

## Accepted Manuscript

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PII: S0300-9572(18)30179-5  
DOI: <https://doi.org/10.1016/j.resuscitation.2018.04.018>  
Reference: RESUS 7575

To appear in: *Resuscitation*

Received date: 9-1-2018  
Revised date: 23-3-2018  
Accepted date: 14-4-2018

Please cite this article as: Haegdorens Filip, Van Bogaert Peter, Roelant Ella, Meester Koen De, Misselyn Marie, Wouters Kristien, Monsieurs Koenraad G. The introduction of a rapid response system in acute hospitals: a pragmatic stepped wedge cluster randomised controlled trial. *Resuscitation* <https://doi.org/10.1016/j.resuscitation.2018.04.018>

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## Title

The introduction of a rapid response system in acute hospitals: a pragmatic stepped wedge cluster randomised controlled trial.

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## **ABSTRACT**

### **Aim**

Deterioration of hospitalised patients is often missed, misinterpreted, and mismanaged. Rapid Response Systems (RRSs) have been proposed to solve this problem. This study aimed to investigate the effect of an RRS on the incidence of

unexpected death, cardiac arrest with cardiopulmonary resuscitation (CPR), and unplanned intensive care unit (ICU) admission.

## Methods

We conducted a stepped wedge cluster randomised controlled trial including 14 Belgian acute care hospitals with two medical and two surgical wards each. The intervention comprised a standardised observation and communication protocol including a pragmatic medical response strategy. Comorbidity and nurse staff levels were collected as potential confounders.

## Results

Twenty-eight wards of seven hospitals were studied from October 2013 until May 2015 and included in the final analysis. The control group contained 34,267 patient admissions and the intervention group 35,389. When adjusted for clustering and study time, we found no significant difference between the control and intervention group in unexpected death rates (1.5 vs 0.7 /1000, OR 0.82, 95%CI 0.34 to 1.95), cardiac arrest rates (1.3 vs 1.0 /1000, OR 0.71, 95%CI 0.33 to 1.52) or unplanned ICU admissions (6.5 vs 10.3 /1000, OR 1.23, 95%CI 0.91 to 1.65).

## Conclusion

Our intervention had no significant effect on the incidence of unexpected death, cardiac arrest or unplanned ICU admission when adjusted for clustering and study time. We found a lower than expected baseline incidence of unexpected death and cardiac arrest rates which reduced the statistical power significantly in this study.

*“WHAT THIS PAPER ADDS”*

**What is already known on this subject**

- The literature shows inconsistent findings about the effect of Rapid Response Systems on patient outcomes in acute hospitals.
- Nearly all previous studies are before-and-after historically controlled trials, therefore the strength of the evidence to support the use of Rapid Response Systems is only low to moderate.
- In systematic reviews, data were often pooled from studies with low methodological quality, heterogeneous interventions and poorly defined outcomes.

**What this study adds**

- Our study found no significant effect of a Rapid Response System on patient outcomes in acute hospitals.
- We reported a lower than expected incidence of unexpected death and of cardiac arrest when using more accurate definitions of these frequently reported outcome indicators.
- The low incidence of our primary outcomes reduced the statistical power of this study significantly. Therefore it is difficult to draw conclusions given the current sample size.

**ABBREVIATIONS**

ALARM: Afferent Limb Ascertainment and Response Method

CCI: Charlson Comorbidity Index

CPR: Cardiopulmonary Resuscitation

DNR: Do Not Resuscitate

EWS: Early Warning Score

GLMM: Generalised Linear Mixed Model ICU: Intensive Care Unit

LMM: Linear Mixed Model

NHPPD: Nursing Hours Per Patient Day

RCT: Randomised Controlled Trial

RR: Relative Risk

RRS: Rapid Response System

SBAR: Situation, Background, Assessment, Recommendation

*MANUSCRIPT*

## **INTRODUCTION**

In-hospital unexpected death, cardiopulmonary arrest and unplanned admissions to the intensive care unit (ICU) are often preceded by long-lasting abnormalities in the patient's vital signs [1]. Clinical deterioration can be missed, misinterpreted, or mismanaged suggesting that some of these adverse outcomes are preventable [2]. Rapid Response Systems (RRSs) aim to detect and interpret in-hospital clinical deterioration, to enhance communication between caregivers, and to initiate an appropriate response in a timely manner [3]. Early Warning Scores (EWSs) are the most common and effective track-and-trigger systems combining vital signs in a weighted score that estimates the risk of deterioration [4]. To date, the quality of the evidence about the effect of RRSs on patient outcomes is poor and there is no consensus regarding the most effective strategy to prevent adverse outcomes [5-8].

This study aims to investigate the effectiveness of an RRS including a standardised observation and communication protocol using the National Early Warning Score (NEWS) and the Situation, Background, Assessment, and Recommendation (SBAR) communication method in acute hospitals in Belgium.

