STUDY PROTOCOL

REVISED Outcomes of out-of-hospital cardiac arrest in Ireland 2012-2020: Protocol for an observational study [version 2; peer review: 3 approved, 1 approved with reservations]

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Abstract

Background

Out-of-hospital cardiac arrest (OHCA) is a leading cause of preventable mortality that now affects almost 3,000 people each year in Ireland. Survival is low at 6–7%, compared to a European average of 8%. The Irish Out-of-Hospital Cardiac Registry (OHCAR) prospectively gathers data on all OHCA in Ireland where emergency medical services attempted resuscitation.

The Irish health system has undergone several developments that are relevant to OHCA care in the period 2012–2020. OHCAR data provides a means of exploring temporal trends in OHCA incidence, care, and outcomes over time. It also provides a means of exploring whether system developments were associated with a change in key outcomes.

This research aims to summarise key trends in available OHCAR data from the period 2012 – 2020, to explore and model predictors of bystander CPR, bystander defibrillation, and survival, and to explore the hypothesis that significant system level temporal developments were associated with improvements in these outcomes.

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Methods

The following protocol sets out the relevant background and research approach for an observational study that will address the above aims. Key trends in available OHCAR data (2012 – 2020) will be described and evaluated using descriptive summaries and graphical displays. Multivariable logistic regression will be used to model predictors of 'bystander CPR', 'bystander defibrillation' and 'survival to hospital discharge' and to explore the effects (if any) of system level developments in 2015/2016 and the COVID-19 pandemic (2020) on these outcomes.

Discussion

The findings of this research will be used to understand temporal trends in the care processes and outcomes for OHCA in Ireland over the period 2012-2020. The results can further be used to optimise future health system developments for OHCA in both Ireland and internationally.

Keywords
out-of-hospital cardiac arrest, registry data, observational research, prehospital emergency care, resuscitation, emergency medical services

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 1**

This updated version provides further clarification on the rational for collapsing various variable categories. It also provides clarification on the proposed method for analysing the effect of the transition and COVID periods via variables 20, 21 and 22. In addition it provides further information on how we plan to assess linearity between continuous predictors and the log odds of the outcome via higher order (polynomial) terms. A small number of typographical issues have also been addressed.

Any further responses from the reviewers can be found at the end of the article

Introduction

Out-of-Hospital Cardiac Arrest

Out-of-hospital cardiac arrest (OHCA) describes the sudden loss of mechanical function of the heart and the absence of blood flow around the body, occurring outside of a hospital setting[1,2]. OHCA is the most time-critical medical emergency, with survival depending on the prompt actions of the community where OHCA occurs, emergency medical services (EMS) and in turn, appropriate follow-on hospital care[3]. Internationally, the annual incidence of OHCA treated by emergency medical services (EMS) is estimated to be 30 – 97 individuals per 100,000 population, median age ranges from 64 to 79 years and more than half of victims are male[4]. OHCA with attempted resuscitation has an incidence of 56 per 100,000 population per year in Europe and is considered the third leading cause of death[5]. Survival to/ immediately after hospital discharge ranges from three to twenty percent internationally and is eight percent in Europe[6]. Of those that do survive to discharge in Europe and North America, approximately seventy percent are still alive at three years[7]. In Ireland there are now almost 3,000 OHCAs with attempted resuscitation each year of which six to seven percent involve survival to hospital discharge[8].

The Chain of Survival

The 'chain of survival' describes the critical actions that can link an OHCA victim with survival[9]. This chain involves early access to care, early cardiopulmonary resuscitation (CPR), early defibrillation and post resuscitation care[10]. CPR and defibrillation are exquisitely time sensitive interventions and thus health systems face a significant challenge in ensuring OHCA patients have timely access to these treatments[11]. Thankfully, the simplicity, affordability and increasing awareness of these interventions mean that they can be cascaded to the community and performed by 'bystanders' when cardiac arrest occurs[12]. Thus, at population level these represent the most important OHCA interventions[13,14]. In circumstances where bystanders have not initiated CPR, dispatch assisted CPR (where the EMS emergency call taker provides CPR instruction to bystanders over the phone) can further improve survival following OHCA[15].

CPR and defibrillation exist alongside several other OHCA interventions that can be delivered in the community and enroute to hospital by EMS. Randomised controlled trials have demonstrated that delivery of medications such as adrenaline and amiodarone may have additional benefits for some patient groups, while trials of airway management and mechanical CPR devices have failed to show significant survival improvements[16–19]. An additional novel but resource intense hospital (or hospital outreach) treatment 'eCPR' (extracorporeal cardiopulmonary resuscitation) uses a mechanical device to temporarily replace heart and lung function. eCPR has shown significant promise in specific OHCA sub-populations[20]. However, the degree to which this treatment can be made available in an equitable fashion at population level is yet uncertain[21,22]. In terms of follow on in-hospital care, international guidelines now recommend that OHCA patients are cared for in specialist cardiac arrest centres, while acknowledging limited evidence for this recommendation outside of specific patient subgroups[22,23].

Out of Hospital Cardiac Arrest & Quality Improvement Registries

The science underpinning the 'chain of survival' is unquestionably of critical importance in OHCA care. However, scientific research alone will not be sufficient to improve OHCA outcomes and must be accompanied by a focus on real world implementation and quality improvement[24]. To this end the European Resuscitation Council recommend that 'health systems should have population-based registries which monitor the incidence, case-mix, treatment and outcomes for cardiac arrest' and that these data 'should inform health system planning and responses to cardiac arrest'[25].

