Supplementary Digital Content

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Checklist for early recognition and treatment of acute illness and injury (CERTAIN): an exploratory multicenter international quality improvement study in the intensive care units with variable resources

Writing group for the CERTAIN investigators of the SCCM Discovery Network

Table of contents

e Table 1.	Participating ICUs…….....	3
e Figure 1.	Admission module …….....	5
e Figure 2.	Rounding module …….	6
e Figure 3.	Paper rounding module……..	7
e Figure 4.	Description of the intervention …….....	8
e Figure 5.	Study design…….....	9
e Figure 6.	Study time line…….....	10
e Table 2.	Missing data……	11
e Table 3.	Definitions of care processes and clinical outcomes……...	12
e Table 4.	Study duration…….	15
e Figure 7.	Study duration by center…..…….	16
e Table 5.	The incidence rates of non-adherence to basic critical care and outcomes in low and middle income countries……	17
e Table 6.	The incidence rates of non-adherence to basic critical care and outcomes in high income countries…….	20
e Figure 8.	Survival analysis according to income strata……..	23
e Table 7.	Modifications from the original analysis plan…….	26
e Table 8.	The incidence rates of non-adherence to daily care processes before and after CERTAIN implementation …….	29
E Text 1	Data Set Development and Statistical Analysis ……	32

e Table 1.Participating ICUs

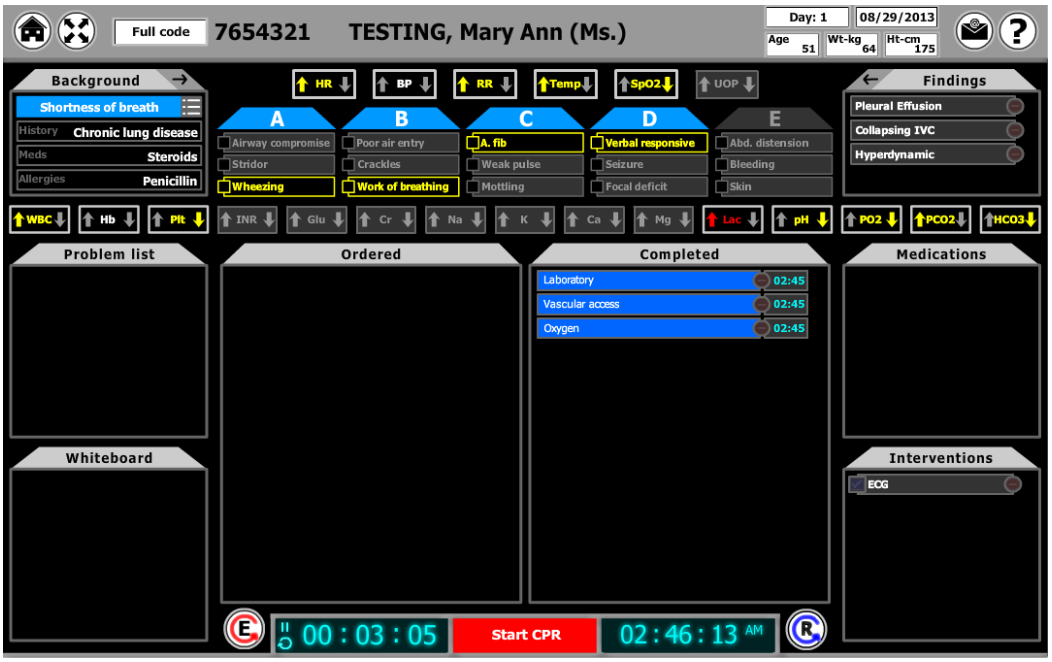
Hospital	Country	Income level	Number of ICU beds	Number of hospital beds	ICU type	Number of ICU physicians	Number of ICU nurses
General Hospital "Prim.drAbdulahNakas"	Bosnia and Herzegovina	LMIC	8	240	MICU	2	2
University Clinical Hospital Mostar	Bosnia and Herzegovina	LMIC	12	650	MIXED	8	30
University Clinical Centre of the Republic of Srpska	Bosnia and Herzegovina	LMIC	8	1100	MICU	12	14
Anhui Province Hospital	China	LMIC	67	3800	MIXED	18	68
Beijing Hospital	China	LMIC	10	1200	SICU	9	21
Chinese PLA General Hospital	China	LMIC	20	4500	SICU	20	60
DongGuanKanghua Hospital	China	LMIC	14	1080	OTHER	36	28
the First Affiliated Hospital of Guangzhou Medical University	China	LMIC	37	1500	MIXED	23	109
Guandong General Hospital	China	LMIC	15	2877	MICU	11	42
Guang'anmen Hospital	China	LMIC	8	680	MICU	8	26
Tianjin First Center Hospital	China	LMIC	30	1400	MICU	30	75
West China Hospital of Sichuan University	China	LMIC	52	4300	MICU	32	140
Xiangya Hospital Central South University	China	LMIC	33	2500	SICU	15	80
Clinical Hospital Center Rijeka	Croatia	HIC	21	1069	MIXED	43	44
CEDIMAT, Plaza de la Salud	Dominican Republic	LMIC	6	97	MIXED	3	2
Ispat General Hospital (IGH)	India	LMIC	19	635	MICU	3	12
Kasturba Medical College Hospital (KMC)	India	LMIC	20	2058	MICU	6	18
LokNayak Hospital, MAMC	India	LMIC	8	2850	MICU	8	8
St. James’s Hospital	Ireland	HIC	15	1010	MIXED	44	120
St. George's hospital	Lebanon	LMIC	10	385	MICU	5	16
Instituto Nacional de CienciasMédicas y Nutrición Salvador Zubirán (INCMNSZ)	Mexico	LMIC	12	167	MICU	/	/
ShaukatKhanum Memorial Cancer Hospital and Research Center	Pakistan	LMIC	11	220	MIXED	12	0
St. Luke's Medical Center	Philippines	LMIC	18	520	MIXED	8	88

The Medical City Hospital (TMC)	Philippines	LMIC	18	800	MICU	8	40
Heliodor Swiecicki Clinical Hospital at the Karol Marcinkowski Medical University	Poland	HIC	7	460	MIXED	2	5
King Abdulaziz Medical City	Saudi Arabia	HIC	21	900	MIXED	10	100
Military Medical Academy (MMA)	Serbia	LMIC	7	1200	SICU	8	12
The Institute for Pulmonary Diseases of Vojvodina Sremska Kamenica	Serbia	LMIC	5	320	MICU	7	21
Mbeya Zonal Referral Hospital	Tanzania	LMIC	6	9	MIXED	3	8
Akdeniz University Hospital	Turkey	LMIC	94	967	MIXED	43	44
Corpus Christi Medical Center	USA	HIC	21	160	MIXED	4	5
Mayo Clinic Health System Mankato	USA	HIC	10	200	MIXED	5	40
Mayo Clinic Health System Franciscan Healthcare	USA	HIC	14	150	MIXED	4	35
Wyckoff Heights Medical Center	USA	HIC	16	350	MICU	60	15

