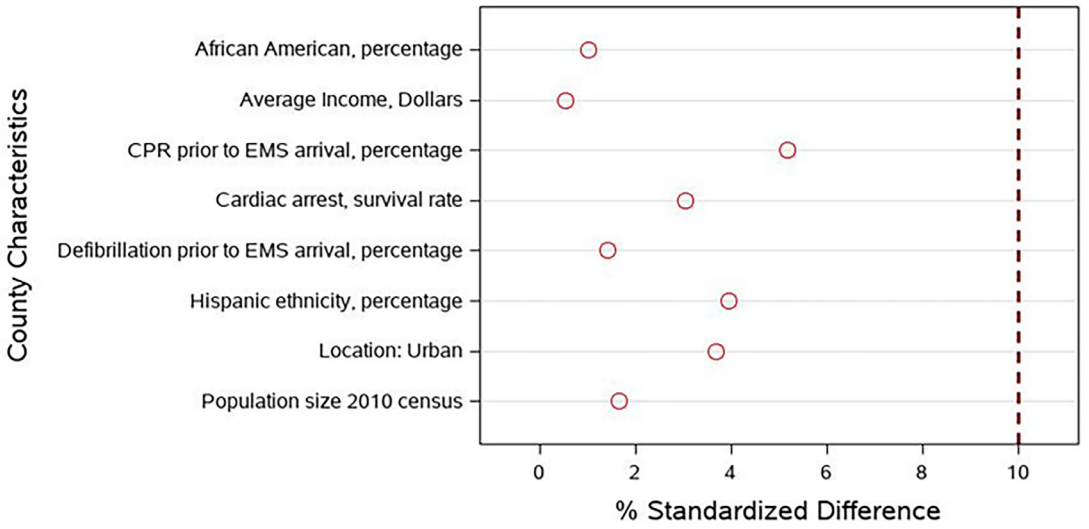


Figure 2. RACE CARS trial design. *AED*, automated external defibrillator; *CARES*, cardiac arrest registry to enhance survival; *CPC*, cerebral performance category; *CPR*, cardiopulmonary resuscitation; *EMS*, emergency medical services; *RACE CARS*, RAndomized cluster evaluation of cardiac ARrest systems.



tients who become pulseless in the presence of first responder or EMS personnel. Furthermore, cardiac arrests occurring in nursing homes and healthcare facilities will be excluded from the primary analysis (Table 2), since these patients are not covered by typical community efforts to improve response to cardiac arrest and there are currently training resources available in nursing homes that may make it challenging to fully assess the effect of the investigational community-based intervention in this trial.

Figure 3. Postrandomization % standardized difference of the 8 baseline cluster characteristics used for the covariate-by-covariate constrained randomization. *CPR*, cardiopulmonary resuscitation; *EMS*, emergency medical system.



Randomization process

In total, 62 of the 100 NC counties agreed to participate in the RACE-CARS trial, which were allocated to 57 clusters based on local EMS agency governance, as some of the smaller counties share the same EMS agency. RACE-CARS was powered at 85% to enroll a minimum of 50 NC counties (25 in each arm). However, the study enrolled/randomized more than 50 counties to account for possible unexpected dropouts, in order to maintain a total of 50 counties at the final analysis. Based on 8 cluster characteristics, a covariate-by-covariate constrained randomization was implemented to balance assignment of clusters to the intervention and control arms of the trial (Figure 3). The 8 baseline cluster characteristics were population size according to the 2010 census, location (rural/urban), percentage of Black or African American, percentage of Hispanic ethnicity living in the county, median household income, percentage of CPR prior to EMS arrival, percentage of defibrillation prior to EMS arrival and cardiac arrest survival rate. Those 8 baseline covariates (or confounders) were considered as important risk factors that could influence survival from out-of-hospital cardiac arrest and were thus selected at the randomization stage to minimize overall imbalances between intervention and control counties.