An internationally agreed 'Utstein' registry dataset has been devised which facilitates national and international comparison of OHCA[26]. A recent pan European survey reported that six countries (including Ireland) had an OHCA registry with full population coverage, fourteen had partial population coverage and seven countries reported not having an OHCA registry[27]. Comprehensive data on the Irish experience of OHCA is provided by the Irish Out-of-Hospital Cardiac Arrest Registry (OHCAR). OHCAR achieved national coverage using the Utstein dataset in 2012, and by 2020 this contains over 20,000 cases. In terms of the period considered in this study OHCAR does not include OHCA with EMS response but without attempted resuscitation. We anticipate that approximately fifty percent of cases recorded in OHCAR are witnessed (European average 66%), and twenty percent have an initial 'shockable rhythm' (European average 20%)[6]. The primary sources of OHCAR data are patient care records and dispatch data from Ireland's statutory ambulance services. OHCAR has provided invaluable continuous quality improvement data on an annual basis to ambulance services. To date however, no temporal analyses have been conducted to assess the impact of national interventions on survival in Ireland. Nor has the database been interrogated to determine whether international trends in OHCA (including increased bystander CPR and associated survival improvements[28–30]) are mirrored in the Irish data.

Emergency medical services in Ireland

Ireland's population is now in excess of five million people, for whom emergency medical services (EMS) are provided by the National Ambulance Service (NAS)[31]. In Ireland's capital

Dublin, Dublin Fire Brigade (DFB) are contracted to provide an emergency ambulance service alongside the NAS. Each year these services respond to in excess of 300,000 ambulance calls[32]. The National Emergency Operations Centre (NEOC) coordinates statutory emergency service responses to OHCA for most of the Irish state. In the Dublin metropolitan area EMS response is coordinated by both NEOC and the DFB east regional communications centre (ERCC). EMS care across the Irish state is provided by Paramedics or Advanced Paramedics who number approximately 2,500 & 700 respectively[33]. All front-line ambulances must be staffed by at least a paramedic grade practitioner. A small number of EMS physicians supplement this care on a voluntary as available basis; however, they are not a core component of the statutory response.

Paramedic and Advanced paramedic scope of practice is determined by a statutory agency, the Pre-Hospital Emergency Care Council (PHECC). PHECC publish clinical practice guidelines and maintain a practitioner register[34]. Only Advanced Paramedics are permitted to provide intravascular medications or to perform endotracheal intubation. Mechanical CPR devices are now widely available on all frontline ambulances. eCPR is generally not available in Ireland. In addition to statutory EMS providers, Ireland also has an extensive network of voluntary community first responders (CFRs) who can be dispatched by NEOC to OHCA to provide early CPR and defibrillation[35,36].

OHCA Health System Developments in Ireland 2012–2020

Over the period 2012–2020 that OHCAR has been in existence, Ireland has undergone several health system developments that are pertinent to OHCA care. Figure 1 summarises a timeline of these developments. The Pre-Hospital Emergency Care Council national Citizen CPR or Call-Check-Compress programme was launched in 2010[37]. This public awareness campaign involved a series of national roadshows combined with a major national television, cinema, on-line and transport advertising designed to increase bystander CPR. Then in 2012 the NAS launched their ‘one life’ quality improvement programme[38]. This ongoing programme focuses on several key aspects of OHCA including community interaction and public education, NEOC call taking and dispatch, EMS quality care on scene, and finally quality data management and audit processes. In 2014 the Irish Health Information and Quality Authority (HIQA) published a health technology assessment of public access defibrillation in Ireland[39]. This was commissioned by government to inform decision making around proposed legislation to mandate public defibrillator availability. The health technology assessment estimated the clinical and cost effectiveness of a range of potential Irish public access defibrillation configurations, ranging from comprehensive to targeted[39]. It estimated that between two and ten additional OHCA survivors could be achieved annually; however, none of the models achieved the threshold for cost effectiveness. It advised that targeted AED deployment in higher incidence locations in combination with an EMS-linked AED register and increased public awareness could potentially render the programmes’ cost effective[39]. Ultimately the proposed legislation was abandoned, and a comprehensive national EMS-linked AED register is yet to be established.

In 2015 and 2016 the National Ambulance Service transitioned from a system of multiple regional independent control centres to a single national control centre (NEOC). This significant change allowed an enhanced level of resource co-ordination and further allowed dispatch assisted CPR to be fully embedded