e Figure 1. Admission module

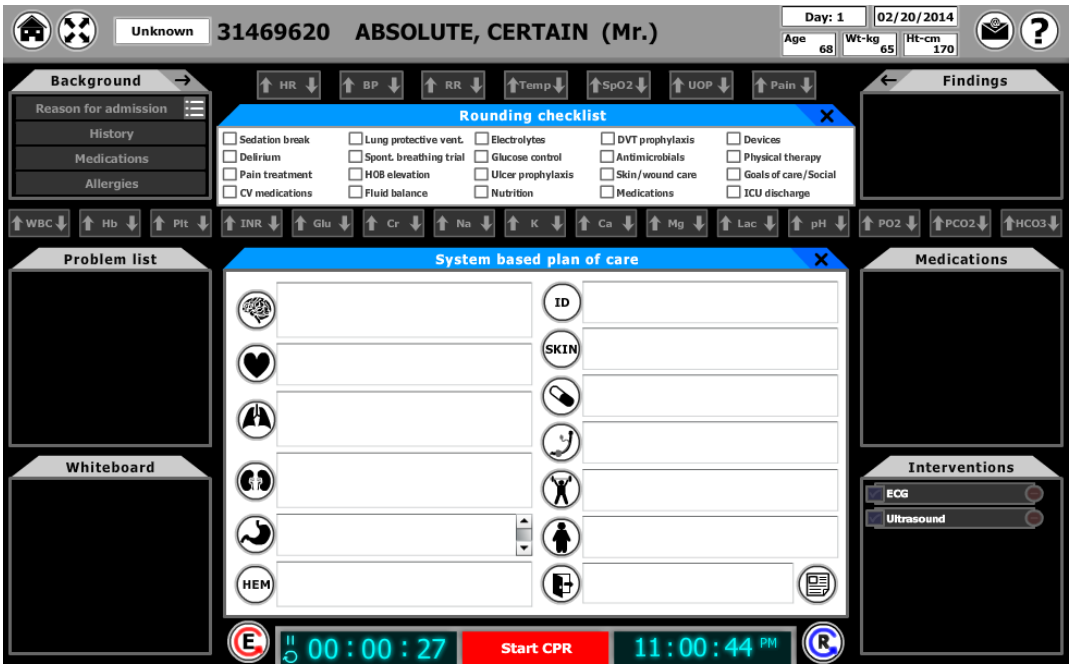
CERTAIN admission/resuscitation module (Online version)

CERTAIN-admission is designed for evaluation of life-threatening emergencies with embedded timer, checklists and decision support cards to facilitate error-free care of acutely deteriorating patient (ICU admission and subsequent emergencies). Reading from up to bottom organizational elements are (1) primary (ABCDE) survey; and (2) secondary patient survey, and from left to right the key organizational elements are: (1) clinical context -reason for admission/patient problem list; (2) provider actions tracked in the status central panel; and (3) proposed medications and interventions.



e Figure 2. Rounding module (Online version)

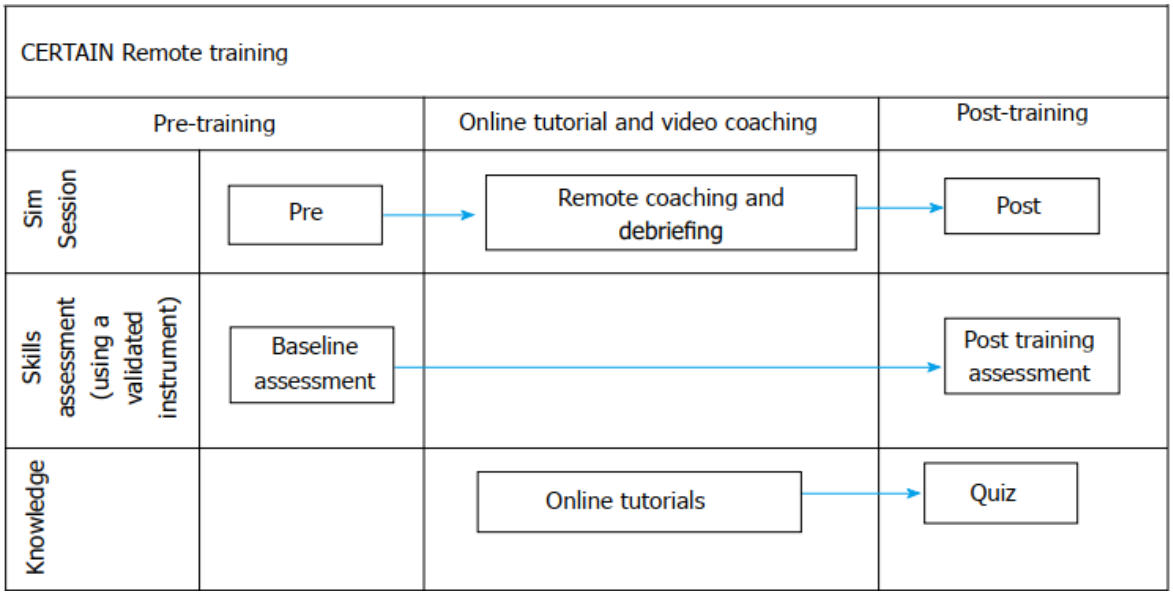
CERTAIN Rounding module is designed as a simple and efficient ICU rounding tool with embedded checklist and decision support cards to facilitate error-free day-to-day care in the ICU. The key characteristic of CERTAIN is the availability of task-specific and concept-oriented views of patient data. CERTAIN serves to organize appropriate data, as determined by a review of end-user data needs, and incorporates evidence-based checklists.



e Figure 3. Paper rounding module

CERTAIN is available in electronic form for PC, in mobile version for cell phones and in paper version in case of problems with internet connection. Below is an example of local adaptation of paper version for rounding in Mexico.

e Figure 4. Description of the intervention



Quiz results were used to assess competency of the participants to use the CERTAIN tool.