## **METHODS**

### **Study design and participants**

We conducted a pragmatic, stepped wedge cluster randomised controlled trial in Belgian acute hospitals from October 2013 to May 2015 [9]. The study comprised five periods of four months each (T0-T4) with phased introduction of the intervention. Acute care hospitals were eligible when they had at least two medical and two surgical wards with each at least 850 admissions per year, an ICU, a resuscitation team available 24/7, and no implemented RRS or EWS. All patients admitted to the participating wards within the study period were included. Patients were excluded if they were pregnant or below 17 years of age. After inviting 104 Belgian acute hospitals to an informative meeting, 14 hospitals were found eligible and willing to participate. Previous research reported an incidence of unexpected death in Belgian hospitals of 0.8% [10]. Assuming the inclusion of six hospitals with in total 24 participating wards with a yearly average of 1400 admissions per ward, the anticipated study would have a statistical power of 83% to detect a 50% reduction of in-hospital unexpected death (from 0.8% to 0.4%) at a significance level of 0.05 [11]. To maintain sufficient statistical power even after dropout, we included all eligible hospitals. Approval of the ethics committees of all local hospitals was obtained before the start of the study (registration number: B300201317835). This study was submitted to a clinical trial registry (clinicaltrials.gov identifier: NCT01949025).

### **Randomisation and blinding**

Each hospital selected two medical and two surgical wards. To prevent imbalance across treatment groups and to ensure that training had to be organised only twice for each hospital, one surgical and one medical ward per hospital were randomly paired and assigned as a block to the intervention. In total 56 wards were enrolled and randomly allocated to four groups. The computerised randomisation was performed by KW who was not involved in the further conduct of the study.

### **Intervention**

The intervention comprised a standardised observation and communication protocol with a pragmatic medical response strategy. At least one project manager per hospital was appointed. We introduced a standardised observation and communication protocol using the NEWS and SBAR communication method. The NEWS was chosen because it showed superior performance when compared to 33 other EWSs [4]. Hospitals integrated the NEWS in their own paper based or electronic patient record. An implementation plan was made and discussed with all project managers to ensure uniformity. One week before the start of the intervention the ward nurses received an interactive training concerning the measurement and interpretation of vital signs, clinical observation, communication skills, and practical tips and tricks in handling NEWS and SBAR. The trainers (FH and MM) were experienced practising nurses. The mandatory training lasted four hours and was based on the innovation-decision theory by Rogers E [12].

Hospitals were expected to organise an around-the-clock medical response strategy for every participating ward. This strategy had to be based on a response flowchart



template which was provided as part of the intervention. The response strategy had to include the clinical risk (low, medium or high) corresponding to the NEWS, appropriate interventions, contacts with telephone numbers, maximum waiting time to medical support and backup procedures in case regular medical support was not available.

We applied a team-directed implementation strategy based on previous healthcare research to maximize adoption [13]. All information about the intervention was available through a study website including a short knowledge test for nurses.

## **Outcomes**

The primary outcomes of this study were unexpected death, cardiac arrest with CPR and unplanned ICU admission. All outcome indicators pertained to the individual participant level (patient admissions to the study wards). A patient's death was classified as unexpected in this study if we found no evidence in patient records of a do not resuscitate (DNR) order, palliative or terminal care, family attending during the process of dying, cessation or limiting of active therapy in untreatable disease. Cardiac arrest was defined as sudden cardiac arrest followed by successful or unsuccessful cardiopulmonary resuscitation (CPR) while admitted to a study ward. Unplanned ICU admission was defined as urgent transfer from a study ward to the highest level of care (e.g. the ICU). Patients who were transferred to the ICU to undergo a technical procedure or for monitoring after surgery were excluded. There was no overlap between the primary outcomes.

Secondary outcomes were total ward mortality, ward mortality in patients without DNR code, and hospital mortality. Hospital mortality included all admitted patients who died on the study ward or up to 72 hours after discharge from the ward.

## Data collection

Three types of data were collected during this study: (I) longitudinal, (II) cross-sectional and (III) patient record review data. Longitudinal data (I) were collected and supplied by the hospitals. It consisted of baseline characteristics and date- and time-stamped crude outcome indicators (crude mortality, DNR code, resuscitation team calls and transfers to the ICU). Next, we collected cross-sectional samples (II) in each period (T0-T4) where we measured: comorbidity using the Charlson Comorbidity Index (CCI) (30 consecutive patient admissions across all wards starting on the last Monday of the second month of each period), the registered vital signs and NEWS values of admitted patients (including all patients admitted to the study wards in a 24-hour timeframe of a randomly chosen Tuesday in the second month of each period), and ward-specific data about nurse staffing levels (mandatory registration by the government, 15 days, four times per year, one registration in each period). We used the CCI to estimate comorbidity for each ward in separate time periods [14]. Nursing Hours Per Patient Day (NHPPD) were calculated for each ward. Hospitals were blinded for the collection date of the process indicators and the measurement of comorbidity. After receiving the database with longitudinal data from each hospital we conducted an extensive patient record review (III). The researchers reviewed each patient record in case of a crude outcome indicator. A standardised electronic checklist was used to collect data. Outcome indicator definitions were matched against patient records. In case of uncertainty, the patient record was reviewed and discussed by two independent researchers (FH and MM) to achieve agreement.