Historical performance of RACE-CARS counties before trial onset

Between the years 2017 and 2020, 47 of the 62 counties had complete consecutive capture of data in the CARES registry. Two clusters had 3 years of data available, and 2 clusters had 1 year of data available. The remaining counties recruited for RACE-CARS either re-engaged with CARES or were recruited for the trial by 2021. Overall, between 2017 and 2020, 16,758 cardiac arrests occurred with an incidence rate of 79/100,000 inhabitants/year. Of those, 38.1% received bystander CPR, 33.5% of patients that were defibrillated, were defibrillated prior to EMS arrival and 9.5% survived to hospital discharge with good neurologic outcome, defined as a CPC score of 1 or 2 (Table 3).

Trial intervention

The intervention is a customized, county-specific prescription for action that is being worked out collaboratively between the counties and the RACE-CARS team. In NC, most EMS systems are county-based and closely linked to respective local 9-1-1 dispatch centers and first responder agencies and have oversight by county government under the leadership of elected county commissioners. To organize the county-specific implementation of the 4 interventions outlined below, each RACE-CARS county is tasked with nominating 1 county EMS coordinator as the primary trial contact, with duties comparable to a site coordinator in a conventional trial. Their primary task is to assemble a group of representatives involved in cardiac arrest care, including EMS, first responder agencies (fire departments and law enforcement), 9-1-1 dispatch centers, hospital and health system representatives, members of county government and community partners (school system, community colleges, athletic associations, large employers, AHA, American Red Cross, YMCA, churches, local news) to develop an implementation plan based on a strategic assessment of cur-

Table 3. Historical characteristics and performance in recruited counties with available data from 2017-2020

Variable Name	Summary Statistics	All Patients
Cardiac arrests	n	16,758
Cardiac arrest incidence / 100,000 / y	Mean (SD)	79 (19)
Age (y)	Mean (SD)	61.1 (17.2)
Male	N (%)	11,346 (64.6%)
Race / ethnicity		
American Indian/Alaskan	N (%)	134 (0.8%)
Hispanic/Latino	N (%)	345 (2.0%)
Asian	N (%)	195 (1.1%)
Native Hawaiian/Pacific Islander	N (%)	18 (0.1%)
Black / African American	N (%)	5,042 (29.5%)
White	N (%)	11,364 (66.5%)
Unknown	N (%)	470 (2.7%)
Medical history		
Unknown	N	2,733
None	N (%)	1,159 (6.6%)
Cancer	N (%)	1,235 (8.3%)
Diabetes	N (%)	3,936 (26.5%)
Heart disease	N (%)	3,976 (26.8%)
Hyperlipidemia	N (%)	1,784 (12.0%)
Hypertension	N (%)	6,446 (43.5%)
Renal disease	N (%)	805 (5.4%)
Respiratory disease	N (%)	2,316 (15.6%)
Stroke	N (%)	807 (5.4%)
Other	N (%)	7,549 (50.9%)
Cardiac arrest characteristics		
Location of arrest		
Home/residence	N (%)	2,673 (15.2%)
Public setting	N (%)	14,894 (84.8%)
Arrest witnessed		
Unwitnessed	N (%)	8,541 (48.6%)
Bystander witnessed	N (%)	9,026 (51.4%)
First rhythm		
Shockable	N (%)	3,874 (22.1%)
Nonshockable	N (%)	13,689 (77.9%)
Cardiac arrest response metrics		
CPR initiated		
Bystander	N (%)	6,689 (38.1%)
First responder	N (%)	7,740 (44.1%)
EMS	N (%)	3,136 (17.9%)
AED applied prior to EMS arrival	N (%)	8,414 (47.9%)
Who first applied AED		
Bystander	N (%)	59 (0.5%)
First responder	N (%)	2,874 (23.8%)
EMS	N (%)	9,152 (75.7%)
Who first defibrillated the patient		
Bystander	N (%)	163 (7.1%)
First responder	N (%)	604 (26.4%)
EMS	N (%)	1,519 (66.4%)
Time to first CPR	Median (q1, q3)	6 (2, 10)
Time to first defibrillation	Median (q1, q3)	14 (9, 24)
Time to first responder on scene	Median (q1, q3)	7 (5, 10)
Time to EMS on scene (minutes)	Median (q1, q3)	9 (7, 12)
Cardiac arrest survival		
Overall survival to hospital admission	N (%)	5,001 (28.5%)
Overall survival to hospital discharge	N (%)	1,996 (11.4%)
Overall survival to hospital discharge with CPC 1 or 2	N (%)	1,674 (9.5%)
Census tract ID data		
Percent male	Mean (SD)	48.4 (3.8)
Percent black	Mean (SD)	24.0 (21.9)
Percent high school diploma or higher	Mean (SD)	69.1 (16.0)
Percent Unemployment	Mean (SD)	6.5 (4.2)
Percent living below poverty	Mean (SD)	10.1 (11.7)
Average household size	Mean (SD)	2.6 (0.3)
Median household income in the past 12 mo	Mean (SD)	51,435 (23,191)