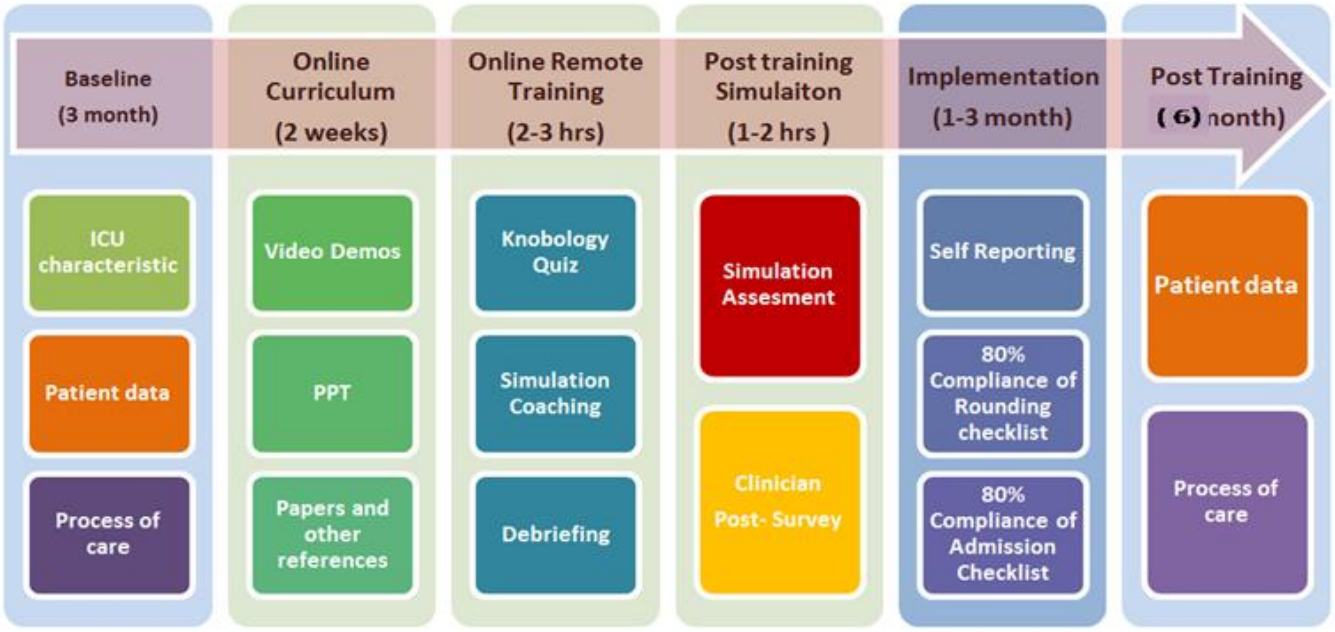
e Figure 5. Study design

CERTAIN is a before-after study. Following successful implementation in a single center pilot ICU, CERTAIN was implemented sequentially in each ICU in their selected turn so that by the end of the study all ICUs have received the intervention.

<table>
<tr><td></td><td colspan="2">Year 1</td><td colspan="4">Year 2-4</td></tr>
<tr><td>Hospital 1 (PILOT)</td><td rowspan="4">Systematic review of best practice

Refine prototype</td><td rowspan="4">Customization based on local needs</td><td rowspan="2">Identification of local champions</td><td colspan="3">Implementation of CERTAIN</td></tr>
<tr><td>Hospital 2</td><td></td><td colspan="2">Implementation of CERTAIN</td></tr>
<tr><td>Hospital 3</td><td rowspan="2">Education on best practices</td><td></td><td></td><td colspan="2">Implementation of CERTAIN</td></tr>
<tr><td>Hospital 4</td><td></td><td></td><td></td><td colspan="2">Implementation of CERTAIN</td></tr>
<tr><td>Hospital X</td><td></td><td></td><td></td><td></td><td colspan="2">Implementation of CERTAIN</td></tr>
<tr><td>All Hospitals</td><td colspan="6">Define, design, implement, validate and maintain key data entry to the CERTAIN environment in support of its clinical utilization</td></tr>
</table>

e Figure 6. Study timeline



e Table 2. Missing data

Manual Checks were performed followed by Microsoft Excel Sheets and custom report forms for each center in REDCap which were specifically designed to identify missing data points. We created online tutorials and hold several online training sessions that explained the data filling rules. The table shows the extent of missing data after attempts to locate missing data had been made.

Form Section (total observations)	Parameters	N (%)
Admission	Date of birth	67 (1.6)
	Weight (kg) at admission	90 (2.1)
	Gender	60 (1.4)
	Hospital Admission Date	87 (2.1)
	Hospital Admission Source	71 (1.7)
	ICU admission source	72 (1.0)
	Discussion of limitation of life support Interventions at admission	93 (2.2)
Daily	Invasive mechanical ventilation	98 (0.8)
	Documented Head of bed elevated at 30 degrees	175 (1.4)
	Documented Peptic ulcer prophylaxis	128 (1.0)
	Documented DVT prophylaxis	135 (1.0)
	Documented Daily oral care	238 (1.8)
	Documented assessment of spontaneous breathing trial	131 (1.0)
	Documented ventilator associated pneumonia	131 (1.0)
	Documented Use of vasoactive medication today	128 (1.0)
	Documented family conference/discussion	203 (1.6)
	Documented Central line	168 (1.3)
	Urinary Catheter	170 (1.3)
	List of Antimicrobial medications	1858 (14.4)
Outcome	Total number of days on mechanical ventilation during the entire hospitalization	185 (4.5)
	Palliative / comfort care given	182 (4.4)
	Date of ICU discharge	172 (4.1)
	Final ICU diagnosis	222 (5.3)
	ICU discharge status	164 (3.9)
	Hospital discharge date	242 (5.8)
	Hospital discharge status	232 (5.6)
	28-day mortality	286 (6.9)

e Table 3. Definitions of care processes and clinical outcomes

Outcome	Definition for calculation of Incident Rates, Infection Rates, Mortality Rates, and Length of Stay	When we assessed	How we assessed
Incidence Rate of omissions in basic care processes per 1000 days event		Observation on day	
DVT prophylaxis	$\frac{\text{Sum (occurrence no DVT prophylaxis documented)}}{\text{Sum (Observed days on IMV)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Peptic ulcer prophylaxis	$\frac{\text{Sum(occurrence no peptic ulcer prophylaxis documented}}{\text{Sum (Observed days on IMV)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Daily Oral Care	$\frac{\text{Sum(occurrence no daily oral care documented)}}{\text{Sum (Observed days on IMV)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
HOB elevation at 30 degrees	$\frac{\text{Sum(occurrence not have HOB at 30 degree documented}}{\text{Sum (Observed days on IMV)}} \times 100$	0, 1,2,3,7,14, 21	Documented on the CRF
Documented assessment of SBT	$\frac{\text{Sum(occurrence no assessment of SBT documented)}}{\text{Sum (Observed days on IMV)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Documented family conference/ discussion	$\frac{\text{Sum(occurrence no family conference documented)}}{\text{Sum (Observed days on IMV)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Documented assessment for CVC removal	$\frac{\text{Sum(occurrence no assessment of removal of CVC documented)}}{\text{Sum(observed days with CVC)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Document Assessment UC Removal	$\frac{\text{Sum(occurrence no assessment for removal of uninary catheter)}}{\text{Sum(observed days with urinary catheter)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Documented assessment to continue or discontinue current antimicrobials	$\frac{\text{Sum(occurrence of non assessment to continue or discontinue meds)}}{\text{Sum(observed days with usage of any antimicrobial medication)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF

Documented assessment to continue or discontinue current sedation meds	$\frac{\text{Sum(occurrence of non assessment to continue or discontinue meds)}}{\text{Sum (observed days with usage of sedation or analgesics)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Incidence Rate of transfusion per 1000 ICU days			
Any RBC transfusion	$\frac{\text{Sum(occurrence of RBC transfusion)}}{\text{Sum(Patient observation days)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Any Platelet transfusion	$\frac{\text{Sum(occurrence of platelet transfusion}}{\text{Sum(patient observation days)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Any FFP transfusion	$\frac{\text{Sum(occurrence of FFP transfusion)}}{\text{Sum(patient observation days)}} \times 1000$	0, 1,2,3,7,14, 21	Documented on the CRF
Infection rates			
Documented VAP	$\frac{\text{Sum(number of patient with VAP ever documented)}}{\text{Sum (number of patients on IMV)}} \times 100$	0, 1,2,3,7,14, 21	Documented on the CRF
Documented CVC infection	$\frac{\text{Sum(number of patient with CL infection documented)}}{\text{Sum (number of patient with central line)}} \times 100$	0, 1,2,3,7,14, 21	Documented on the CRF
Documented UC infection	$= \frac{\text{Sum(number of patient with UC infections documented)}}{\text{Sum (number of patient with urinary catheter)}} \times 100$	0, 1,2,3,7,14, 21	Documented on the CRF
Mortality			
ICU Mortality	$\frac{\text{(number of ICU deaths)}}{\text{ICUpatientsdischargedalive} + \text{ ICUpatients dischargeddead}} \times 100$	Deaths of patients in ICU	Documented on the CRF
Hospital mortality	$\frac{\text{(number of hospital deaths)}}{\text{Hospitalpatientsdischargedalive} + \text{ Hospital patientsdischargeddead}} \times 100$	Deaths of patients in Hospital	Documented on the CRF