## Statistical analysis

All data was analysed using IBM SPSS Statistics version 24 for MAC OS and SAS 9.4 for Windows. One-way ANOVA and Pearson's Chi-Squared tests were used for baseline comparison of cluster characteristics. We calculated the baseline Relative Risk (RR) for all primary outcome indicators comparing surgical and medical ward patients [15]. All crude and primary outcomes are presented per 1000 patient admissions. Cross-over patients, who were admitted to a ward that transitioned from the control to the intervention group, were readmitted as a new study participant in the consecutive period. We used the Pearson's Chi-Squared test to compare the proportions of registered NEWS values between the control and intervention group. When analysing individual level data in stepped wedge trials, appropriate methods are needed to adjust for data clustering and temporal trends [16]. An individual-level Generalised Linear Mixed Model (GLMM) analysis automatically provides proper weighting when cluster sizes vary [17]. A GLMM was fitted with intervention and study time (period) as fixed effects and cluster (ward) as random effect. When GLMMs did not converge, as an approximation we fitted the dichotomous variables using linear mixed models (LMM) [18]. LMM was also used for continuous outcomes. A Mann-Whitney U test was used to compare the mean rate per 1000 admissions of all primary outcomes between the control and intervention group in each period.

## RESULTS

We initially included 14 hospitals but only seven hospitals completed the study (Fig 1). Four hospitals withdrew from the study because of the burden of data collection. One hospital had insufficient equipment available to measure a full set of vital signs. Two hospitals withdrew owing to shortage of staff. These seven hospitals were excluded from analysis because of unavailable data. Group three contained four more wards than the other groups because of hospital dropout. Half of all wards had a predominantly surgical focus. A total of 69,656 patient admissions were registered from October 1<sup>st</sup> 2013 until May 31<sup>st</sup> 2015 accounting for 350,397 patient days. The control group contained 34,267 patient admissions (Fig 2).

Baseline characteristics between clusters were compared in Table 1. Half of the participating wards (12 surgical and 2 medical wards) did not have a single patient who died unexpectedly during the baseline four-month period. Patients on surgical wards had a reduced risk of unexpected death compared to those on medical wards (RR 0.08, 95% CI 0.02-0.32). Seven wards, of which five surgical wards, had no unplanned ICU admissions during baseline measurements. Surgical ward patients had a reduced risk of unplanned ICU admission compared to medical ward patients (RR 0.46, 95% CI 0.29-0.73). We found no difference in the incidence of cardiac arrest with CPR between wards in T0 (Pearson's Chi-Squared,  $p=0.095$ ). On seventeen wards (61% of all wards), of which nine surgical wards, not a single patient had a cardiac arrest with CPR during baseline measurements. Patients on surgical wards had a similar risk of cardiac arrest with CPR compared to patients on medical wards (RR 0.58, 95% CI 0.21-1.62). In total, 25 patients died unexpectedly in T0 while admitted to a study ward. Accordingly, the baseline incidence of unexpected death was 2.21 per 1000 admissions. Fifteen patients experienced a cardiac arrest with CPR resulting in a

baseline incidence of 1.19 per 1000 admissions. A total of 78 patients were admitted to the ICU unplanned resulting in a baseline incidence of 5.68 per 1000 admissions.

In Table 2 patient characteristics, clinical confounders and crude outcome indicators were compared between the control and intervention group. The mean CCI (1.44 vs 1.59,  $p<0.001$ ) and mean NHPPD (2.49 vs 2.75,  $p<0.001$ ) were significantly higher in the intervention group than in the control group. Crude outcome indicators did not differ significantly between the study arms.

In 3001 patients of which 1381 in the control group, we collected during a 24-hour timeframe in each period (T0-T4) all registered vital signs and NEWS values. We found no patients with a single registered NEWS value in the control group while 79 percent of all patients in the intervention group had at least one registered NEWS value (Pearson's Chi-Squared,  $p<0.001$ ).

The incidence of unexpected death was 1.5 per 1000 admissions in the control group and 0.7 per 1000 admissions in the intervention group (Table 3). The proportion of patients with a cardiac arrest with CPR in the control group was 1.3 per 1000 admissions and 1 per 1000 admissions in the intervention group. We found an incidence of unplanned admissions to the ICU of 6.5 per 1000 admissions in the control group and 10.3 per 1000 admissions in the intervention group. We found no significant difference when comparing all three primary outcomes between the control and the intervention group after adjusting for clustering and study time (model 1) or when additionally controlling for the ward's CCI and NHPPD (model 2).

Primary outcomes were plotted on line charts comparing mean rates per 1000 admissions over study time periods (Fig 3). The mean incidence of unexpected death and cardiac arrest with CPR for each time point in the intervention group was consistently lower in the intervention group but not significantly different between

groups. The mean rate of unplanned ICU admissions was consistently higher in the intervention group but also not significantly different between groups.

## DISCUSSION

The introduction of our intervention did not have a significant effect on the primary outcomes. Odds ratios for unexpected death and unplanned ICU admissions only adjusted for clustering showed significance, but after adjusting for study time this effect disappeared. The most evident explanation for our findings is that our study is underpowered. Our power analysis was based on previous research with a mortality rate of 0.8% [10]. Studies evaluating the effect of an RRS on patient outcomes often include mortality as an outcome [6]. However, different definitions for mortality are used in the literature. In the MERIT trial, unexpected death was defined as 'all deaths without pre-existing DNR code' [8]. Nonetheless, a significant amount of seriously ill hospitalised patients who wanted CPR to be withheld, did not have a DNR code [20]. A death without DNR code may therefore have taken place in a palliative or terminal care setting and cannot automatically be categorised as unexpected. Accordingly, we adjusted the definition for unexpected death in our study to achieve a more accurate result. This resulted in a lower than expected baseline incidence which reduced the statistical power. Internationally, the baseline incidence of unexpected death varies between 0.16-2.08%, which is up to nine times higher than found in our study [8,21–23]. It is possible that the incidence of unexpected death on general wards has been overestimated in some studies due to the use of an imprecise definition. This could especially be the case in hospitals without embedded DNR protocols. Moreover, when comparing the incidence of ward mortality without DNR code in this study with our new

definition of unexpected death, we also noticed that the incidence of the latter is at least five times lower than the former.