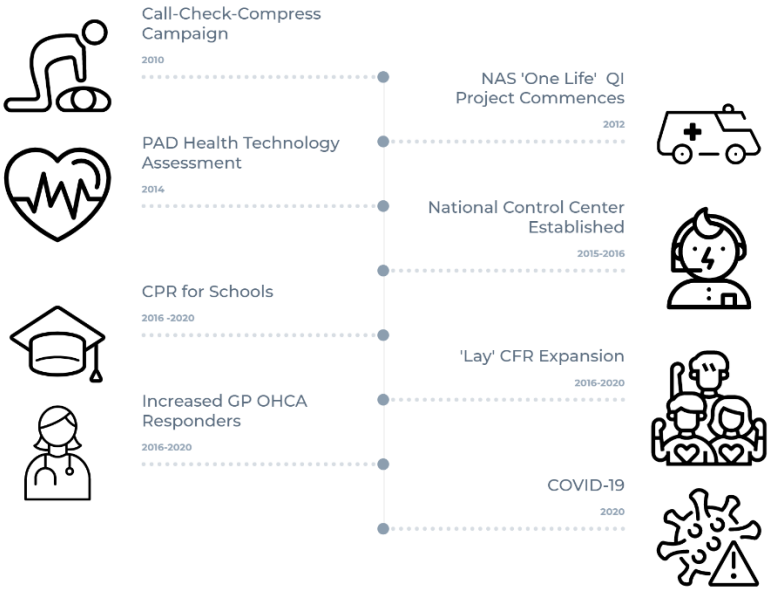

Figure 1. OHCA Health System Developments in Ireland 2012–2020. NAS: National Ambulance Service, QI: Quality Improvement, PAD: Public Access Defibrillation, CPR: Cardiopulmonary Resuscitation, CFR: Community First Responder, GP: General Practitioner, OHCA: Out-of-Hospital Cardiac Arrest.

as a standard of care at national level. Between 2016 and 2020 the Irish Heart Foundation 'CPR 4 schools' programme trained 1,827 teachers in 531 schools to perform CPR training for a potential 288,197 students. Between 2016 and 2020 lay community first responder groups increased from 100 to 175 nationally. In 2017 the NAS created four new Community Engagement Officer posts to support CFR activities and expansion. Also between 2016 and 2020 GP (general practitioner) first responder numbers doubled to almost 200 individuals[40]. The final year of this study period 2020 is exceptional in that it represented the first year of the Covid-19 pandemic, the first wave of which occurred between February and July 2020[41]. The Irish health service responded by introducing a range of public health measures including travel restrictions, schools and business closure, cessation of large indoor gatherings, and other social distancing measures[42]. In terms of OHCA, internationally Covid-19 is known to have detrimentally affected systems of care and was associated with prolonged EMS response and worse short-term outcomes including survival compared to pre-pandemic periods[43]. The effects of COVID-19 on OHCA in Ireland have not yet been systematically evaluated; however similar trends are probably likely. Thus, it is necessary to consider this as a significant OHCA development in the 2020 period.

Focus of this study

This study will examine data from the Irish Out-of-Hospital Cardiac Arrest Registry (OHCAR) to describe OHCA incidence and its care processes in Ireland over the period 2012 to 2020. We will further interrogate this data to identify key OHCAR variables that predict key outcomes. We anticipate approximately 18,000 relevant observations will be available for analysis. We will consider survival to hospital discharge, bystander CPR, and bystander defibrillation to be key outcomes of interest over the study period. We hypothesise that of the timeline of OHCA developments described above, two key developments are likely to be associated with a significant change in outcomes. Given the scale of reorganisation and centralisation of EMS control in 2015 and 2016 on the backdrop of the ongoing NAS 'one life' project we hypothesise that the NAS transition from a system of multiple regional independent control centres to the single national control centre (NEOC) would be associated with improvements in bystander CPR and survival to hospital discharge. In turn, given Covid-19's detrimental effect on OHCA internationally we hypothesise that COVID-19 would be associated with significant reductions in bystander CPR, bystander defibrillation and survival to hospital discharge in Ireland.

Study aims

The study will have four aims.

- To summarise key trends in available OHCAR data from the period 2012 – 2020
- To harness available OHCAR data to explore and model predictors of 'bystander CPR', 'bystander defibrillation' and 'survival to hospital discharge'
- To explore the hypothesis that significant system level developments in 2015 & 2016 (the National Ambulance Service transition to a single national control centre) were associated with a temporal improvement in the above outcomes
- To explore the effect of COVID-19 on the above outcomes.

Methods

Study design

Key trends in available OHCAR data from the period 2012 – 2020 will be described and evaluated using descriptive summaries and graphical displays. Multivariable logistic regression will be used to model predictors of 'bystander CPR', 'bystander defibrillation' and 'survival to hospital discharge' and to explore the effects (if any) of system level developments in 2015/2016 and the COVID-19 pandemic on these outcomes. The R software for statistical computing will be used for analysing the data.

Study population, setting and time frame

The population for this study will be patients of all ages who suffered un-witnessed, or bystander witnessed OHCA during the time period 2012 – 2020 and are included in the Irish national OHCAR cardiac arrest registry database. Patients who had an EMS witnessed OHCA will be specifically excluded from this current study. Follow on work will consider this distinct excluded group separately.

Variables and categories of concern

All analysis will be based on the variables shown in Table 1. Variables 1–19 will be obtained from the OHCAR. Variables 20, 21 and 22 represent component time periods that are a priori considered to be potentially significant in the context of either system level developments or key population health challenges (Covid-19) during the study time period. Variables 20,21 and 22 will be dummy variables created using the 'Year' variable. Variables 20 and 21 will be linked dummy variables derived from the same 3-level categorical indicator of period and will be simultaneously included in regression models. We do not expect collinearity of these predictors, as transition and post-transition period correspond to years 2015 and 2016, and 2017 through 2020, respectively. The Covid period dummy variable (variable 22) will be an indicator of 2020 only, and thus should allow us to estimate any shift in survival in the final year of the study data. Table 1 highlights the independent variables that will be explored for each outcome of interest. Where an original OHCAR variable has multiple potential associated categories, we will collapse these categories to avoid decreased statistical power from analysis of an excessive number of potentially sparse categories. Original and collapsed categories are shown in Table 1. Season will represent the 'winter' healthcare period (October to March) as compared to other as 'winter' is a period of increased demand for the Irish healthcare service. The three time categories chosen are adopted based on previous OHCA research[44].