Day 28 mortality	$\frac{(\text{number of deaths in the first of 28 days after admission})}{\text{Patients alive day 28} + \text{Patients dead day 28}} \times 100$	28 days after ICU admission	Documented on the CRF
Length of stay			
Hospital length of stay, days	$\text{HospitalDischargeDate} - \text{HospitalAdmissionDate}$	The hospital length of stay for each patient was calculated. If hospital LOS exceeded 2 years, we truncated it.	Documented on the CRF
ICU length of stay, days	$\text{ICUDischargeDate} - \text{ICUAdmissionDate}$	The length of day in ICU for each patient was calculated. ICU stay greater than 2 years was truncated at 2 years.	Documented on the CRF.

The infection rate of patients experiencing central venous catheter (CVC) infections, urinary catheter (UC) infections, and ventilator associated pneumonia (VAP) was calculated as follows: the denominator was the number of patients undergoing central line placement, urinary catheter placement or invasive mechanical ventilation. The numerator was the number of patients having the infection on any observation day (only one episode per patient was included in the analysis).

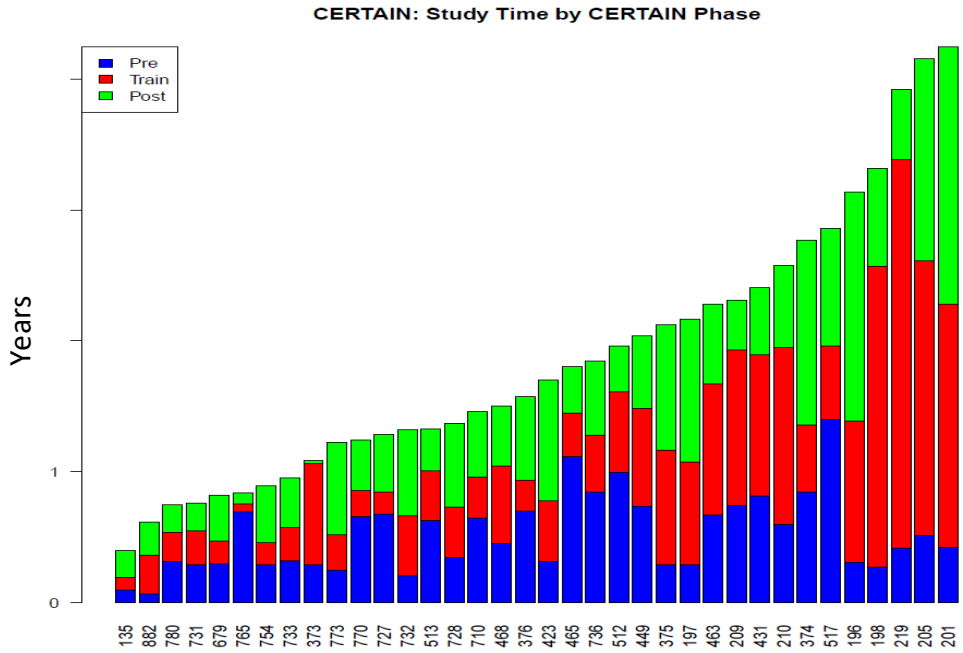
CRF, case report form; DVT, deep vein thrombosis; FFP, fresh frozen plasma; HOB, head of bed; IMV, invasive mechanical ventilation; RBC, red blood cell; SBT, spontaneous breathing trial

e Table 4. Study duration

Length of Time to Complete Each Phase, (weeks)		
	N	Median (IQR)
Pre-implementation: study set-up time	44	5.8 (1.6-18.5)
Stage 1. Baseline data collection	38	16.1 (10.3-29.4)
Stage 2. Remote training	38	7.1 (3.8-16.1)
Stage 3. Local implementation	35	15.0 (8.6-26.6)
Stage 4. Post implementation patient data collection and maintenance of processes of care	34	30.2 (19.3-45.0)
Completion of whole study includes phases 1-4	34	96.1 (54.0-139.3)
IQR = interquartile range		

e Figure 7. Study duration by center

Important variations in the length of time to complete each stage in different centers was noted.



e Table 5. The incidence rates of non-adherence to basic critical care and outcomes in low- and middle-income countries

Total 3233	Pre intervention N=1065				Post intervention N= 2168					
Mechanical ventilation										
Observed event	**Incidence rate 95%CI**	**Observation days n**	**Observed event n**	**Patients n**	**Incidence rate 95%CI**	**Observation days n**	**Observed event n**	**Patients n**	**aIRR**	**p**
	per 1000 ventilator days	2678		725	**per 1000 ventilator days**	5250		1472		
No DVT prophylaxis	327.9 (306.9-350.3)	2678	878	725	231.0 (218.4-244.4)	5250	1213	1472	0.72 0.66-0.78)	<0.001
No Daily oral care	38.8 (32.0-47.1)	2678	104	725	40.8 (35.6-46.6)	5250	214	1472	0.95 (0.75-1.20)	0.66
No HOB elevation at 30 degrees	45.2 (37.8-54.0)	2678	121	725	45.1 (39.7-51.3)	5250	237	1472	1.09 (0.87-1.36)	0.46
No peptic ulcer prophylaxis	66.8 (57.7-77.4)	2678	179	725	32.0 (27.5-37.2)	5250	168	1472	0.45 (0.37-0.56)	<0.001
No documented assessment of SBT	589.6 (561.2-619.4)	2678	1579	725	498.1 (479.4-517.6)	5250	2615	1472	0.87 (0.81-0.92)	<0.001
No documented family conference/ discussion	458.9 (434.0-485.3)	2678	1229	725	347.6 (332.0-363.9)			1472	0.76 (0.71-0.82)	<0.001
Central venous catheters										
	per 1000 CVC days				**per 1000 CVC days**					
No documented assessment for central line removal	664.6 (636.1-694.5)	2988	1986	732	613.1 (593.1-633.7)	5727	3511	1470	0.90 (0.85-0.95)	<0.001