AED, automated external defibrillation; *CPC*, cerebral performance category; *CPR*, cardiopulmonary resuscitation; *ED*, emergency department; *EMS*, emergency medical services; *IQR*, interquartile range; *SD*, standard deviation.

rent care patterns and performance metrics as reported within CARES. Detailed plans for each intervention are developed during the initial training meetings between county EMS coordinators, a team of county representatives and RACE-CARS investigators and are instituted during the 1-year training phase of the trial. Yearly, during the 4-year intervention phase, for each county, at least 1 county-specific, 1 regional and 1 state meeting are being held in-person to review intervention county progress and re-evaluate the implementation plan based on CARES data. In parallel, a series of educational, (bi-) weekly calls are being organized. EMS coordinators will receive quarterly feedback on their county's performance.

All data are being collected through the CARES registry, except for data on long-term quality of life and functional status, which will be assessed in cardiac arrest survivors who have provided consent, at 3-months and 12-months via telephone follow-up as part of the long-term outcome ancillary study, and telephone and survey data to inform implementation science analyses.

EMS agencies within clusters randomized to the control group have continued their standard of care practice without any restrictions. Clusters assigned to the intervention group are expected to implement the 4 interventions outlined below. Specific details of the intervention are provided in the Manual of Operations, a guidance document describing scientific evidence for the interventions, guideline recommendations, and suggested approaches to improve process performance and outcomes with the planned interventions.

Specific interventions

Intervention 1. *Rapid cardiac arrest recognition that triggers immediate priority EMS/first responder dispatch by 9-1-1 telecommunicators.*

Intervention 2. *Systematic, rapid bystander resuscitation instruction by 9-1-1 telecommunicators.*

Intervention 1 aims to improve the rate and timing of 9-1-1 telecommunicator recognition of cardiac arrest to trigger response by EMS and first responders, while intervention 2 aims to further increase dispatch assisted bystander CPR rates. During the training phase, intervention counties are required to review current protocols and existing data and to implement the CARES dispatch module, a novel module within CARES offering systematic 9-1-1 dispatch center data collection. The 9-1-1 dispatch centers receive monthly feedback on their own performance. Each county will develop a plan to optimize overall dispatch performance, specifically cardiac arrest recognition, CPR and AED instruction to bystanders, as well as timeliness of call receipt to hands on chest by bystanders. The RACE-CARS intervention team assists each county with developing their plan based on historical performance reports and interventions outlined in the Manual of Operations.

Intervention 3. *Comprehensive community training of lay people in CPR and AED use.*

Current community training strategies and estimated numbers of individuals trained per year have been reviewed and each county has been tasked with training an additional 10% of the population in hands-only CPR over the first 2 years and increased use of AEDs. A dedicated RACE-CARS community outreach coordinator is helping with designing a community outreach program specifically tailored to individual county needs, involving large employers, community, and civic organizations, as well as health care systems. Furthermore, counties are tasked with organizing a community survivor event at least once a year to increase awareness and highlight successful cases and honor the individual's involved, as well as to motivate engagement of community members to participate.