Table 1. **Variables for analysis.**

Variable Number	Variable	Categories	Collapsed Categories	Outcome of Interest		
				Bystander CPR	Bystander Defibrillation	Survival to Hospital Discharge
1	Airway Management	Basic Management	None of the listed devices used, OPA/NPA, No advanced airway			*
		Supraglottic airway device				
		Intubation				
2	Aetiology	Presumed Other	Trauma, Respiratory, Submersion, Non-cardiac, Other	*	*	*
		Presumed Cardiac				
3	Age	Age (years)		*	*	*
4	Sex	Female		*	*	*
		Male				
5	Call Response Interval	Call Response Interval (minutes)		*	*	*
6	Incident location	Other Location	Industrial, Public building, GP Surgery, Farm, Sport place, Residential institution, Street, Ambulance, Other	*	*	*
		Home Location				
7	Mechanical CPR	No Mechanical CPR Provided				*
		Mechanical CPR Provided				
8	Season	Winter	October–March	*	*	*
		Other	April–September			
9	Year	Year (continuous variable 2012–2020)		*	*	*
10	First Shock Delivered By	Not Applicable				*
		Bystander Defibrillation				
		EMS Defibrillation				
11	Shockable Initial Rhythm	Non-Shockable Initial Rhythm				*
		Shockable Initial Rhythm				
12	Chest Compressions Started By	EMS initiated CPR				*
		Bystander CPR				
13	Time of Day	Night		*	*	*
		Evening				
		Morning				

Variable Number	Variable	Categories	Collapsed Categories	Outcome of Interest		
				Bystander CPR	Bystander Defibrillation	Survival to Hospital Discharge
14	Total No of Shocks Delivered	Total No of Shocks Delivered				*
15	Who Witnessed Collapse	Not Witnessed		*	*	*
		Bystander Witnessed				
16	Urban or Rural	Rural Location		*	*	*
		Urban Location				
17	Weekday or Weekend	Weekend		*	*	*
		Weekday				
18	Number of Adrenaline Doses	Number of Adrenaline Doses				*
19	Amiodarone Administered	Amiodarone Not Administered				*
		Amiodarone Administered				
20	Transition Period (2015 & 2016)	Transition Period (2015 & 2016)		*	*	*
		Not Transition Period				
21	Post Transition Period (2017–2020)	Post Transition Period (2017–2020)		*	*	*
		Not Post Transition Period				
22	Covid Period	Covid Period (2020)		*	*	*
		Not Covid Period				

Home (versus other) location was chosen as home represents the most common location for OHCA in Ireland. 'Year' (variable 9) will be treated as a continuous variable to conserve degrees of freedom and statistical power.

Statistical model building and interpretation procedures

For each outcome we will build a logistic model: initially a full model with all relevant predictors will be fitted. A refined model will then be built using a stepwise model selection procedure (STEPAIC function in R). This procedure builds several models from all possible combinations of the predictors by sequentially adding and dropping predictors and finally selects the model with the lowest AIC. The stepwise model will then be further improved by examining addition of pairwise interaction variables and retaining any interactions which improve fit. We will evaluate each model (full, stepwise and with interactions) based on AIC. In addition, the model deviance and a Hosmer-Lemeshow Goodness of Fit (GOF) test will be inspected for each model. To assess linearity between continuous predictors and the log odds of the outcome we will rely on good model fit as indicated by the Hosmer-Lemeshow goodness of fit test. We will also use logistic regression with higher order terms (polynomial terms) to explore if the relationship between the outcome and the continuous predictors is indeed non-linear. If higher-order terms are significant, these will be retained in the model, otherwise they will be dropped from the model. We will also attempt to ameliorate fit by including pair-wise interaction terms between predictors. We will summarise the effect of each individual variable in the final model using odds ratios and 95% confidence intervals. The effect of any significant interactions in the final model will be explored graphically. After selecting the final model from the three models, we will evaluate the predictive ability of the final best fitting model using 10-fold cross-validation and evaluate the prediction accuracy for the model.

Missing data and sensitivity analysis

We anticipate some missing data in both the outcome and predictor variables. We will document the amount of missing data for each variable and graph missing data patterns across the entire dataset. To conduct sensitivity analysis, results from complete case analysis and multiple imputation will be presented. Multiple imputation will be done using the mice package in R, ten imputations will be derived, and the selected model will then be fit to these datasets, and the results will be compared with the complete case dataset.

Ethical considerations

Research ethics approval has been obtained from National University of Ireland Galway, Research Ethics Committee (Reference 2020.01.012; Amend 2106).

The dataset used for this study will be anonymised prior to receipt by the research team. It will be impossible for the research team to identify or contact participants.

The National Ambulance Service Research Group have given permission for this anonymised data to be utilised for the purposes of this study.

OHCAR operates under 'implied consent'. OHCAR does not contact patients, hospitals are advised to inform patients that they are included in OHCAR and what their rights in this regard are. Patients can have their data removed from the registry at their request.

