**SUPPLEMENTAL DIGITAL CONTENT**

**Appendix A – Complete Inclusion and Exclusion Criteria**

**Inclusion Criteria:**

* 19 years old or greater
* admitted to the Intensive Care Unit
* suspected infection
* at least 2 SIRS criteria:
  + HR > 90
  + RR > 20 or paCO2 < 32 mmHg
  + Temperature > 38°C or <36°C
  + WBC > 12000/uL or < 4000/uL or >10% band forms
* any sign of end-organ damage
  + GCS < 15
  + new seizure
  + new lateralizing neurologic signs
  + new brady- or tachyarrhythmia
  + hypotension: SBP < 90 mmHg or 40 mmHg below baseline
  + hypoxemia: spO2 or saO2 less than 90%
  + new need for mechanical ventilation
  + jaundice
  + upper GI bleed
  + lower GI bleed
  + oliguria or anuria
  + azotemia
  + platelet < 100
  + INR > 1.5

**Exclusion Criteria:**

* not admitted to the ICU
* Do Not Attempt Resuscitation status upon ICU admission
* Do Not Intubate status upon ICU admission

**Appendix B – Members of The Medical City Sepsis Alert Working Group 2007-2018**

Irmingarda Gueco MD

Jude Erric Cinco MD

Marissa Alejandria MD

Jose Emmanuel Palo MD

Debbie Noblezada-Uy MD

Gerardo Briones MD

Joanne Robles MD

May Agno MD

Armi Carlos MD

Karen Ilagan MD

Kelly Chiu MD

Stephanie Ang MD

Marides San Juan MD

Nina Bumanglag MD

Raul Destura MD

Maan Ponte MD

Patricia Puno-Ramos MD

Meg Goco MD

Israeli Roque MD

Gemma Sarapuddin MD

Nicco Salalima MD

Marian Vita Nova Sodusta MD