Beside unexpected death, we also collected cardiac arrest and unplanned ICU admission rates. Previous studies regarding cardiac arrest rates are associated with multiple issues. First, cardiac arrest is defined in numerous ways in the literature (e.g., calling of a resuscitation team, no palpable pulse, respiratory arrest) [24]. Secondly, researchers sometimes report hospital-wide cardiac arrest rates, which are biased because they include ICU and emergency department cardiac arrest rates that are, in most cases, not a part of the exposure group. Lastly, when overlap between primary endpoints is allowed (e.g. death after cardiac arrest equals unexpected death), it becomes less clear what exactly is measured. In this study, only patients admitted to the study wards experiencing a cardiac arrest followed by successful or unsuccessful resuscitation were withheld. A baseline incidence of 3.74 cardiac arrests per 1000 admissions (range 1.11-7.76) can be deduced using data from a recent systematic review [25]. Baseline cardiac arrest rates were relatively low in this study (1.19 per 1000 admissions). We found an increasing trend in unplanned ICU admissions after RRS implementation. The effect of RRSs on ICU admission rates remains uncertain [25,27]. The baseline unplanned ICU admission rate in our study was 5.68 per 1000 admissions which is comparable to the findings in the MERIT trial (4.68 per 1000 admissions) [8]. Ludikhuize et al reported substantially more (19.80 per 1000) unplanned ICU admissions in their control group [26]. This shows that ICU admission rates are difficult to interpret when studying the effectiveness of RRSs. When deteriorating patients are detected timely, ICU admission rates could increase in hospitals where patients cannot be monitored continuously or treated effectively on the general ward.

We were only able to include 7 of the 14 hospitals initially agreeing to join this study which adds some risk of bias. After our randomisation procedure, four hospitals dropped out because of the perceived burden of data collection. During the first months of this study hospitals acknowledged that, despite good intentions, they were not able to deliver the data necessary for this study. One hospital dropped out because of insufficient equipment to measure a full set of vital signs and could therefore not participate. Lastly, two hospitals withdrew due to a shortage of staff and explained that their nurse staffing levels were too low to adhere to our observation protocol. Our baseline NHPPD data (T0), which concerned nurse staffing and workload, ranged from 1.53 to 3.57. In comparison, the industrial relations commission of Australia published NHPPD targets to improve the quality of care [28]. Their minimal advised target for moderate complexity acute care is 5.0 NHPPD. Only 4 of 28 wards included in this study had a baseline NHPPD greater than 3. Therefore, it is likely that adherence to our intervention could be difficult considering the comparatively low staffing levels of nurses.

## CONCLUSION

To our knowledge, this is the only randomised controlled trial that investigated the effect of a standardised observation and communication protocol using the NEWS and SBAR method. Although we did not prove the effect of our intervention on patient outcomes, our study has meaningful implications for future research, hospital management and governments. We showed that common outcome indicators measured when implementing RRSs can be biased and should be collected with care. Although systematic reviews were published trying to prove the effect of RRSs, data



were often pooled from studies with low methodical quality and using heterogeneous interventions and outcomes [6,25,27,29]. Researchers should publish clearly defined outcome indicators making it possible to pool data in a meta-analysis. Lastly, although critically ill patients may receive inadequate care in hospitals worldwide, the incidence of serious adverse events is possibly lower than reported previously. It is likely that these events are also less common because of patient safety and quality improvement initiatives over time. This does not imply, however, that new interventions to improve the quality of care should be abandoned.

### **Conflicts of interests**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: the authors received a grant from the Federal Public Service of Health, Food chain safety and Environment of Belgium for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; PVB is co-author of an ongoing update of a Cochrane systematic review with the following title: "Outreach and EWS for the prevention of ICU admission and death of critically ill adult patients on general hospital wards."

### **Funding statement**

The Belgian federal government sponsored this study but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The researchers assume final responsibility.

### **Transparency declaration and contributors**

FH is the guarantor of this paper and accepts full responsibility for the work and the conduct of the study, had access to all data, and controlled the decision to publish. The guarantor of this paper affirms that this manuscript is an honest, accurate, and transparent account of the reported study. We omitted no important aspects and explained discrepancies where needed.

FH and KDM did the literature search. FH, KDM, KW, PVB and KGM designed the study. FH designed the intervention strategy. FH and MM conducted the intervention and collected data. FH and ER analysed data. FH, KDM, ER, PVB and KGM contributed to data interpretation, writing, and revision of the report.

### **Acknowledgements**

The department of quality of care and patient safety of the Federal Public Service of Health, Food chain safety and Environment of Belgium with special thanks to dr. Margareta Haelterman.