Dissemination plan

Study results will be disseminated via presentation at national and international scientific meetings and will be published in a peer reviewed scientific journal. No other associated data will be disseminated.

Discussion

This project will provide the most comprehensive analysis of Irish out-of-hospital, cardiac arrest registry data to date. By exploring and modelling predictors of 'bystander CPR', 'bystander defibrillation' and 'survival to hospital discharge' over time, the project will yield a more granular and context specific understanding of the factors that can influence these key outcomes. In turn these data can be used to inform the evolution and future design of the system of community emergency care in Ireland. At the outset it is important to highlight that this project will have some important limitations. Beyond the OHCAR registry data set and the high-level overview of system developments presented in Figure 1, there is limited process data available on the system initiatives described. For instance, little data is available on community first responder activations over the relevant time period[40]. Furthermore, the involvement of these responders in the OHCA care process has traditionally not been well captured although recent efforts will address this data deficit into the future[36]. Ultimately if system developments are found to be associated with key outcomes it may be that in reality other confounding variables are in fact driving these outcomes. Previous work has demonstrated that the internationally agreed 'Utstein' registry variables that are the basis for this planned study explain only 51% of the variation in survival following OHCA[45]. Thus, even following this planned research exercise important gaps in our understanding of OHCA outcomes in Ireland will remain. A further follow-on project is already planned to address this issue and is currently negotiating data linkage approvals. This project will aim to link OHCAR registry data with hospital in-patient data and geospatial census data to further enhance the scientific understanding of the variation in survival following OHCA. In the interim this current planned project serves to provide a critical baseline understanding of outcomes based on the registry dataset.

Data availability

No additional data are associated with this article.

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Open Peer Review

Current Peer Review Status: ✔ ? ✔ ✔

Version 2

Reviewer Report 10 November 2023

https://doi.org/10.21956/hrbopenres.15142.r36870

✔ **Kyndaron Reinier**
Smidt Heart Institute, Cedars-Sinai Health System, Los Angeles, California, USA

The authors have adequately addressed concerns in my earlier review.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Prediction of out of hospital sudden cardiac arrest risk.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 08 November 2023

https://doi.org/10.21956/hrbopenres.15142.r36873

? **Stuart Howell**
Monash University, Melbourne, Australia

I still have concerns over the assessment of effects associated with the transition period, the post transition period and the COVID period on the outcomes of interest. The authors don't expect collinearity because the 3 variables represent different time periods. However, this overlooks the fact that the time periods for the reference groups for these 3 variables overlap (Not transition, Not post transition and not COVID). The additional inclusion of year as a continuous variable in their models as implied in the variables section may exacerbate this.

The analysis of the transition period versus not transition period (Q20) remains problematic since

the reference category (not transition) would include 2012-2014 and 2017-2020 data. Any improvement post-transition could well be offset by poorer performance in the pre-transition period, resulting in estimates biased toward the null (no difference between transition and not transition).

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics; statistics; analysis of OHCA registry data.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 02 November 2023

https://doi.org/10.21956/hrbopenres.15142.r36871

Christopher M Smith
Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, England, UK

Thank you for clarifying the points raised last time.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Out-of-hospital cardiac arrest

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 04 September 2023

https://doi.org/10.21956/hrbopenres.14984.r35455

Kyndaron Reinier

Smidt Heart Institute, Cedars-Sinai Health System, Los Angeles, California, USA

Summary:
This manuscript provides a clearly written, comprehensive plan for analysis of the Irish Out of Hospital Cardiac Arrest Registry (OHCAR) data from 2012-2020. The authors have provided good rationale for their planned studies. They have also defined their research questions and outcomes explicitly, and carefully defined their variables of interest. The proposed analysis plan is appropriate.

Major comments:

1. In Figure 1, is the "Call-Check-Compress" campaign the same as the "Pre-Hospital Emergency Care Council national Citizen CPR" programme (described in text, pg. 4)? If so, consider clarifying this?

2. Table 1 – clarify in the text and in Table 1 whether the registry includes OHCA with EMS response but without attempted resuscitation (eg, an unwitnessed arrest with an EMS assessment that resuscitation would be futile, or an individual with EMS response but with a do-not-resuscitate order) and briefly describe how or if these cases will be included in analysis.

3. Table 1 – if the data is available, consider dividing non-shockable rhythm into pulseless electrical activity and asystole, at least for initial analyses.

4. Pg. 5, aims: For analysis of system-level developments (aim 3) consider excluding the COVID-19 pandemic time period, or if this time period is included, consider conducting a sensitivity analysis to determine whether conclusions are influenced by potential COVID-related changes in patient-level or system-level factors.

Minor comments:

1. Pg. 3, 2nd para under heading of "Out of Hospital Cardiac Arrest & Quality Improvement Registries", "Register (OHCAR)" should be "Registry (OHCAR)".

2. Pg. 3, paragraph under heading of "Emergency medical services in Ireland", the relationships between Health Services Executive and National Emergency Operations Center are a bit confusing.