Roland Reyes MD

Claire Orden MD

Ma Patricia Therese Virata MD

Agnes Cubillas MD

Ma Antonia Elisa Abello MD

Joan Kristina Diaz MD

Lourdes Trinidad RN

Rina Uriarte

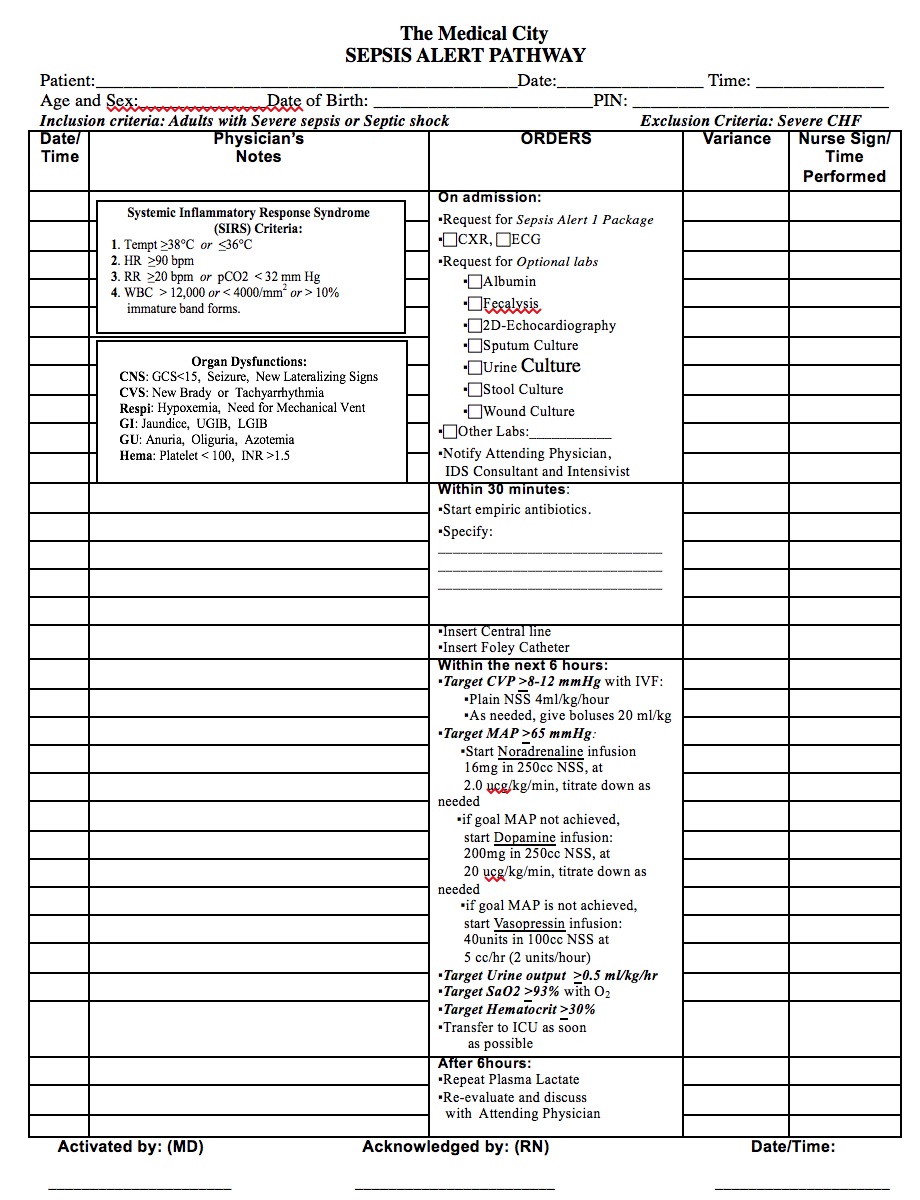
Rose Leopando RN

Alicia Inocencio RN

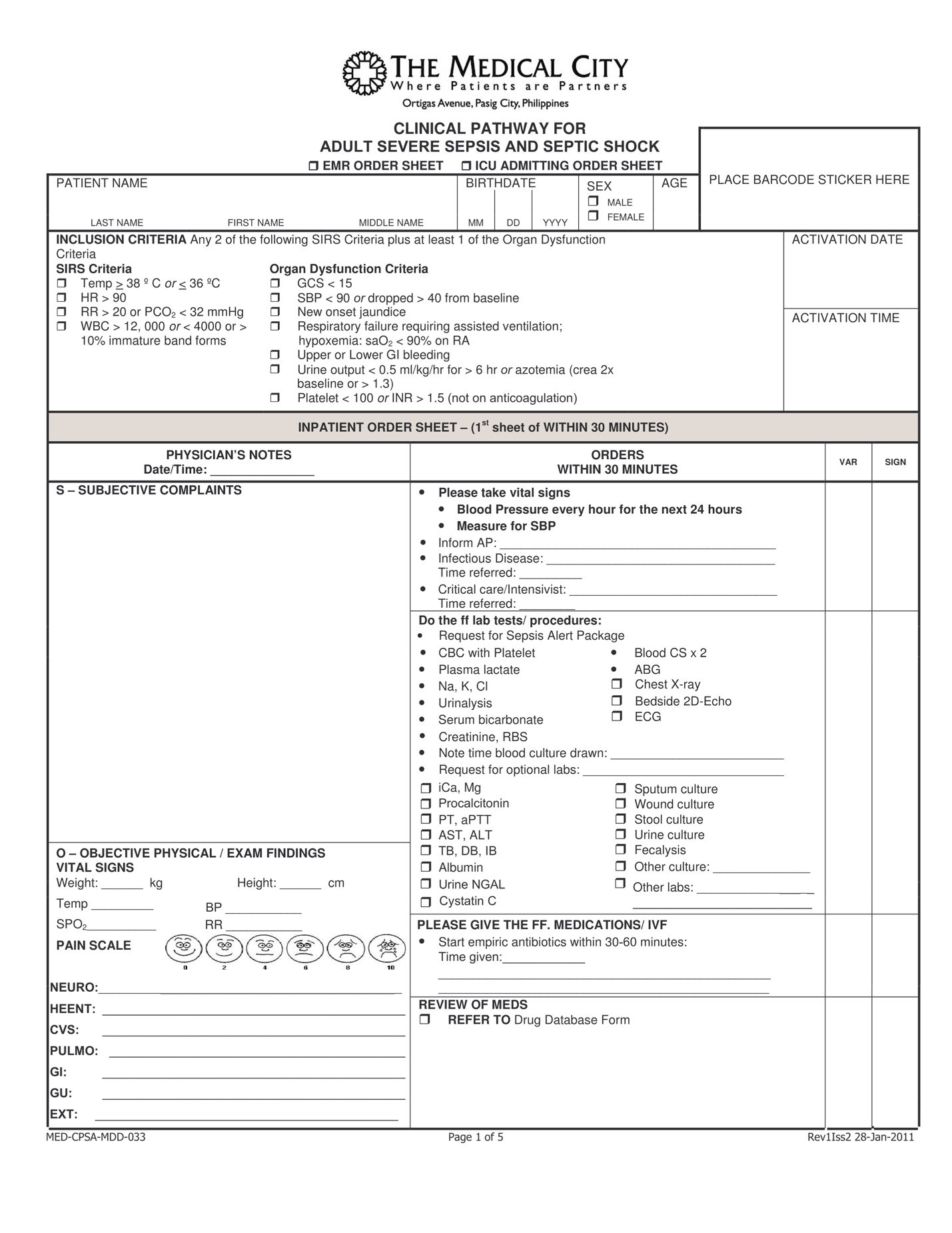
Cecil Contreras RN

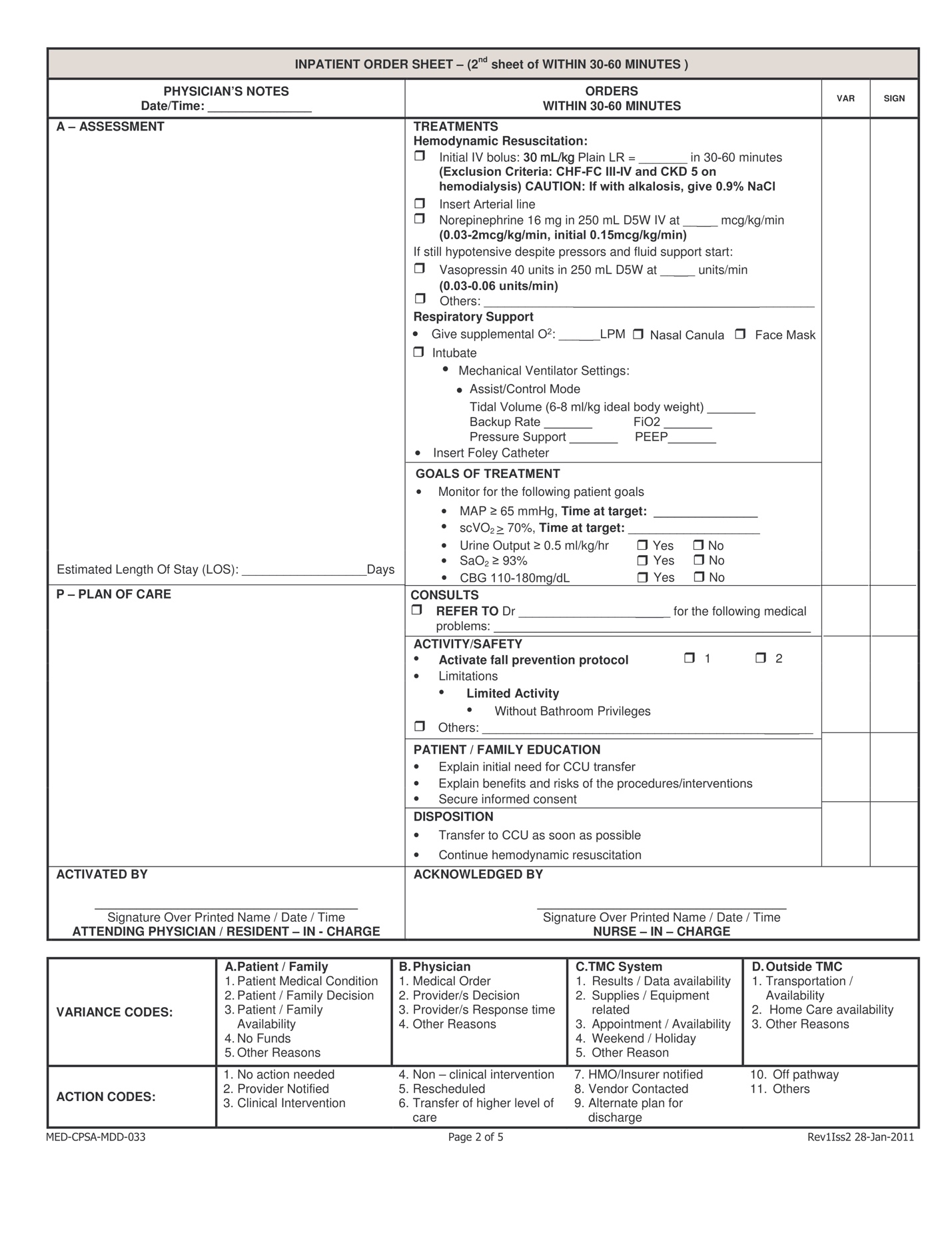
Carson Cortez RN

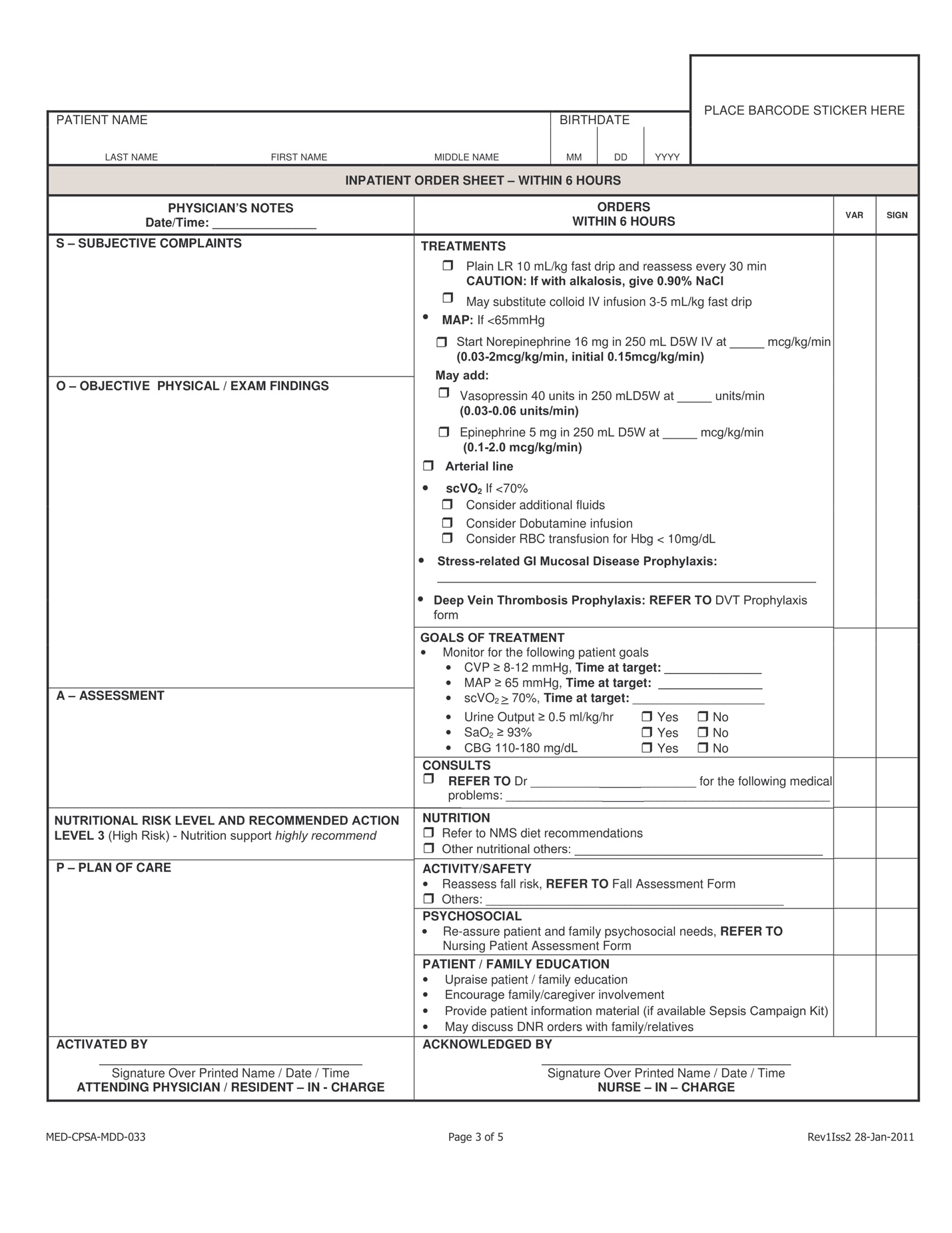
**Appendix C: TMC Sepsis Alert Pathway Version 1**