Urinary catheters										
	per 1000 urinary catheter days				**per 1000 urinary catheter days**					
No documented assessment for urinary catheter removal	668.2 (643.7-693.6)	4138	2765	1007	609.5 (593.0-626.5)	8362	5097	2094	0.92 (0.87-0.96)	<0.001
Antimicrobials and sedation										
	per 1000 days of use				**per 1000 days of use**					
No documented assessment to continue or discontinue current antimicrobials	357.7 (339.7-376.6)	4054	1450	986	235.1 (224.5-246.3)	7588	1784	1950	0.67 (0.62-0.72)	<0.001
No documented assessment to continue or discontinue current sedation meds	366.9 (342.8-392.8)	2251	826	684	223.9 (210.6-238.1)	4546	1018	1456	0.64 (0.59-0.71)	<0.001
Transfusions										
	per 1000 ICU days				**per 1000 ICU days**					
RBC	115.7 (106.3-125.9)	4650	538	1065	110.0 (103.4-117.1)	9000	990	2168	0.93 (0.84-1.04)	0.21
PLT	20.4 (16.7-25.0)	4650	95	1065	22.0 (19.1-25.3)	9000	198	2168	0.93 (0.73-1.20)	0.58
FFP	85.2 (77.2-94.0)	4650	396	1065	59.7 (54.8-64.9)	9000	537	2168	0.73 (0.64-0.83)	<0.001
Infections										
	% (95%CI)				% (95%CI)				aOR	
CRBSI	4.9 (3.6-6.7)		36	732	2.9(2.2-3.9)		43	1470	0.60 (0.38-0.95)	0.03

Urinary catheter infections	4.3 (3.2-5.7)		43	1007	4.0 (3.2-4.9)		84	2094	0.89 (0.61-1.31)	0.56
VAP	22.9 (20.0-26.1)		166	725	23.1 (21.0-25.3)		340	1472	1.01 (0.80-1.28)	0.94
Mortality										
	Mortality rates				Mortality rates					
ICU	31.6 (28.9-34.5)		332	1049	23.4 (21.7-25.3)		507	21062	0.63 (0.53- 0.75)	<0.001
Hospital	36.3 (33.4-39.3)		378	1041	28.5 (26.7-30.5)		616	21059	0.64 (0.54-0.76)	<0.001
DAY 28	39.8 (36.8-42.8)		408	1025	30.9 (29.0-32.9)		668	2159	0.65 (0.55-0.76)	<0.001
LOS										
	Geometric mean (SD)				Geometric mean (SD)				aRoGM	
ICU	7.3 (3.0)			1037	6.2 (2.8)			2127	0.84 (0.77-0.90)	<0.001
Hospital	16.0 (3.0)			1019	15.7 (2.7)			2118	0.97 (0.90-1.05)	0.45

Footnote. LMIC-Low and middle income countries, a-adjusted for center effect , OR-odds ratio, IRR-incident rate ratio, DVT-deep vein thrombosis, HOB-head of bed, SBT-spontaneous breathing trial, VAP-ventilator associated pneumonia, CRBSI–catheter related bloodstream infection, RBC-red blood cell, Plt-platelets, FFP-fresh frozen plasma, LOS-Length of stay, RoGM-ratio of geometric means

eTable 6. The incidence rates of non-adherence to basic critical care and outcomes in high income countries

Total 1023	Pre intervention N= 382				Post intervention N= 641					
Observed event	**Incidence rate 95%CI**	**Observation Days n**	**Observed event n**	**Patients n**	**Incidence rate 95%CI**	**Observation Days**	**Observed event n**	**Patients n**	**aIRR**	**p**
Mechanical ventilation										
	per 1000 ventilator days				**per 1000 ventilator days**					
No DVT prophylaxis	61.9 (46.7-82.2)	775	48	241	79.8 (66.1-96.3)	1366	109	402	1.17 (0.83-1.66)	0.36
No daily oral care	65.8 (50.0-86.6)	775	51	241	49.0(38.6-62.3)	1366	67	402	0.95 (0.65-1.39)	0.79
No HOB at 30 degrees	18.1 (10.7-30.5)	775	14	241	5.1(2.4-10.7)	1366	7	402	0.27 (0.11-0.67)	0.004
No peptic ulcer prophylaxis	18.1 (10.7-30.5)	775	14	241	12.4 (7.7-20.0)	1366	17	402	0.64 (0.31-1.31)	0.23
No documented assessment of SBT	473.5 (427.5-524.6)	775	367	241	267.2 (241.1-296.1)	1366	365	402	0.57 (0.49-0.66)	<0.001
No documented family conference/ discussion	268.4 (234.3-307.5)	775	208	241	414.3 (381.6-449.93	1366	566	402	1.56 (1.33-1.84)	<0.001
Central venous catheters										
	per 1000 CVC days				**per 1000 CVC days**					
No documented assessment for central line removal	591.0 (543.7-642.4)	934	552	258	395.3 (365.5-427.6)	1581	625	426	0.70 (0.63-0.79)	<0.001

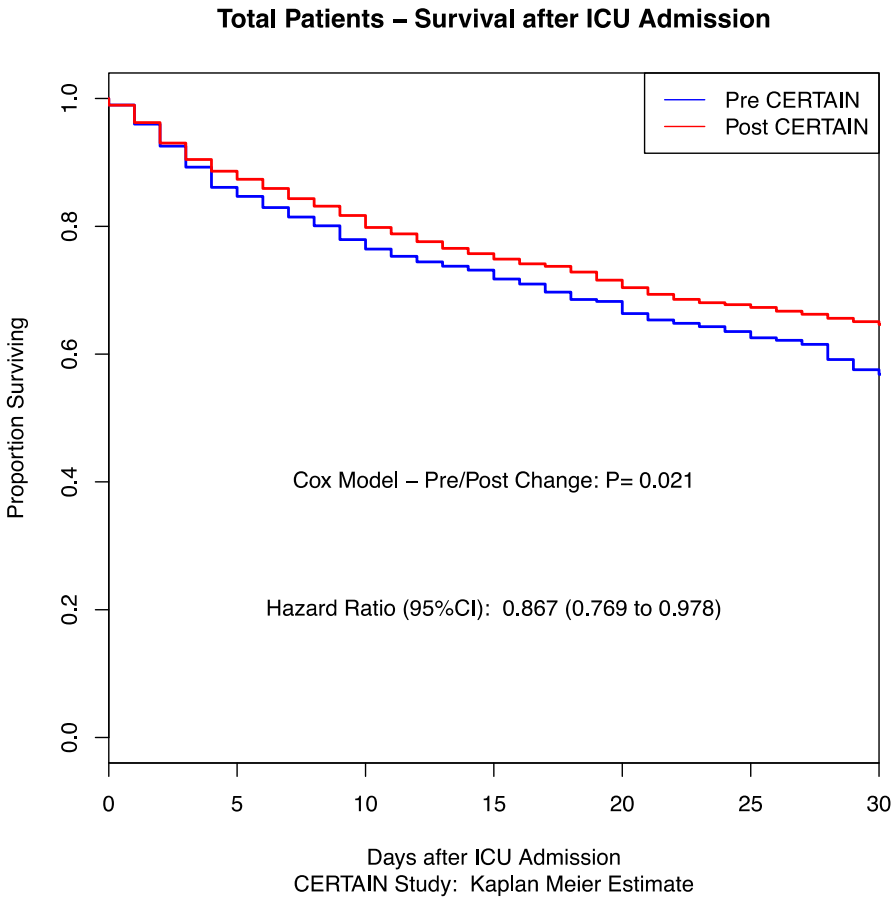
Urinary catheter										
	per 1000 urinary catheter days				**per 1000 urinary catheter days**					
No documented assessment for urinary catheter removal	697.3 (650.3-747.8)	1130	788	315	358.5 (332.4-386.7)	1866	669	515	0.56 (0.50-0.62)	<0.001
Antimicrobials and sedation										
	per 1000 days of use				**per 1000 days of use**					
No documented assessment to continue or discontinue current antimicrobials	276.5 (24.3-309.1)	1114	308	324	154.5 (137.9-173.2)	1909	295	548	0.67 (0.57-0.78)	<0.001
No documented assessment to continue or discontinue current sedation meds	337.1 (299.0-380.2)	789	266	257	172.8 (152.0-196.5)	1348	233	439	0.56 (0.47-0.67)	<0.001
Transfusion										
	per 1000 ICU days				**per 1000 ICU days**					
RBC	94.5 (79.899-111.8)	1439	136	382	84.5(73.5-97.2)	2330	197	641	0.91 (0.73-1.14)	0.41
PLT	32.7 (24.5-43.5)	1439	47	382	28.3 (22.2-36.1)	2330	66	641	0.81 (0.55-1.20)	0.3
FFP	27.8 (20.4-37.9)	1439	40	382	24.5(18.9-31.7)	2330	57	641	0.94 (0.62-1.42)	0.76
Infections										
	% (95%CI)				% (95%CI)				aOR	p
CBRSI	3.1 (1.6-6.1)		8	258	2.3(1.3-4.3)		10	426	0.92 (0.33-2.55)	0.87
Urinary catheter infection	4.8 (2.9-7.7)		15	315	4.1(2.7-6.2)		21	515	0.96 (0.49-1.95)	0.97