Intervention 4. *Optimized first responder performance including earlier use of AEDs.*

Each EMS agency has provided an overview of their current first responder programs, including its participating agencies, their structure, their dispatch strategies, their level of training and resources available (AEDs) and their coverage of the county. In NC, first responders mainly consist of fire departments (professional and volunteer) and law enforcement (police in municipalities and sheriffs in rural areas). Together, with existing CARES data on first responder AED use and CPR rates as well as arrival times, a county-specific strategy to improve early defibrillation and CPR rates has been formulated. Specific interventions include expanding the first responder systems with the aim to include all fire departments as well as law enforcement in the cardiac arrest response. Further, 9-1-1 dispatch and first responder response are being optimized (direct dispatch to location, app-based dispatch, strategic AED dissemination) as well as training protocols reviewed (high-quality team-based CPR). This will include local governments, health systems, EMS, 9-1-1 dispatch centers and local first responder agencies (Figure 2).

Data collection

All enrolled counties enter consecutive data on OHCA in CARES.[11] The CARES registry is a voluntary, prospective clinical registry of patients with cardiac arrest in the U.S., established by the Centers for Disease Control and Prevention and Emory University for public health surveillance and continuous quality improvement. It is the major national registry of unselected patients with cardiac arrest in the U.S. and is currently implemented in 33 statewide participants and over 50 communities in

14 additional states with a catchment area that includes 175 million people or 53% of the US population.[13] Standardized international Utstein definition of variables and outcomes are used for data uniformity.[14]

Trial enrollment of cardiac arrest patients is being exclusively conducted through the CARES registry. The standardized data elements from CARES[15,16] are being used for the primary analysis. EMS agencies are working with hospitals and 9-1-1-dispatch centers to ensure timely data entry into CARES registry. Therefore, RACE-CARS is enrolling essentially the entire target population given near complete capture in the registry and with waiver of individual patient consent, as agreed to by the Institutional Review Board and by each county EMS system.

Potential impact of the COVID-19 pandemic on trial conduct

The COVID-19 pandemic impacted public health treatment and outcomes in the US. In particular, there was higher incidence of OHCA, lower treatment, and lower survival rates. Delays in EMS response times related to overburdened EMS systems and the cessation of first responder services were causally implicated in those observations,[17-19] while data on a potential reduction in bystander CPR related to fear of transmission remain inconclusive.[20-22] Importantly, cardiac arrest incidence increased in regions with a high COVID-19 burden, but the overall observed decrease in survival to hospital admission was independent of the regional COVID-19 incidence.[23]

The COVID-19 pandemic completely halted in-person CPR training, with most training efforts shut down and only slowly reopening. The RACE-CARS trial start-up phase between October 2020 and March 2021 coincided with the COVID-19 pandemic. Therefore, all recruitment meetings were conducted via teleconference or videoconference systems, as were the initial intervention meetings. By mid-2021, state guidelines and the pandemic situation allowed in-person meetings, keeping the overall impact on county meetings and trial conduct minimal. CPR training reopened and EMS response patterns returned to normal. While the overall cardiac arrest response and the trial conduct are now unaffected by the COVID-19 pandemic, staffing shortages in the wake of the pandemic remain a challenge. We further expect OHCA outcomes to recover gradually; however, given the randomized design of this trial, we do not expect differences between intervention and nonintervention clusters in the impact of COVID-19.

Sample size

Sample size and power calculations were based on an assumed effect size using a binary outcome in a cluster-randomized design with adjustment based on intracluster correlation. Historical data in NC approximated 9% survival rate with good neurologic outcome for OHCA. Based on prior nonrandomized controlled studies,[9,10] we estimated a 33% improvement in outcome could be achieved with our multifaceted intervention. We also estimated that we could improve bystander CPR rates by 33% and defibrillation prior to EMS arrival by 50%.[9] To achieve 85% power with a patient-level randomization, in a 1:1 allocation ratio, with a 2-sided type I error rate of 0.05, would require a total of 3,880 cardiac arrest patients (assuming 9% survival in the control arm and 12% survival in the intervention arm). This sample size estimate is based on the continuity corrected chi square test using PASS15 Package. To account for potential correlation among patients within a county due to the cluster-randomized design, the sample size must be adjusted by multiplying what one would obtain when assuming that participants are statistically independent by a design-effect (DE), where $DE = 1 + (m\text{-}1)\,\rho$, ρ is the ICC within each county, and m is an average number of cardiac arrest patients in each county. Assuming an ICC of 0.01 and an average annual county size of 100 cardiac arrest patients (ie, 400 over 4 years of data collection period), would yield a total sample size of 19,400 (roughly 20,000) cardiac arrest patients needed to detect an absolute 3% survival benefit in the intervention arm with 85% power.