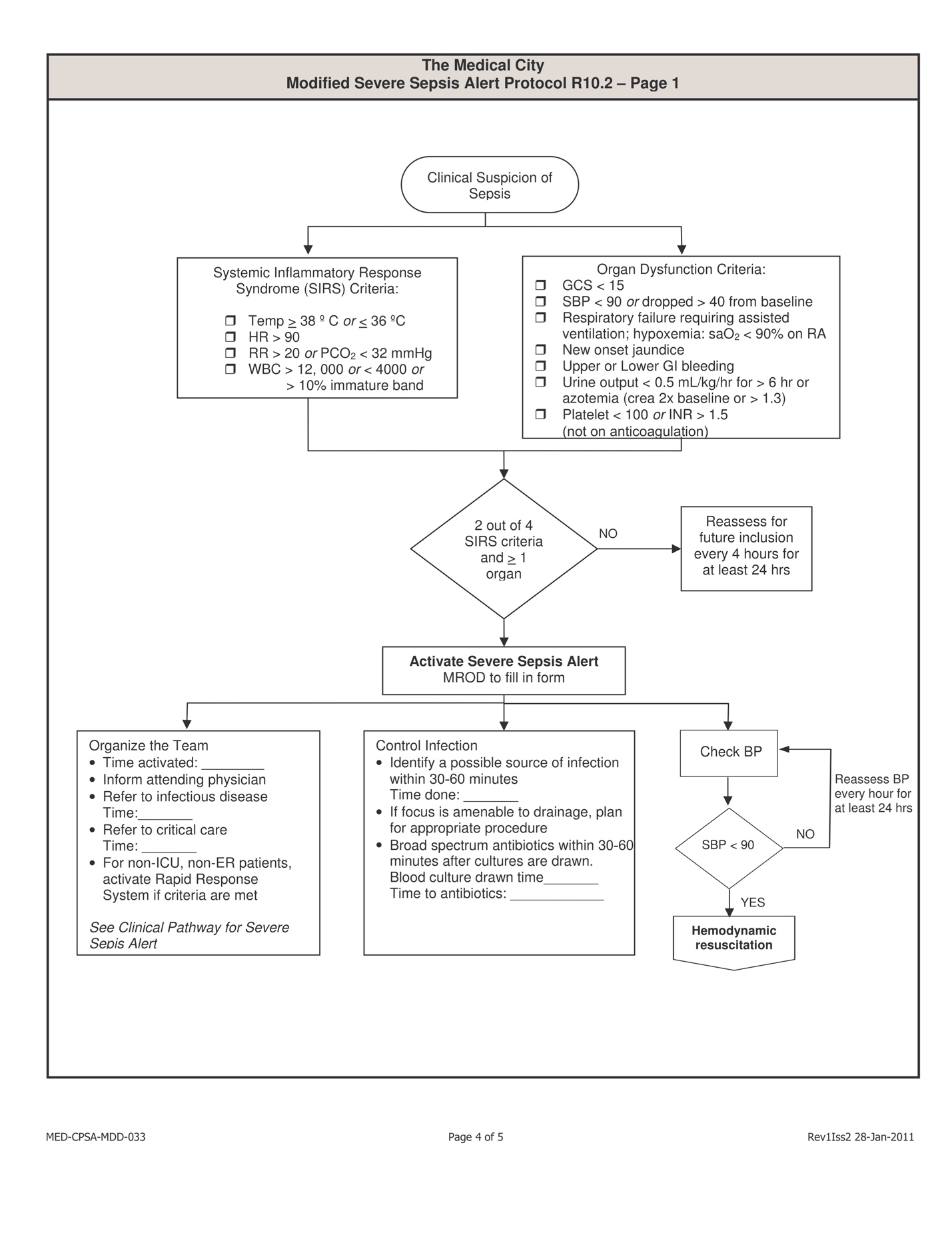


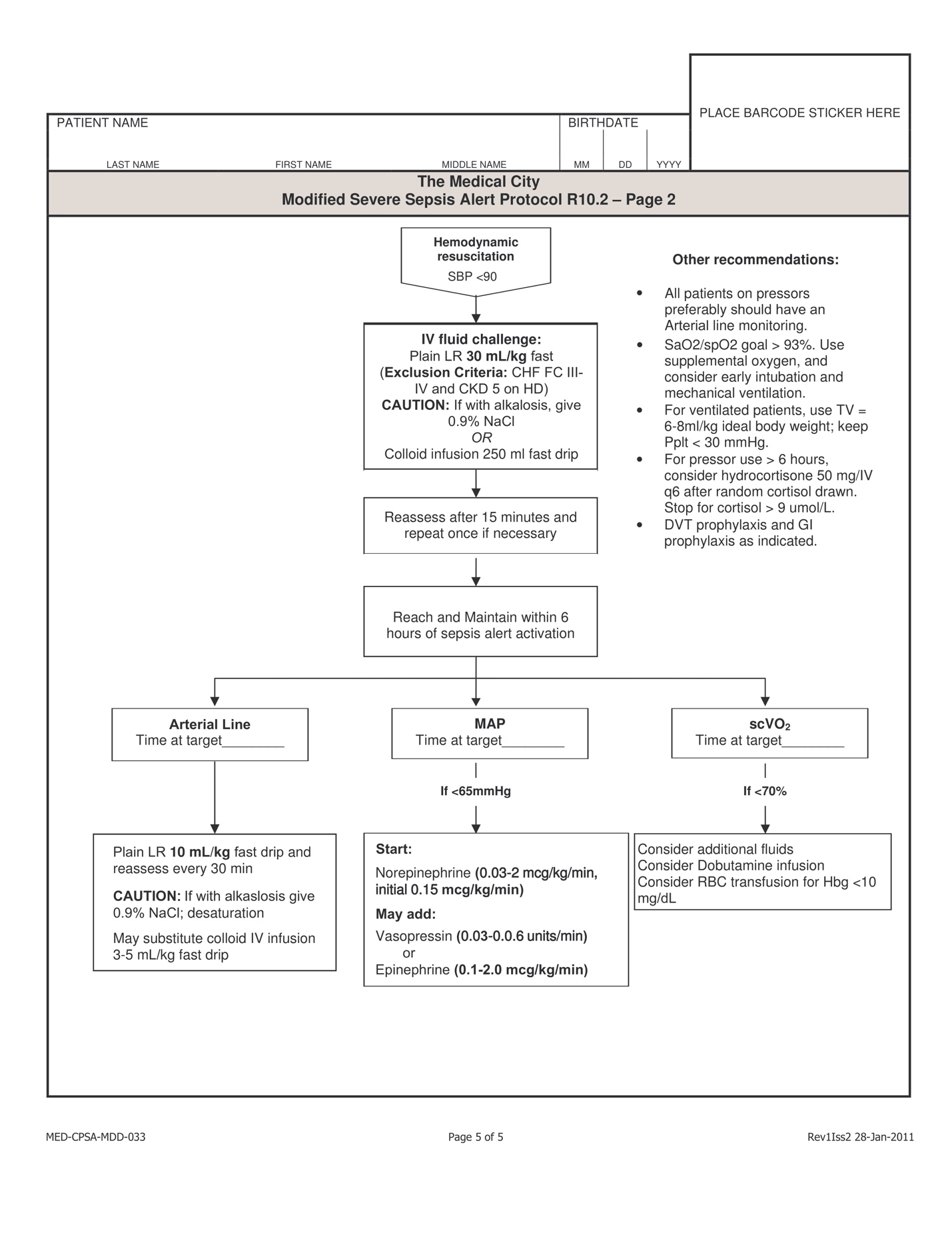
**Appendix D: TMC Sepsis Alert Pathway Version 2**