3. Pg. 4, "potentially render the programmes' cost effective" – the apostrophe is not necessary.

4. Figure 1 is very readable. However, I wonder whether it could be improved by putting community-level efforts (eg, Lay CFR expansion (?)) on one side and health system-specific efforts (eg, NAS One Life QI project) on the other? Please disregard if I have misinterpreted the distinction between the two efforts.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Prediction of out of hospital sudden cardiac arrest risk.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 Oct 2023

Tomás Barry

Many thanks for your review and comments. Your input has been most useful in improving our paper.

- We have now clarified in the manuscript that the "Call-Check-Compress" campaign is the same as the "Pre-Hospital Emergency Care Council national Citizen CPR" programme.
- We have now clarified in the manuscript that during the period considered in this study OHCAR does not include OHCA with EMS response but without attempted resuscitation.
- We have not divided non shockable rhythm into PEA and asystole as this specific rhythm data is only available for a portion of cases. We anticipate though that follow on analysis will focus on patients with these individual rhythms for whom these data are available.

Competing Interests: No competing interests were disclosed.

Reviewer Report 01 September 2023

https://doi.org/10.21956/hrbopenres.14984.r33549

?

Christopher M Smith
Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, England, UK

Thank you for the opportunity to review this protocol. I have set out my thoughts and a few queries below.

Rationale

- The rationale for this project, the burden of OHCA and the potential to use this project as a springboard for inclusion is well described.

- Page 3, paragraph 5: "*We anticipate that approximately fifty percent of cases recorded in OHCAR are witnessed (European average 66%), and twenty percent have an initial 'shockable rhythm' (European average 20%).*"

  Your reasoning for anticipating these figures is not clear to me. Is it from previous interrogation of the registry?

- There are a number of potential confounders that will affect the certainty of any conclusions drawn from this project. However, importantly, these limitations are recognised, have been explicitly stated in the discussion section, and there are plans to address these potential shortcomings in the future. This transparency and recognition of the limitation of registry-based research is important and good to see.

Study Design

- A review of data submitted to a national database, with a well-defined population. I have no concerns about the overall approach.

Methods

- I have some experience with logistic regression modelling, including when applied to an OHCA dataset. While the statistical methods sound reasonable to me, I must make it clear that I am not a statistical expert and cannot therefore provide a comprehensive statistical opinion or review.

- Page 7, paragraph 4: Ethical considerations: "*hospitals are advised to inform patients that they are included in OHCAR and what their rights in this regard are.*"

  Do patients have the opportunity then to opt-out of having their data in the registry? I anticipate that this number of cases that this applies to would be small if so, but do you have any information about this?

- The Irish OHCAR is clearly the right source of information for this data. The registry and its case are adequately described. There is some potentially useful data that are not available from this source – e.g. actions of CFRs – but this limitation is acknowledged and discussed.

Some queries about the data being used:

1. Item 11: does non-shockable rhythm have PEA, asystole (+/- others e.g. bradycardias in infants) in its collapsed categories?

2. Page 6, Table 1, Item 20/21. I am slightly confused by this. If you were to look at item 20 alone, you might think that you were comparing both before (2012-2014) and after (2017-2020) together to the transition period (2015-16). I don't quite understand that rationale as I

think a reasonable hypothesis (alongside your existing hypothesis that the NEOC transition was a beneficial thing) might be that 2017-20 (or at least 2017-2019) outcomes would be better than 2012-14, as a result of the changes brought about during the transition phase. If you then look at item 21 I wonder whether you actually are doing a three-way comparison of before-during-after transition. This could perhaps be clarified. If we then look at item 22, is there an argument for making the post-transition period 2017-19. If you have a strong argument for not doing that, then this could be made clearer.

Other minor points

- Last line of abstract, background: "*and to explore the hypothesis that significant system level temporal developments were associated with improvements in these outcomes.*" This presumes that there were improvements in these outcomes in the first instance for you to hypothesise what the causes were. Would 'changes' rather than 'improvements' be a better word, or do you know already that these outcomes improved over the study time-period?

- Last sentence of abstract, discussion. You have capitalised and spelled out 'Out-of-Hospital Cardiac Arrest' rather than 'OHCA' used earlier.

- Page 3, paragraph 1: "appropriate" rather than "on appropriate"; "survive to hospital discharge" rather than "involve survival to hospital discharge"

- Page 3, paragraph 2: "*CPR and defibrillation are complemented by several other OHCA interventions…*" Consider the wording of this, as you then go on to describe a number of interventions for which there is NOT (yet, perhaps) evidence of benefit at population level.

- Page 3, paragraph 5: You use the term 'Register' not 'Registry' when describing the OHCAR.

- Page 4, last paragraph: "*In 2015 and 2016 the National Ambulance Service transitioned from a system of multiple regional independent control centres to a single national control centre NEOC* ". Needs either a hyphen before or brackets around NEOC.

- Page 5, paragraph 2: "reduction" or similar may be a better word than "dis-improvement".

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Out-of-hospital cardiac arrest

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 Oct 2023

Tomás Barry

Many thanks for your review and comments. Your input has been most useful in improving our paper.