Statistical considerations

The statistical analysis plan contains all statistical considerations of this trial and its analysis. In brief, comparisons in the primary outcome of survival to hospital discharge with good neurologic outcome (CPC score 1 or 2) between intervention and control groups, will be analyzed using logistic regression with generalized estimation equation (GEE), or modeling proportions, and quantitative variables, taking into account the dependence between observations within a county and using an appropriate working correlation structure. In addition to correlated-data adjustment via GEE, the model will be adjusted for select baseline risk factors. Review of baseline risk factors differences between intervention and control groups will be used to select the variables of interest. Estimated odds ratio (ORs) and the 95% confidence intervals (CIs), will be calculated for both crude and adjusted models. Furthermore, we plan to perform subgroup analyses according to EMS response times.

All outcomes will be analyzed using the intention-to-treat principle.

Substudies and ancillary studies

Implementation science substudy

A systematic examination using qualitative and quantitative methods of the implementation of the interventions will be conducted using the RE-AIM (reach, effectiveness, adoption, implementation, maintenance) framework.[24] The use of implementation methods will

allow assessment of how well the interventions were implemented and which elements were associated with effectiveness, with the ultimate goal of being able to inform the community on how to disseminate and scale the results, if effective. A baseline assessment of potential barriers and facilitators that may be anticipated was conducted to identify implementation strategies for the multiple RACE-CARS interventions.

For the qualitative assessment, randomly selected interviews will be conducted with the responsible parties of both low and high performing clusters for each intervention on a quarterly basis. Every quarter 1 to 2 counties are selected, and partners participate in a qualitative interview that is based on the Consolidated Framework for Implementation Research (CFIR). We use rapid analysis to assess barriers. A 3-level score will be assigned to each cluster regarding the implementation level of each of the 4 interventions. These interviews will be guided by CFIR.

At the completion of the trial, a mixed methods approach consisting of quantitative and qualitative assessments will be applied to assess the barriers and facilitators of implementation of each of the interventions. Together with findings obtained from quantitative analyses, factors predictive of successful intervention implementation will be described, including county- and community-based characteristics (including resources, culture and context) as well as the type of successful intervention and more granular data on the success in specific subgroups, such as Black patients and women. Such findings will be used to inform and adapt implementation strategies and dissemination methods.

Long-term quality of life substudy

In addition to the primary outcome of survival to hospital discharge with good neurologic outcome, a dedicated long-term outcome and quality of life substudy is being conducted. Cardiac arrest survivors in both control and intervention clusters are being invited to telephone interviews at 3-(accounting for variable timing of case entry into CARES database) and 12-months after cardiac arrest. In structured interviews, the SF-36 health survey[25], the EQ-5D-5L[26] quality of life measure, as well as the modified Rankin scale are being determined.[27,28] The SF-36, the most widely used generic health status assessment tool in medicine, assesses several domains: 1) physical functioning, 2) general health, 3) mental health (anxiety/depression), 4) vitality, 5) role functioning-physical, 6) role functioning-emotional 7) bodily pain, and 8) social functioning.

Trial governance

Data and safety monitoring board (DSMB)

A NHLBI-appointed independent committee oversees the safety of research participants and integrity of trial conduct. It consists of 3 clinicians with both clinical and research expertise in this topic, a senior statistician and a bioethicist.

Steering committee

The Steering Committee serves as the primary decision-making body of the RACE-CARS trial. It consists of the RACE CARS principal investigators, co-principal investigators, the National Heart, Lung and Blood Institute program director, national and international academic experts in cardiac arrest care as well as a patient representative. Members review and approve the Trial Protocol, the Manual of Operations, training materials, the data management plan and the Statistical Analysis Plan and meet at least quarterly to discuss progress of the trial.

Clinical coordinating center (CCC)

The CCC functions as the clinical trial center and is responsible for all aspects of conducting the trial- from the planning and development phase, to all aspects of recruitment and intervention to leadership in data analysis, presentations and publications.