The Centre for Research and Innovation in Care (CRIC) of the Department of Nursing and Midwifery at the University of Antwerp, Belgium.

All participating hospitals including hospital managers, project managers and health care providers in the participating wards.

We would like to thank Antonius Baeke, Jonas De Wolf, Hilde Driessens, Marleen Corremans, Caroline Roels, Katrien Vandamme, Karen Van Opstal, and Carine Van Vynckt for assisting during data collection.

## References

1. Findlay GP, Shotton H, Kelly K, Mason M (2012) Time to Intervene? A Review of Patients Who Underwent Cardiopulmonary Resuscitation as a Result of an In-hospital Cardiorespiratory Arrest: A Report by the National Confidential Enquiry into Patient Outcome and Death.
2. Sankey CB, McAvay G, Siner JM, Barsky CL, Chaudhry SI (2016) Deterioration to Door Time": An Exploratory Analysis of Delays in Escalation of Care for Hospitalized Patients. *J Gen Intern Med* 31: 895-900.
3. Devita MA, Bellomo R, Hillman K, Kellum J, Rotondi A, Teres D et al. (2006) Findings of the first consensus conference on medical emergency teams. *Crit Care Med* 34: 2463-2478.
4. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI (2013) The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation* 84: 465-470.
5. Edelson DP, Churpek MM (2012) Sifting through the heterogeneity of the Rapid Response System literature. *Resuscitation* 83: 1419-1420.
6. Alam N, Hobbelink EL, van Tienhoven AJ, van de Ven PM, Jansma EP, Nanayakkara PW (2014) The impact of the use of the Early Warning Score (EWS) on patient outcomes: a systematic review. *Resuscitation* 85: 587-594.
7. Priestley G, Watson W, Rashidian A, Mozley C, Russell D, Wilson J et al. (2004) Introducing Critical Care Outreach: a ward-randomised trial of phased introduction in a general hospital. *Intensive Care Med* 30: 1398-1404.
8. Hillman K, Chen J, Cretikos M, Bellomo R, Brown D, Doig G et al. (2005) Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet* 365: 2091-2097.
9. Brown CA, Lilford RJ (2006) The stepped wedge trial design: a systematic review. *BMC Med Res Methodol* 6: 54.
10. De Meester K, Haegdorens F, Monsieurs KG, Verpooten GA, Holvoet A, Van Bogaert P (2013) Six-day postoperative impact of a standardized nurse observation and escalation protocol: a preintervention and postintervention study. *J Crit Care* 28: 1068-1074.
11. Hughes J, Goldenberg LR, Wilfert CM, Valentine M, Mwinga KG, Guay LA et al. (2011) Design of the HIV Prevention Trials Network (HPTN) Protocol 054: A cluster randomized crossover trial to evaluate combined access to Nevirapine in developing countries. *UW Biostatistics Working Paper Series* 1-12.
12. Rogers EM (1995) *Diffusion of Innovations*, Fourth Edition. New York: The Free Press.
13. Huis A, Schoonhoven L, Grol R, Borm G, Adang E, Hulscher M et al. (2011) Helping hands: a cluster randomised trial to evaluate the effectiveness of two different strategies for promoting hand hygiene in hospital nurses. *Implement Sci* 6: 101.
14. Needham DM, Scales DC, Laupacis A, Pronovost PJ (2005) A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. *Journal of Critical Care* 20: 12-19.
15. Altman DG, De Stavola BL (1994) Practical problems in fitting a proportional

- hazards model to data with updated measurements of the covariates. *Stat Med* 13: 301-341.
16. Davey C, Hargreaves J, Thompson JA, Copas AJ, Beard E, Lewis JJ et al. (2015) Analysis and reporting of stepped wedge randomised controlled trials: synthesis and critical appraisal of published studies, 2010 to 2014. *Trials* 16: 358.
  17. Hussey MA, Hughes JP (2007) Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials* 28: 182-191.
  18. Hannan PJ, Murray DM (1996) Gauss or Bernoulli? A Monte Carlo comparison of the performance of the linear mixed-model and the logistic mixed-model analyses in simulated community trials with a dichotomous outcome variable at the individual level. *Eval Rev* 20: 338-352.
  19. Chen YF, Hemming K, Stevens AJ, Lilford RJ (2016) Secular trends and evaluation of complex interventions: the rising tide phenomenon. *BMJ Qual Saf* 25: 303-310.
  20. Yuen JK, Reid MC, Feters MD (2011) Hospital do-not-resuscitate orders: why they have failed and how to fix them. *J Gen Intern Med* 26: 791-797.
  21. Mitchell IA, McKay H, Van Leuvan C, Berry R, McCutcheon C, Avarad B et al. (2010) A prospective controlled trial of the effect of a multi-faceted intervention on early recognition and intervention in deteriorating hospital patients. *Resuscitation* 81: 658-666.
  22. Simmes FM, Schoonhoven L, Mintjes J, Fikkers BG, van der Hoeven JG (2012) Incidence of cardiac arrests and unexpected deaths in surgical patients before and after implementation of a rapid response system. *Ann Intensive Care* 2: 20.
  23. Howell MD, Ngo L, Folcarelli P, Yang J, Mottley L, Marcantonio ER et al. (2012) Sustained effectiveness of a primary-team-based rapid response system. *Crit Care Med* 40: 2562-2568.
  24. Winters BD, Weaver SJ, Pfoh ER, Yang T, Pham JC, Dy SM (2013) Rapid-response systems as a patient safety strategy: a systematic review. *Ann Intern Med* 158: 417-425.
  25. Maharaj R, Raffaele I, Wendon J (2015) Rapid response systems: a systematic review and meta-analysis. *Crit Care* 19: 254.
  26. Ludikhuizen J, Brunsveld-Reinders AH, Dijkgraaf MG, Smorenburg SM, de Rooij SE, Adams R et al. (2015) Outcomes Associated With the Nationwide Introduction of Rapid Response Systems in The Netherlands. *Crit Care Med* 43: 2544-2551.
  27. Smith MEB, Chiovaro JC, O'Neil M, Kansagara D, Quinones A, Freeman M et al. (2014) Early Warning System Scores: A Systematic Review.
  28. Munro PR (2002) The nurses (WA Government Health Services) Exceptional Matters Order. Available: <http://www.health.wa.gov.au/awardsandagreements/docs/PR914193%20EMO.pdf> via the Internet. Accessed 29/09/2017.
  29. McGaughey J, Alderdice F, Fowler R, Kapila A, Mayhew A, Moutray M (2007) Outreach and Early Warning Systems (EWS) for the prevention of intensive care admission and death of critically ill adult patients on general hospital wards. *Cochrane Database Syst Rev* CD005529.