VAP	6.2 (3.8-10.1)		15	241	9.0 (6.5-12.2)		36	402	1.40 (0.73-2.67)	0.30
Mortality										
	Mortality rates									
ICU	20.6 (16.7-25.0)		74	360	23.5 (20.3-27.1)		141	600	1.18 (0.83-1.68)	0.35
Hospital	27.9 (23.5-32.8)		99	355	29.6 (26.1-33.4)		177	598	1.03 (0.75-1.42)	0.84
DAY 28	28.1(23.6-33.1)		96	342	30.9(27.3-34.8)		177	572	1.20 (0.87-1.64)	0.27
LOS										
	Geometric mean (SD)				Geometric mean (SD)				aRoGM	p
ICU LOS	4.6 (2.6)			357	4.6 (2.8)			599	0.93(0.81-1.06)	0.28
Hospital LOS	11.9 (3.2)			353	11.3 (3.2)			593	0.82 (0.71-0.94)	0.01

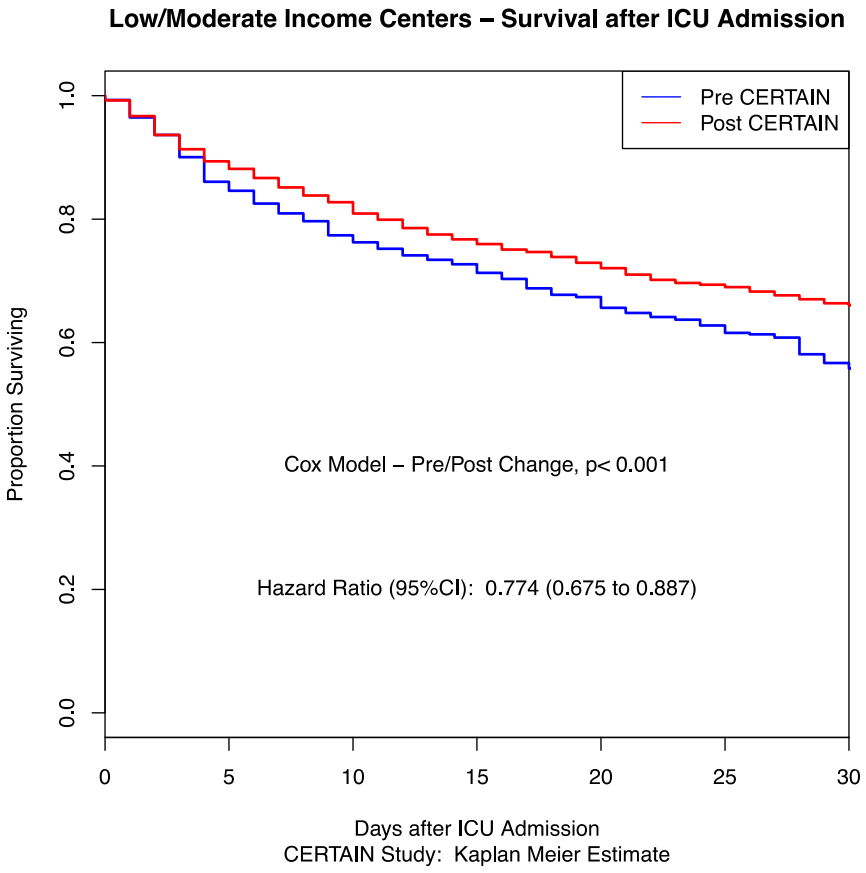
Footnote: HIC-High income countries, A-adjusted for center effect , OR-odds ratio, IRR-incident rate ratio, DVT-deep vein thrombosis, HOB-head of bed, SBT-spontaneous breathing trial, VAP-ventilator associated pneumonia, CRBSI–catheter related bloodstream infection, RBC-red blood cell, Plt-platelets, FFP-fresh frozen plasma, LOS-Length of stay, RoGM-ratio of geometric means

e Figure 8. Survival analysis according to income strata

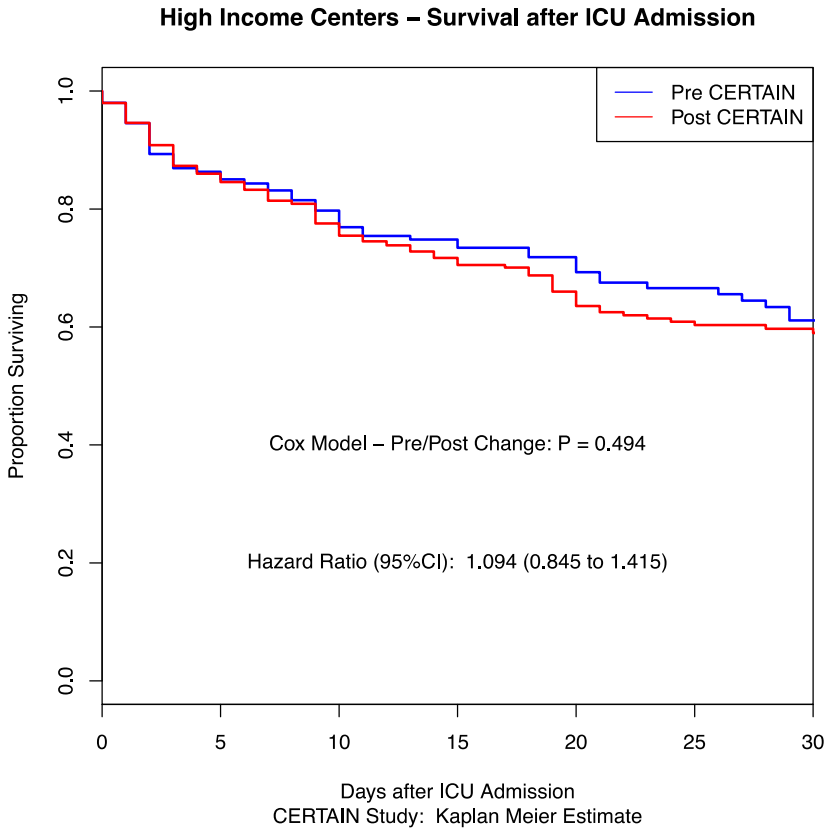
a) Survival analysis: Shown is the unadjusted Kaplan-Meier estimate of survival. P value for the Pre/Post Change is based on a Cox mixed model (treating centers as a random effects) that adjusts for imbalances in the following baseline risk factors: Invasive mechanical ventilation, Comorbidities, Life Support limitations, Home Admission Source and the center's income classification (HIC vs. LMIC). Hazard Ratio of the CERTAIN effect is also adjusted for the above risk factors.