Data coordinating center (DCC)

The DCC supports the CCC and is involved in planning, design, data collection, quality assurance, data management, data analysis, study interpretation, and dissemination of results.

NHLBI

A designated NHLBI program officer participates actively in study leadership together with investigators from the CCC and DCC as well as the chair of the Steering Committee. The program officer will participate in monitoring study progress and attend and participate in regular meetings of the Steering Committee, the DSMB and other committees as needed.

Discussion

An efficient approach to improving OHCA survival involves optimizing early community-based, dispatch, and first responder actions.[29] Despite widespread knowledge about effective life-saving interventions, more than 90% of OHCA victims do not survive until hospital discharge.[30] The current state of community response is not optimal, with only 40% of cardiac arrest victims receiving chest compressions by a bystander. Even in the ideal situation of a witnessed cardiac arrest, only half of patients receive layperson CPR as demonstrated in the 2022 CARES report.[30] Fewer than one third of cardiac arrest patients had an AED applied by laypersons or first responders prior to EMS arrival and of all patients with a shockable rhythm, only 1 out of 4 was defibrillated prior to EMS arrival, a strategy associated with dramatically improved outcomes.[6] As in prior years, cardiac arrest response metrics and outcomes in 2022 showed substantial regional variation, with reported survival rates

varying between 3% and 18% and bystander CPR rates ranging between 15% and 80% across national EMS agencies.[30] Similar results were shown in an analysis from the Resuscitation Outcomes Consortium including cardiac arrests from 10 North American sites between 2006 and 2007. There, overall survival of OHCA patients varied between 3% and 16% and patients with an initial shockable rhythm had survival rates between 8% and 40%.[31]

Care for cardiac arrest victims in the U.S. is organized on the local level, involving more than 15,000 EMS agencies and local 9-1-1 dispatch centers that lack integration and coordination.[32,33] In 2010, as part of the HeartRescue project, RACE CARS pilot tested the implementation of several of the interventions noted in the Institute of Medicine report, including community CPR training, enhanced 9-1-1 dispatch protocols, first responder programs and improved, guideline based pre and in-hospital care.[8,34] Cardiac arrest care patterns and outcomes were measured using the existing CARES registry. Within 11 counties with complete case capture, a 25% increase in bystander CPR and first responder defibrillation was noted, accompanied by a 37% increase in survival with good neurologic function.[9] Treatment within the first 2 minutes was particularly effective, as evidenced by a 59% survival rate, underscoring the survivability of an OHCA with initial shockable rhythm.[6,35]

Still, ongoing substantial variability in processes of care and outcomes remain. Fragmented care and lack of coordination among all stakeholders involved as well as the predominance of evidence from observational studies, call for focused, high quality, randomized-controlled intervention trials. By testing systematic, multilayered, comprehensive and customized interventions focused on early CPR and defibrillation, as recommended by the IOM report, and by adopting a highly pragmatic and innovative design based on an existing data collection system, the CARES registry, the RACE CARS trial can generate the high-level evidence needed to persuade health and community leaders to prioritize achieving a much higher community-wide level of CPR and AED use. By customizing our approaches to the heterogeneous settings of cardiac arrest care across NC, our findings will be better suited for dissemination across similar settings in the U.S.[5,7,29,36,37] In addition, RACE-CARS directly addresses the current AHA guideline recommendation based on the 2020 International Liaison Committee on Resuscitation (ILCOR) systematic review on community initiatives,[29] which states that "*it may be reasonable for communities to implement strategies for increasing awareness and delivery of bystander CPR.*" The recommendation was designated as class 2b based on a level of evidence C—limited data highlighting the need for new, high-quality evidence.