Table 1: comparison baseline (T0) characteristics between clusters

Cluster (ward)	Ward type	Patient admissions (n)	Age (mean, SD) *	Males (%) *	Charlson Comorbidity Index (mean, SD) *	Nursing Hours Per Patient Day (mean, SD) *	Unexpected death (n) *	Cardiac arrest with CPR (n)	Unplanned admissions (n) *	ICU
1 <sup>#</sup>	S	360	57.24 (15.0)	50.9	1.37 (2.2)	3.57 (0.3)	0	0	3	
2 <sup>#</sup>	S	408	57.01 (18.4)	63.0	1.44 (2.4)	3.14 (0.3)	0	0	0	
3 <sup>#</sup>	M	639	64.42 (15.8)	65.1	2.24 (2.1)	3.33 (0.4)	1	0	0	
4 <sup>#</sup>	M	527	58.85 (15.9)	60.3	2.62 (2.9)	3.08 (0.4)	1	1	4	
5	S	336	60.66 (16.3)	46.5	0.53 (1.1)	2.14 (0.4)	0	0	0	
6	S	575	55.00 (18.7)	38.4	0.43 (1.1)	2.06 (0.5)	0	0	1	
7	M	328	64.68 (18.0)	47.4	2.57 (2.7)	1.53 (0.2)	1	1	0	
8	M	393	69.73 (15.8)	57.8	2.10 (1.6)	1.59 (0.3)	2	2	3	
9	S	692	52.68 (18.8)	35.3	0.67 (1.4)	2.50 (0.2)	0	0	3	
10	S	724	57.70 (17.9)	50.9	1.00 (1.5)	2.61 (0.3)	0	1	4	
11	M	422	61.93 (17.6)	56.9	1.83 (2.0)	2.18 (0.2)	1	0	9	
12	M	645	61.04 (19.1)	44.4	0.80 (1.4)	2.25 (0.4)	1	0	10	
13	S	540	58.63 (19.0)	48.6	0.90 (1.6)	2.74 (0.5)	1	1	0	
14	S	519	59.73 (17.4)	51.4	0.87 (1.7)	2.58 (0.4)	0	1	0	
15	M	473	66.13 (15.4)	54.7	3.40 (2.6)	2.43 (0.5)	1	0	4	
16	M	634	67.08 (14.6)	58.9	2.66 (2.3)	2.60 (0.4)	2	0	2	
17	S	355	50.49 (19.5)	51.4	0.13 (0.3)	2.34 (0.3)	0	0	2	
18	S	416	54.76 (20.5)	41.2	0.50 (1.3)	2.39 (0.4)	0	0	0	
19	M	249	65.21 (19.7)	47.0	1.77 (2.1)	1.90 (0.3)	3	1	3	
20	M	410	59.36 (18.7)	46.9	0.70 (0.9)	2.06 (0.2)	2	0	4	
21 <sup>#</sup>	S	514	48.79 (17.3)	48.1	0.77 (1.3)	2.12 (0.4)	0	0	2	
22 <sup>#</sup>	S	537	49.17 (17.9)	39.6	1.53 (2.1)	1.82 (0.4)	0	0	3	
23 <sup>#</sup>	M	334	55.23 (19.0)	51.9	4.10 (3.3)	2.25 (0.3)	2	0	1	
24 <sup>#</sup>	M	412	60.35 (17.1)	57.8	3.63 (2.7)	2.31 (0.3)	6	3	1	
25	S	840	58.78 (18.3)	56.8	0.50 (0.8)	2.58 (1.7)	0	1	7	
26	S	529	58.54 (17.6)	48.5	0.25 (0.5)	2.43 (0.3)	1	2	2	
27	M	503	67.92 (16.2)	51.5	1.77 (1.9)	2.10 (0.2)	0	1	8	
28	M	384	64.69 (15.7)	56.3	1.83 (2.0)	2.59 (0.3)	0	0	2	
total		13698	57.24 (15.0)	51.0	1.54 (2.2)	2.40 (0.7)	25	15	78	