b) LMIC Survival: Shown is the unadjusted Kaplan-Meier estimate of survival. P value for the Pre/Post Change is based on a Cox mixed model (centers random effects) that adjusts for imbalances in the following baseline risk factors: Invasive mechanical ventilation, Comorbidities, Life Support limitations, and Home Admission source. Hazard Ratio of the CERTAIN effect is also adjusted for the above risk factors.



c) Survival for HIC: Shown is the raw Kaplan-Meier estimate of survival. P value for the Pre/Post Change is based on a Cox mixed model (centers random effects) that adjusts for imbalances in the baseline following risk factors: Invasive mechanical ventilation, Comorbidities, Life Support limitations, and Home Admission source. Hazard Ratio of the CERTAIN effect is also adjusted for the above risk factors.



e Table 7. Modifications from the original analysis plan

ANALYSIS	ORIGINAL PLAN (**eIRB ID: 12-007998 9/16/2013)**	**PROTOCOL UPDATE (***https://clinicaltrials.gov/ct2/show/record/NCT01973829)*	**IN THE PAPER**	**POST HOC***
Settings	LMIC	Variable resources including HIC	Variable resources including HIC	
Study type	Stepped wedge cluster RCT	Before-after study	Before-after study	
Primary outcomes	Increased compliance to 90% of processes of care (ICU prophylaxis, ventilator bundles, sedation reduction and other recommended processes of care)	Adherence to best critical care practices • Appropriate shock resuscitation** • Appropriate sepsis treatment** • Appropriate mechanical ventilation • Appropriate peptic ulcer, deep vein thrombosis and infectious disease prophylaxis • ICU and hospital lengths of stay	Non-adherence to 10 critical care practices • deep vein thrombosis (DVT) and peptic ulcer prophylaxis • daily oral care • head of bed (HOB) elevation to at least 30 degrees above horizontal • Spontaneous breathing trial (SBT) • Family conference discussion • assessment of central line (CL) and urinary catheter removal • and assessment to continue or discontinue current antimicrobials and sedation	According to country income group (HIC vs. LMIC)

			• ICU and hospital lengths of stay	According to country income group with adjustment for baseline imbalances
Secondary outcomes	Rate of ICU acquired complications, discharge home, hospital mortality, ICU and hospital readmission.	• Mortality for 4 weeks	• ICU, hospital and 28-day mortality	According to country income group with adjustment for baseline imbalances
			• Infection rates	According to country income group
Subgroup analyses	Not specified	Not specified	LMIC vs. HIC settings	
Statistical approach	Generalized linear mixed models will be used to model changes in event rates using Poisson and negative binomial outcome distributions.	Not described	Primary outcomes: Non-adherence to basic care: procedures: A generalized linear model with a log link function (Poisson regression) was used to calculate the adjusted incident rate ratio.	

	LOS: Center was modeled as fixed effect, accounting for the clustering of patients within centers. A linear mixed model was used to calculate the adjusted ratio of the geometric means.Center was treated as a random variable in order to account for the clustering of patients within centers Secondary outcome: A generalized linear mixed model with a logit link function was used to calculate the adjusted odds ratio. Center was treated as a random effect and CERTAIN intervention and patient characteristics as fixed effects

*Not considered neither in the original plan nor in the updated SAP

** Not included due to feasibility limitations including the need for real time data collection for shock resuscitation and assessment of adequacy of antibiotics.

LMIC-low and middle income countries, HIC-High income countries, LOS-Length of stay

eTable 8. The incidence rates of non-adherence to daily care processes before and after CERTAIN implementation

Total 4256	Pre intervention N= 1447				Post intervention N= 2809					
Mechanical ventilation										
Observed event	**Incidence rate 95% CI per 1000 ventilator days**	**Observation Days n**	**Observed events n**	**Patients n**	**Incidence rate 95%CI per 1000 ventilator days**	**Observation days n**	**Observed events n**	**Patients n**	**aIRR**	**p**
No DVT prophylaxis	268 (251-286)	3453	926	966	200 (189-211)	6616	1322	1874	0.74 (0.68-0.81)	<.001
No daily oral care	45 (38-52)	3453	155	966	42 (38-48)	6616	281	1874	0.94 (0.77-1.16)	0.60
No HOB elevation at 30 degrees	39 (33-46)	3453	135	966	37 (32-42)	6616	244	1874	1.00 (0.81-1.23)	0.98
No peptic ulcer prophylaxis	55 (48-64)	3453	193	966	28 (24-32)	6616	185	1874	0.46 (0.38-0.57)	<.001
No documented assessment of SBT	563 (539-589)	3453	1946	966	450 (434-467)	6616	2980	1874	0.81 (0.76-0.86)	<.001

No documented family conference/ discussion	416 (395-438)	3453	1437	966	361 (347-376)	6616	2391	1874	0.86 (0.81-0.92)	<.001
Central venous catheters										
	per 1000 CVC days				**per 1000 CVC days**			1896		
No documented assessment for central venous catheter removal	647 (622-673)	3922	2538	990	566 (549-583)	7308	4136	1896	0.85 (0.81-0.90)	<.001
Urinary catheters										
	per 1000 urinary catheter days				**per 1000 urinary catheter days**					
No Documented assessment for urinary catheter removal	674 (653-697)	5268	3553	1322	564 (549-578)	10228	5766	2609	0.84 (0.80-0.88)	<.001
Antimicrobials and sedation										
	per 1000 days of use				**per 1000 days of use**					
No documented assessment to continue or discontinue current antimicrobials	340 (324-356)	5168	1758	1310	219 (209-228)	9497	2079	2498	0.66 (0.62-0.71)	<.001
No documented assessment to continue or discontinue current sedation	359 (338-381)	3049	1092	941	212 (201-224)	5436	1251	1895	0.62 (0.57-0.67)	<.001
Transfusion										

	per 1000 ICU days				**per 1000 ICU days**					
RBC	110 (102-119)	6089	647	1447	105 (99-111)	11330	1187	2809	0.92 (0.84-1.02)	0.13
PLT	23.32 (19.78-27.49)	6089	142	1447	23. (21-26)	11330	264	2809	0.89 (0.72-1.10)	0.3
FFP	71.60 (65.18-78.65)	6089	436	1447	52 (48-57)	11330	594	2809	0.75 (0.66-0.85)	<.001
Infections										
	%, (95% CI)				%, (95% CI)				aOR	p
CRBSI	4.4 (3.3-5.9)	N/A	44	990	2.8 (2.1-3.6)	N/A	53	1896	0.59 (0.38-0.90)	0.018
Urinary catheter infections	4.4 (3.0-5.6)	N/A	58	1322	4.0 (3.3-4.8)	N/A	105	2609	0.88 (0.62-1.23)	0.46
VAP	18.7 (16.0-21.3)	N/A	181	966	20.1 (18.3-21.9)	N/A	376	1874	1.08 (0.80-1.28)	0.88