- Our anticipation that 50% of cases will be witnessed is indeed based on co-authors existing experience of the registry.
- We have clarified in the manuscript that patients can have their data removed from the registry at their request.
- Non-shockable rhythm does incorporate PEA ,asystole etc. For some patients the actual rhythm is documented, however for others it is only known whether the rhythm is shockable or non-shockable.
- In relation to the confusion concerning variables 20 and 21 we have now further clarified this in the manuscript. Our approach is to examine transition period and post-transition (including 2020 as the post-transition effect should still be present despite having a Covid-19 effect layered on top), as contrasts with pre-transition. Variables 20 and 21 are linked dummy variables, and will not be modelled separately.
- In relation to our hypothesis 'that significant system level temporal developments were associated with improvements in these outcomes', we appreciate your suggestion to use alternative language, however feel 'improvements' is appropriate as this is a hypothesis based on said temporal developments having a stated aim of improving those outcomes.
- Typographical suggestions have been incorporated as advised.

Competing Interests: No competing interests were disclosed.

Reviewer Report 01 September 2023

https://doi.org/10.21956/hrbopenres.14984.r35454

?

Stuart Howell
Monash University, Melbourne, Australia

Overall:

This is a unique study in that it is attempting to explore the impact of system level developments and COVID on trends in bystander CPR rates, bystander defibrillation and survival to hospital discharge as well as to identify key predictors of each outcome. I have no concerns with the overall design of the study as it replicates the methodology applied in similar research. However, I am not convinced that the proposed analysis will address the study's aims. Some areas that the authors should consider are as follows:

Study population:

The study population excludes EMS-witnessed arrests, which is reasonable and has precedent in previous research. The authors should also consider restricting the sample to arrests in adults as the characteristics of arrests in paediatric patients are fundamentally different to those in adult samples.

Variable definitions:

The decision to restrict categorical variables to three levels seems arbitrary and the reclassification of variables should be determined on a variable-by-variable basis. There are two variables where this strategy leads to a loss of information – seasonality, which is dichotomised as winter versus summer, when a four-level categorical variable (spring, summer, autumn, winter) makes better sense; in time of day, afternoon is missing without any justification given apart from (presumably) the restriction to three categories.

The authors should consider separating "Other" location (of arrest) into public places versus other (non-public) locations. Arrests in public locations are more likely to be witnessed, which may influence bystander CPR and defibrillation rates, and consequently, survival via these mechanisms.

Age, year and epinephrine dose are included as continuous variables and non-linearity needs to be considered. In particular, non-linearity is implied with respect to year as your expectation is that the transition period will lead to improvements in the outcomes, while COVID will have a detrimental effect. The authors need to explain how they will assess and deal with any non-linearity in their continuous variables.

Analysis:

I think that the authors' proposed method for analysing the effect of the transition and COVID may lead to results that are biased. In variable 20, the transition period is compared to the non-transition period, which presumably includes the pre- and post- transition period. This may bias results to the null as gains in the post-transition period may be offset by poorer outcome performance in the pre-transition period. Similar problems may occur in aggregating the pre-transition and transition periods in the comparison with the post-transition period (variable 21) and when comparing the COVID to the pre-COVID period (variable 22). Furthermore, including all three variables as well as year may introduce problems with collinearity during modelling.

In my opinion, the authors should consider a piecewise logistic regression model, which would provide them with separate slopes and intercepts to describe the trends associated with the pre-transition, transition, post-transition and COVID periods. They could then include the remaining predictors in their model (except for year, transition periods and COVID) which would describe the effect of each variable on the outcome after adjusting for the trend over periods. If the year range doesn't provide sufficient data points for modelling, then the analysis could be done using quarter rather than year (i.e.: 36 quarters over the 9 year study period). It is easy enough to extrapolate the model coefficients to report the outcomes as annual trends if need be.

The authors also need to be clear on what type of modelling they are undertaking. Their proposed approach is closely aligned to risk prediction (or prognostic) modelling where the goal is to develop an algorithm that allows the prediction of risk in an individual with a given set of covariate values. In this case, issues such as model discrimination and validity and prediction accuracy are important and should be investigated thoroughly.

However, I'm not convinced that this consistent with the study aims. In my mind, the goal here is effect estimation, where the goal is to identify and describe variables that are associated with the outcomes of interest. In this instance, model reduction provides fewer gains than for risk prediction models and model validation is generally unnecessary.

The authors should also note that stepwise regression has numerous problems and is no longer widely recommended as a variable selection strategy. Its application via automated programs such as STEPAIC is not to be recommended.
The following book is a useful resource:

Frank E Harrell, Jr. Regression modelling strategies. With applications to linear models, logistic and ordinal regression and survival analysis. 2nd Edition. Springer Series in Statistics.

References

1. Harrell, Jr FE: Regression modelling strategies. With applications to linear models, logistic and ordinal regression and survival analysis. 2nd Edition. *Springer Series in Statistics*.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics; statistics; analysis of OHCA registry data.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 Oct 2023

Tomás Barry

Many thanks for your review and comments. Your input has been most useful in improving our paper.