# university hospital, S: surgical ward, M: medical ward, \* p<0.05

Age, Charlson Comorbidity Index, Nursing Hours Per Patient Day: One-way ANOVA, proportions: Pearson's Chi-Squared

mean (SD) Charlson Comorbidity Index calculated using 30 patient admissions per ward in T0

mean (SD) Nursing Hours Per Patient Day calculated using 15 consecutive days per ward in T0

**Table 2: Patient characteristics, clinical confounders and crude outcomes**

	Control	Intervention	p
<b>Patient characteristics</b>			
Patient admissions	34,267	35,389	
Age (mean, SD)	58.9 (18.6)	59.9 (18.2)	0.165 <sup>#</sup>
Males (%)	49.0	51.0	0.268 <sup>*</sup>
Reason for admission: medical (%)	52.3	47.7	0.419 <sup>*</sup>
<b>Clinical confounders</b>			
Charlson Comorbidity Index (mean, SD)	1.44 (1.0)	1.59 (1.1)	<0.001 <sup>#</sup>
Nursing Hours Per Patient Day (mean, SD)	2.49 (0.6)	2.75 (0.7)	<0.001 <sup>#</sup>
<b>Crude outcome indicators §</b>			
Ward mortality	12.5	12.8	0.156 <sup>*</sup>
Ward mortality without DNR code	7.3	7.2	0.055 <sup>#</sup>
Hospital mortality (72h after discharge from the ward)	13.7	14.1	0.170 <sup>*</sup>
Resuscitation team calls	2.7	2.2	0.556 <sup>*</sup>
All transfers to the ICU	10.4	20.1	0.819 <sup>*</sup>

\* Generalised Linear Mixed Model (GLMM), # Linear Mixed Model (LMM), § rate per 1000 admissions

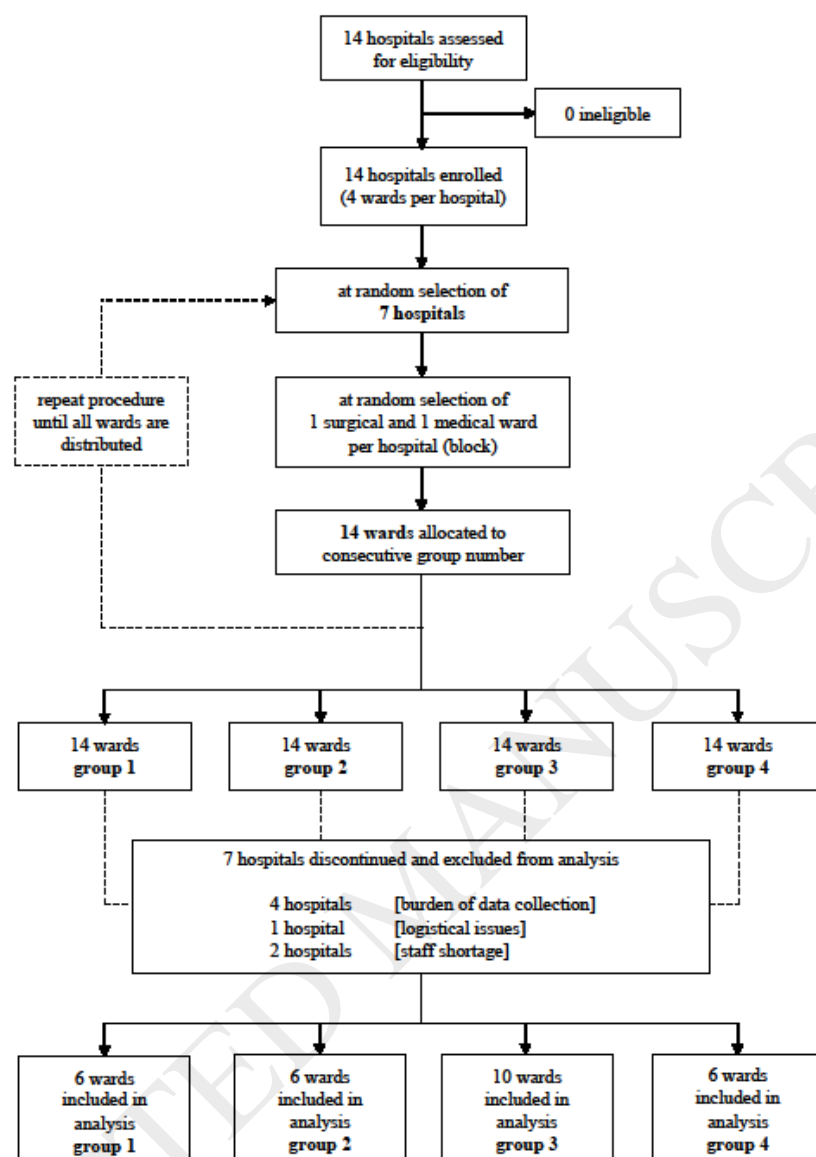
(Generalised) Linear Mixed Model adjusted for clustering (ward) and study time (period)  
SD: standard deviation, DNR: Do Not Resuscitate, ICU: Intensive Care Unit