Footnote 2. A-adjusted for center effects, OR-odds ratio, IRR-incident rate ratio, DVT-deep vein thrombosis, HOB-head of bed, SBT-spontaneous breathing trial, VAP-ventilator associated pneumonia, CRBSI–catheter related bloodstream infection, RBC-red blood cell, Plt-platelets, FFP-fresh frozen plasma,

Supplement: Data Set Development and Statistical Analysis

As this was a non-randomized study, we adjusted for patient severity of illness for the LOS, mortality and survival time outcomes. The following patient severity factors had significantly changed from pre to post CERTAIN implementation and were judged as likely to influence patient outcome: 1) use of invasive mechanical ventilation, 2) ICU admission source, 3) life support limitation at admission, and 4) comorbidity. Thus, these patient factors were included in the statistical models. Each of the study outcomes was analyzed within LMIC and HIC ICUs as defined by the World Bank.[11]

The statistical analysis for each outcome is outlined as follows:

Daily care Processes - Data set development: Each patient was observed during an intervention (e.g., invasive mechanical ventilation) and the number of observation days was recorded. For each observation day, non-adherence to daily care-processes (e.g. DVT prophylaxis) was recorded as either Yes or No. Thus, each patient had an intervention time interval (exposure) during which an event was noted. Poisson regression was used to model such data. Non-adherence (the 'No' outcome) was chosen as the endpoint to fit the assumptions of the Poisson probability distribution which is used in the maximum likelihood estimation of the model's parameters. The Poisson distribution can be applied to systems with a large number of possible events, each of which is rare. In our study, non-adherence was the rare event. The data analysis aggregated events and exposures within each ICU using a property of the Poisson distribution where the sum of a Poisson random variable is Poisson distributed.

Daily care Processes - Statistical Analysis: A generalized linear model (GLM) with a log link function (Poisson regression) was used to calculate the adjusted incidence rate ratio as a measure of the effect of CERTAIN. Specifically, the number of non-adherence events was the dependent variable, center and the CERTAIN intervention were the independent variables, and exposure was an offset. Center was modeled as fixed effect, accounting for the clustering of patients within centers. The likelihood ratio test was used to determine the statistical significance of the incident rate ratio (CERTAIN effect), using two models: 1) a full model with center and CERTAIN and 2) a nested model with only center. The difference in log likelihood between the two models indicated the significance of the incident rate ratio (CERTAIN effect) adjusted for the centers.

Blood products utilization - Data set development: The exposure variable was ICU observation days and for each observation day, whether the patient received a blood product was recorded as Yes/No. For these analyses, the Yes outcome was the event as Yes occurred less frequently.

Blood products utilization -Statistical Analysis: A generalized linear model (GLM) with a log link function (Poisson regression) was used to calculate the adjusted incident rate ratio (CERTAIN effect) using the above statistical methods.

Infections-Data set development: The unit of analysis was the individual patient. In case of repeated episodes of VAP, CBRSI or urinary catheter infections, during the observation interval, only one episode per patient was used. Thus, the statistical endpoint was that patient experienced an infection.

Infections-Statistical Analysis: A generalized linear model (GLM) with logit link function (binomial regression) was used to calculate the adjusted odds ratio (CERTAIN effect).

Specifically, the dependent variable was infection or non-infection (coded 1/0), and center and the CERTAIN intervention were the independent variables. Center was modeled as fixed effect, accounting for the clustering of patients within centers. The likelihood ratio test was used to determine the statistical significance of the odds ratio (CERTAIN effect), using two models: 1) a full model with center and CERTAIN and 2) a nested model with only center. Thus, the difference in log likelihood between the two models indicated the significance of the odds ratio (due to CERTAIN intervention) adjusted for the centers.

LOS - Data set development: The interval (in days) between the ICU admission date and the ICU discharge date was the ICU LOS measurement and the interval (in days) between the hospital admission date and the hospital discharge date was the hospital LOS measurement. The individual patient's LOS was the unit of analysis. The distributions of LOS was examined using histograms and density plots. As LOS data was highly positively skewed, a log transformation of LOS was calculated rendering a symmetrical log normal distribution. LOS was capped at two years.

LOS-Statistical Analysis: A linear mixed model (LMM) was used to calculate the adjusted ratio of the geometric means (CERTAIN effect). Specifically, the log transformed LOS was the dependent variable; the independent variables were the CERTAIN intervention and the aforementioned patient severity factors. In these analyses, center was treated as a random variable in order to account for the clustering of patients within centers. The model's CERTAIN coefficient is the log of the ratio of the geometric means. The values reported in the tables is the anti-log of the coefficient, which is a ratio of geometric means. The F test comparing a nested and full model was used to determine the statistical significance of the adjusted ratio of geometric means. The lmer package in the R statistical library was utilized for these analyses.

Mortality-Data set development: The unit of analysis was the individual patient and the statistical endpoints were ICU mortality, hospital mortality and 28 days mortality.

Mortality-Statistical Analysis: A generalized linear mixed model (GLMM) with a logit link function (logistic regression) was used to calculate the adjusted odds ratio (CERTAIN effect). Specifically, the dependent variable was 0/1 coded mortality and the independent variables were the cited patient severity factors, and the CERTAIN intervention. Center was treated as a random effect and CERTAIN intervention and patient characteristics as fixed effects. The likelihood ratio test was used to determine the statistical significance of the adjusted odds ratio, using the nested and full models. The glmer package in the R statistical library was utilized for these analyses. The analysis was conducted separately for ICU mortality, hospital mortality, and 28-day mortality.

Survival time-Data set development: The unit of analysis was the individual patient and the statistical endpoint the patient's survival time. Survival time was calculated as the interval between ICU admission date and hospital discharge date. Patient who were discharged alive were censored (coded 0) at their discharge date. Patients who died were coded 1. The statistical endpoint was survival time, capped at 2 years, with a censoring indication.

Survival time-Statistical Analysis: The proportion who survived was estimate using the Kaplan-Meier method and summarized using unadjusted Kaplan-Meier survival curves. The Cox proportional hazards mixed effect model was used to calculate the adjusted hazard ratio (CERTAIN effect). Specifically, the dependent variable was the censored survival time and the independent variables were the cited patient severity factors, and the CERTAIN intervention. The adjusted hazard ratio was calculated by treating center as a random effect and the CERTAIN intervention and patient severity factors as fixed effects. The likelihood ratio test was used to

determine the statistical significance of the adjusted odds ratio, using the nested and full models. The coxme package in the R statistical library was utilized for these analyses.

LMIC/HIC Centers: Each of the above outcomes were studied in 1) high-income and 2) low-middle income ICUs and 3) all ICUs. For the statistical models including all ICUs, ICU income level (HIC/LMIC) was added as a stratification factor. All data analyses were conducted using the R statistical software, version 3.4 (R reference). All tests were 2-sided with $p < 0.05$ denoting statistical significance.