- In relation to considering restricting the sample to arrests in adults. We agree that the characteristics of OHCA in paediatric patients may be different to those in adults. However, we also anticipate that even within the adult population there may be significant variation in characteristics. For this reason, we have adopted an initial whole population-based approach. We do acknowledge that follow on research that focuses on relevant subgroups may well be warranted.
- In relation to collapsing categorical variables we have clarified the justification in the manuscript as suggested on a variable by variable basis. Season represents the 'winter' healthcare period (October to March) v other as 'winter' represents a period of increased demand for the Irish healthcare service. The three time categories were adopted based on previous OHCA research (https://doi.org/10.1016/j.ijcard.2020.09.043.) Home versus other location was chosen as home represents the most common location for OHCA in Ireland. While we agree that public locations are very important in terms of OHCA, some of the other categories do not clearly fall fully under public locations and thus a home v other categorisation was felt most appropriate. We do acknowledge that follow on research may be necessary to focus on OHCA at more specific locations.
- We acknowledge the reviewer's concern about potential non-linearity in our analysis, given the fact that we have several continuous predictor variables. In logistic regression models it is difficult to assess linearity between continuous predictors and the log odds of the outcome, so we rely on good model fit as indicated by the Hosmer-Lemeshow goodness of fit test. We will also use logistic regression with higher order terms (polynomial terms) to explore if the relationship between the outcome and the continuous predictors is indeed non-linear. If higher-order terms are significant, these will be retained in the model, otherwise they will be dropped from the model. We will also attempt to ameliorate fit by including pair-wise interaction terms between predictors.
- In relation to the proposed method for analysing the effect of the transition and COVID periods the reviewer is correct that an analysis of variable 20 alone would produce incorrect results. However, variables 20 and 21 are linked dummy variables derived from the same 3-level categorical indicator of period and will be simultaneously included in regression models. When variable 20 is adjusted for variable 21, the inference for transition period compared with pre-transition should be as expected. We do not expect collinearity of these predictors, as transition and post-transition period correspond to years 2015 and 2016, and 2017 through 2020, respectively. The Covid period dummy variable is an indicator of 2020 only, and thus should allow us to estimate any shift in survival in the final year of the study data.
- We appreciate your suggestion to consider a piecewise logistic regression model and

note that this is similar to the approach we are taking with dummy-coding for period, along with the plan to test for pair-wise interactions (including between period dummy variables, and continuous year). The plan is to aggregate data by year, examining yearly trends, while also controlling for seasonal (winter v other) effects, and there are sufficient data points in each year to allow this approach.

- We do acknowledge the fact that our proposed methodology may be related to the prediction of risk or prognostic modelling. Our main goal in this study is, in fact, effect estimation. We aim to identify and describe variables that are associated with the outcomes of interest. Below are our considerations.
- Effect Estimation: Our main aim is to estimate the effects of various predictor variables on the binary outcomes. We want to understand how these factors are associated with the outcomes. We are not focused on developing a predictive algorithm for individual risk assessment.
- Model Reduction: We agree that for estimating effect sizes, extensive model reduction efforts may provide few gains and fail to reduce important confounding. We have some concerns about estimation with relatively rare interventions or small risk groups, in which context maintaining some precision can be done by removing predictors with no, or negligible, effects. We also view simple and easily interpretable models as an advantage.
- Model Validation: We appreciate the reviewer perspective that for effect estimation, model validation may be considered unnecessary. However, we still believe it is essential to assess the performance of our models, even in an effect estimation framework. Generation of predicted probabilities can provide diagnostics for outliers or poor fit for subsets of the sample, and re-sampling based methods also give a less biased estimate than the R-squared, for example, of the fit of the model, circumventing the 'Winner's Curse' effect.
- In relation to the reviewers concerns regarding stepwise regression and the reference highlighted - We acknowledge that methods such as penalized regression have certain advantages for selecting variables with important effects, although may bias effect size towards zero. Given our concerns mentioned about inference with rare interventions or categories, and wishing to remove clearly irrelevant predictors, we believe the approach we have outlined is reasonable. We acknowledge that effect sizes may be inflated, and p-values too liberal, as is also the case in sample sizes this large (potentially including for clinically irrelevant effects). We do not plan to make claims of effects based on statistical significance, and will interpret the effect sizes and confidence intervals with a degree of caution given the inflation.

Competing Interests: No competing interests were disclosed.

Reviewer Report 12 July 2023

https://doi.org/10.21956/hrbopenres.14984.r34169

Marc Conterato

[1] North Memorial Emergency Medical Services, Robbinsdale, Minnesota, USA

[2] School of Medicine, University of Minnesota Twin Cities, Minneapolis, Minnesota, USA

This proposed study is well thought out and has a relatively broad scope to evaluate and discern the effect of multiple changes to the Irish OHCAR network and data capturing. The modeling proposed is quite well thought out and should yield a least two strongly linked initiatives that enhanced improvements in OHCAR. Use of the AIC system should yield adequate models to point to system changing events.

While some data may not be adequately captured do to information gathering deficiencies in the system, I would find it interesting if those were reported with the final study report, as they would indicate areas for further study and system improvement.

In addition, it might be better for the study to possibly exclude or alternatively factor data that could be affected by COVID. It has been well shown that COVID caused an increase in cardiac arrest numbers and increase in mortality. My concern is that these data sets may produce confounding results that may affect the final modeling sets that are reached. Perhaps having the study show models with and without COVID data may offer clearer results.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Emergency medicine, EMS systems and oversight, pre-hospital cardiac resuscitation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 27 Oct 2023

Tomás Barry

Many thanks for your review and comments. Your input has been most useful in improving our paper.

- In relation to data not adequately captured, we endeavour to describe the level of missing data across the dataset and consider the implications when interpreting our findings.
- In relation to data that is potentially affected by COVID-19. We agree this is important and thus have included a dummy variable that represents the Covid period. This will allow us to model, estimate and adjust for any independent effect that may be present.

Competing Interests: No competing interests were disclosed.