**Table 3: Primary outcomes**

	<b>control</b> rate per 1000 admissions (n)	<b>intervention</b> rate per 1000 admissions (n)	<b>model</b> OR (95% CI)	<b>1</b> <b>model</b> PD/OR (95% CI)	<b>2</b>
Unexpected death	1.5 (52)	0.7 (23)	0.82 (0.34-1.95)	-0.00023 (-0.00128-0.00083) §	
Cardiac arrest with CPR	1.3 (46)	1.0 (35)	0.71 (0.33-1.52)	0.54 (0.18-1.64)	
Unplanned ICU admission	6.5 (224)	10.3 (363)	1.23 (0.91-1.65)	1.24 (0.84-1.83)	

- model 1: Generalised Linear Mixed Model (odds ratio) adjusted for clustering (ward) and study time (period)
- model 2: Generalised Linear Mixed Model (odds ratio) adjusted for clustering (ward), study time (period), CCI and NHPPD
- model 2 §: Linear Mixed Model (proportional difference) adjusted for clustering (ward), study time (period), CCI and NHPPD
- OR: odds ratio
- PD: proportional difference (intervention effect)

Fig. 1. CONSORT trial profile.





**Fig. 2. stepped wedge cluster randomised controlled trial design.**

Stepped wedge cluster randomised controlled trial design with group sizes per study period.

H = Hospitals, W = Wards, n = number of patient admissions

	<b>T0</b> Oct. 2013 Jan. 2014	<b>T1</b> Feb. 2014 May 2014	<b>T2</b> June 2014 Sept. 2014	<b>T3</b> Oct. 2014 Jan. 2015	<b>T4</b> Feb. 2015 May 2015
<b>group 1</b> 3H x 2W	Control n=3457	Intervention n=3137	Intervention n=2961	Intervention n=3430	Intervention n=3349
<b>group 2</b> 3H x 2W	Control n=3049	Control n=3201	Intervention n=3054	Intervention n=3300	Intervention n=3240
<b>group 3</b> 5H x 2W	Control n=4711	Control n=5048	Control n=4896	Intervention n=5164	Intervention n=5256
<b>group 4</b> 3H x 2W	Control n=2481	Control n=2504	Control n=2221	Control n=2699	Intervention n=2498

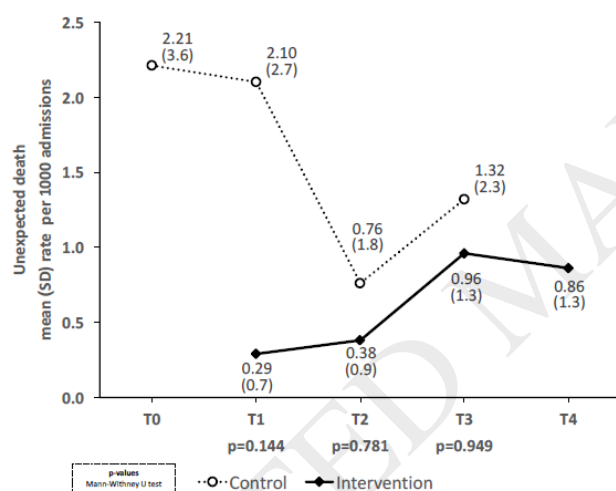
**Fig. 3. Trend of primary outcomes.**

Control and intervention group mean rates calculated using cluster (ward) means per study period

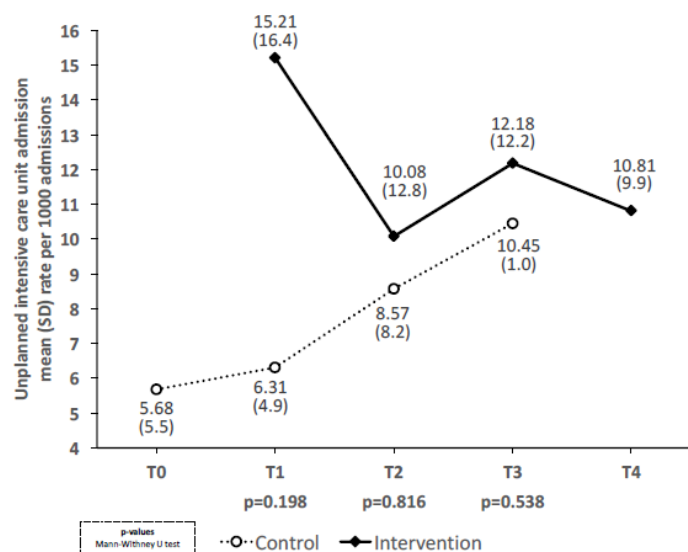
CPR = Cardiopulmonary Resuscitation

p-values calculated using the Mann-Withney U test

**Panel 3A.** Unexpected death mean (SD) rate per 1000 admissions from T0 to T4 in the control and intervention group.



**Panel 3B.** Cardiac arrest with CPR mean (SD) rate per 1000 admissions from T0 to T4 in the control and intervention group.



**Panel 3C.** Unplanned intensive care unit admission mean (SD) rate per 1000 admissions from T0 to T4 in the control and intervention group.