We have recruited 62 counties of NC, representing approximately 80% of the state's population and more than 8 million inhabitants. The recruited counties range from very small, rural counties with few thousand inhabitants to densely populated urban areas with over 1 million inhabitants. These counties cover a variety of landscapes, income levels, racial compositions, political orientation and cardiac arrest outcomes. The covariate-by-covariate constrained randomization ensured balanced assignment of intervention and control based on 8 cluster characteristics including demographics, socioeconomic factors and current cardiac arrest care and outcomes with the goal of a 10% standardized difference or less between trial arms achieved for all 8-cluster characteristics. As such, RACE-CARS will provide evidence for the impact of implementation strategies for a variety of communities and systems. A dedicated implementation study will provide granular, qualitative data on implementation success. Several interventions within RACE-CARS target 9-1-1 dispatch centers, an area that has received less attention by the scientific community. Almost all cardiac arrests in a county will go through one of the 9-1-1 telecommunicators (an average county with a population of 100,000 will employ approximately 30 telecommunicators), quality improvement strategies aimed at those professionals offer an efficient opportunity. The implementation of a dedicated 9-1-1 dispatch center module for CARES allows collection of granular data on cardiac arrest recognition rates and specifics and timings of dispatch assisted CPR instructions.[16] It will allow us to investigate associations between achieved and recommended times until CPR initiation and outcomes in a variety of systems.[38] Another important objective of RACE-CARS is to investigate long-term neurologic outcome, recovery, and quality of life in survivors. Prior data suggest that a high percentage of survivors end up with little or no neurologic impairment allowing them to resume their roles as contributing members of their community,[39] but this has never been addressed in the context of a randomized trial.[40]

Several features render RACE-CARS highly innovative; first, we apply a highly efficient design that derives from our ability to take advantage of the established relationships with North Carolina EMS agencies use of an existing data collection system, the CARES registry. This resource has enabled to use the registry to capture consecutive OHCAs and hospital follow-up, thus substantially reducing the administrative requirements and cost of our trial. Registry-based trials have been highlighted as an important innovative and "disruptive technology" to conduct pragmatic and efficient trials, including by the NHLBI. However, to this date, few large trials that are fully integrated into registries have been conducted successfully in the U.S. RACE-CARS is an unusually pragmatic trial, enrolling essentially the entire target population since there is near complete capture in the registry and waiver of individual patient consent. In addition, RACE-CARS is designed to fill a gap in knowledge

around T4 translation[41] on how to implement community and EMS interventions.

In conclusion, by being a randomized controlled, registry-based trial with near-complete capture of patients and outcomes in participating counties, the RACE-CARS trial will provide high level evidence on the effectiveness of a strategic, systematic, multilayered and customized intervention focused on improving early CPR and defibrillation rates. By so doing, this trial directly addresses the call by the IOM report to improve the implementation of known effective strategies to improve survival of OHCA and has the potential to change current guideline recommendations.

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CRediT authorship contribution statement

Konstantin A. Krychtiuk: Writing – review & editing, Writing – original draft, Visualization, Visualization, Investigation, Funding acquisition, Data curation, Conceptualization. **Monique A. Starks:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Hussein R. Al-Khalidi:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Daniel B. Mark:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Lisa Monk:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation. **Eric Yow:** Writing – review & editing, Software, Resources, Methodology, Formal analysis, Data curation. **Lisa Kaltenbach:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation. **James G. Jollis:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Sana M. Al-Khatib:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Hayden B. Bosworth:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Kimberly Ward:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation. **Sarah Brady:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology. **Clark Tyson:** Writing – review & editing, Software, Resources, Project administration, Methodology, Investigation, Formal analysis. **Steve Vandeventer:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation. **Khaula Baloch:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation. **Megan Oakes:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Audrey L. Blewer:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Allison A. Lewinski:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Carolina Malta Hansen:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Edward Sharpe:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Thomas D. Rea:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **R. Darrell Nelson:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Comilla Sasson:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Bryan McNally:** Writing – review & editing, Validation, Supervision, Software, Resources, Methodology, Investigation, Conceptualization. **Christopher B. Granger:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization.

Conflicts of Interest

Konstantin A. Krychtiuk: Speaker Fees: Daichii Sankyo, Zoll Medical; Consulting Fees: Sanofi, Amarin; Travel Support: Amgen, Novartis Monique A Starks: - NHLBI- 1K23HL153889-04: AHA HERN Grant- 23HERN-PRH1150361

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