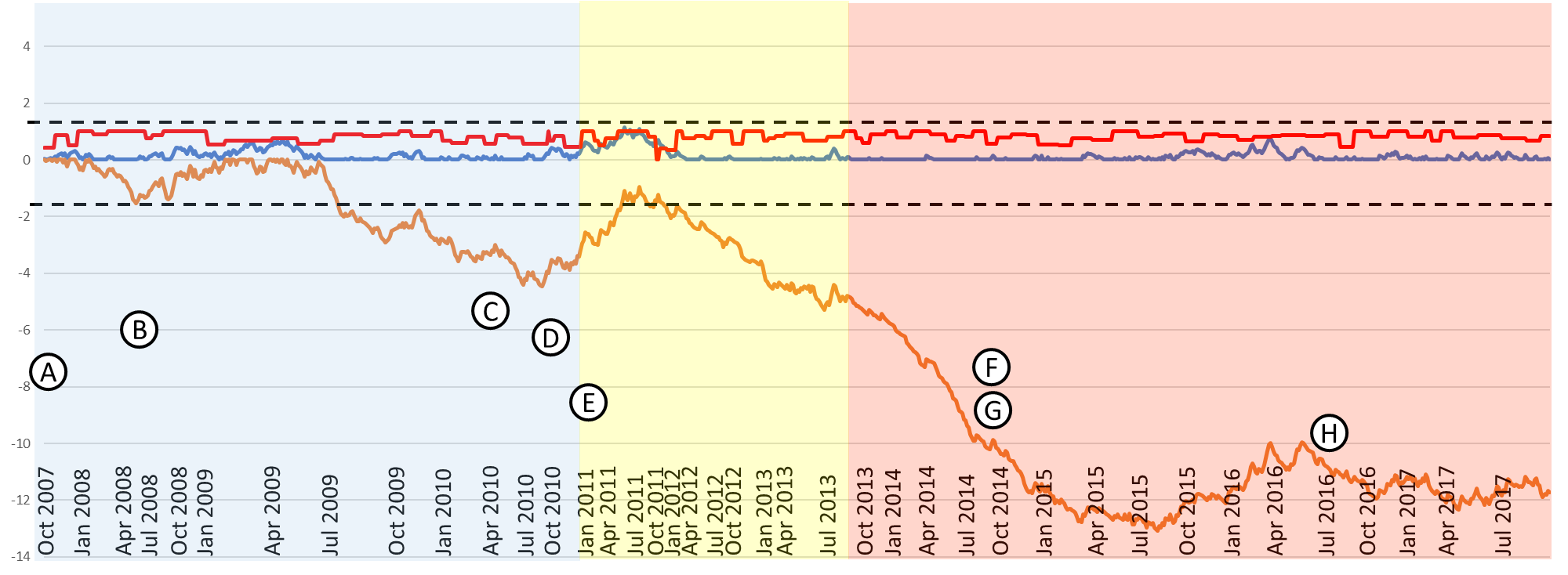
**Appendix E – Control Charts**

**I. Risk-Adjusted Cumulative Sum Control Charts**

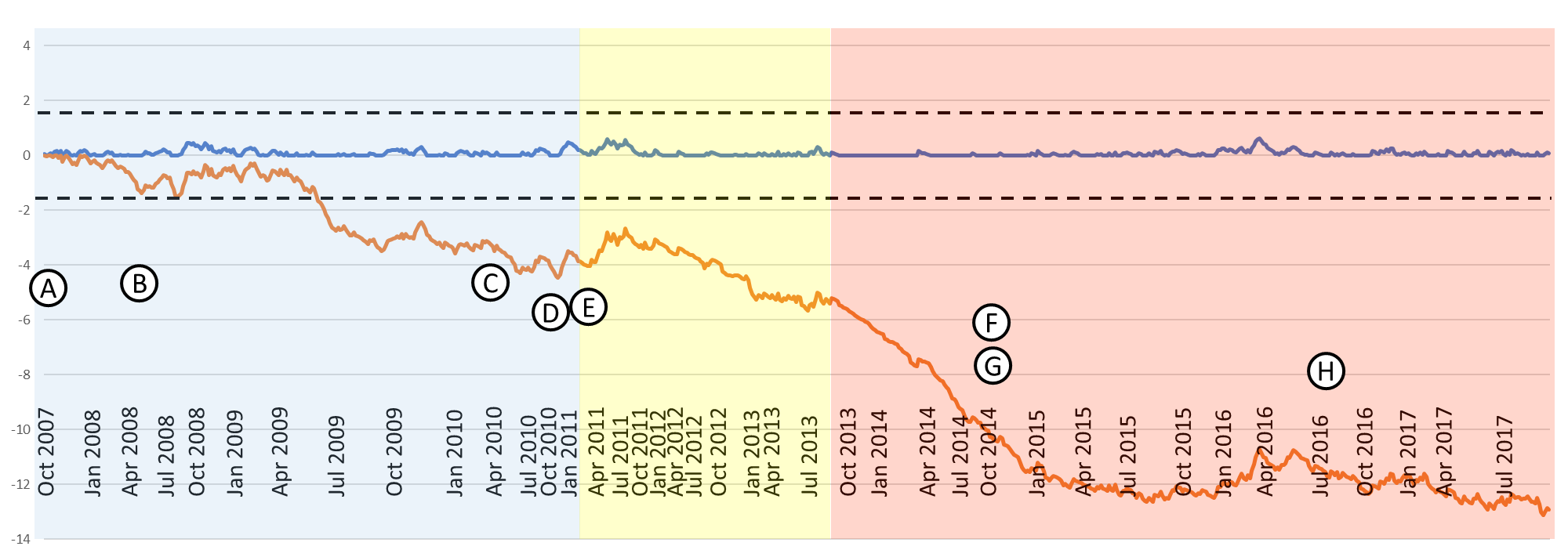
We constructed RA-CUSUM charts that plot the functions:

Where weight is calculated using:

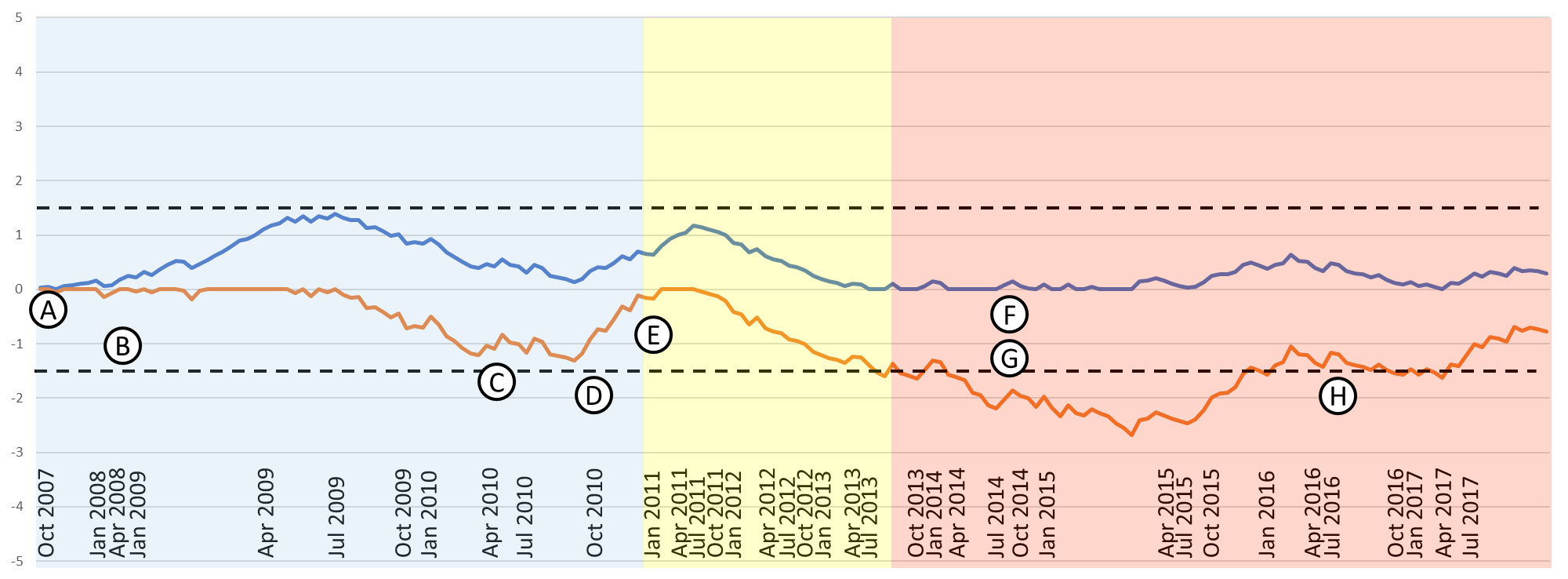
, the expected probability of mortality was estimated from the Apache II score of each patient. is the specified odd ratio increase or decrease in mortality rate that the risk-adjusted CUSUM chart is set to detect. The control limit (CL) is the value that the chart needs to cross in order to “signal” a significant change in mortality. In this study, we set at 1.5 for the max function and 0.5 for the min function in order to detect 50% increase and decrease in mortality, respectively. Control limit was set at 1.5 with an average run length (ARL) of 60 (approximately 6 months).



**Figure 1**. RA-CUSUM chart of entire population. Blue series – Max function with of 1.5. Orange series – Min function with of 0.5. Red series – quarterly pathway activation rates. Dashed lines indicate control limits at 1.5 and -1.5. Implementation of Institutional changes and events are marked as follows: A. Pilot study of Sepsis Alert Pathway (Sept 2007), B. Hospital-wide launch of first version of the Sepsis Alert Pathway (May 2008), C. Start of fellowship in Critical Care Medicine (April 2010), D. Implementation of Rapid response system (Oct 2010), E. Implementation of RFID in ICU (Jan 2011), F. Start of residency in Emergency Medicine (September 2014), G. Purchase of ultrasound machine dedicated to the ICU (September 2014), I. Management directive regarding pathway activation (July 2016). Pathway version in implementation differentiated by the background: blue – version 1, yellow – version 2, red – version 3.



**Figure 2**. RA-CUSUM for Protocol-Based Group. Blue series – Max function with of 1.5. Orange series – Min function with of 0.5. Dashed lines indicate control limits at 1.5 and -1.5. Implementation of Institutional changes and events are marked as follows: A. Pilot study of Sepsis Alert Pathway (Sept 2007), B. Hospital-wide launch of first version of the Sepsis Alert Pathway (May 2008), C. Start of fellowship in Critical Care Medicine (April 2010), D. Implementation of Rapid response system (Oct 2010), E. Implementation of RFID in ICU (Jan 2011), F. Start of residency in Emergency Medicine (September 2014), G. Purchase of ultrasound machine dedicated to the ICU (September 2014), I. Management directive regarding pathway activation (July 2016). Pathway version in implementation differentiated by the background: blue – version 1, yellow – version 2, red – version 3.



**Figure 3**. RA-CUSUM for Non-protocolized Management Group. Blue series – Max function with of 1.5. Orange series – Min function with of 0.5. Dashed lines indicate control limits at 1.5 and -1.5. Implementation of Institutional changes and events are marked as follows: A. Pilot study of Sepsis Alert Pathway (Sept 2007), B. Hospital-wide launch of first version of the Sepsis Alert Pathway (May 2008), C. Start of fellowship in Critical Care Medicine (April 2010), D. Implementation of Rapid response system (Oct 2010), E. Implementation of RFID in ICU (Jan 2011), F. Start of residency in Emergency Medicine (September 2014), G. Purchase of ultrasound machine dedicated to the ICU (September 2014), I. Management directive regarding pathway activation (July 2016). Pathway version in implementation differentiated by the background: blue – version 1, yellow – version 2, red – version 3.

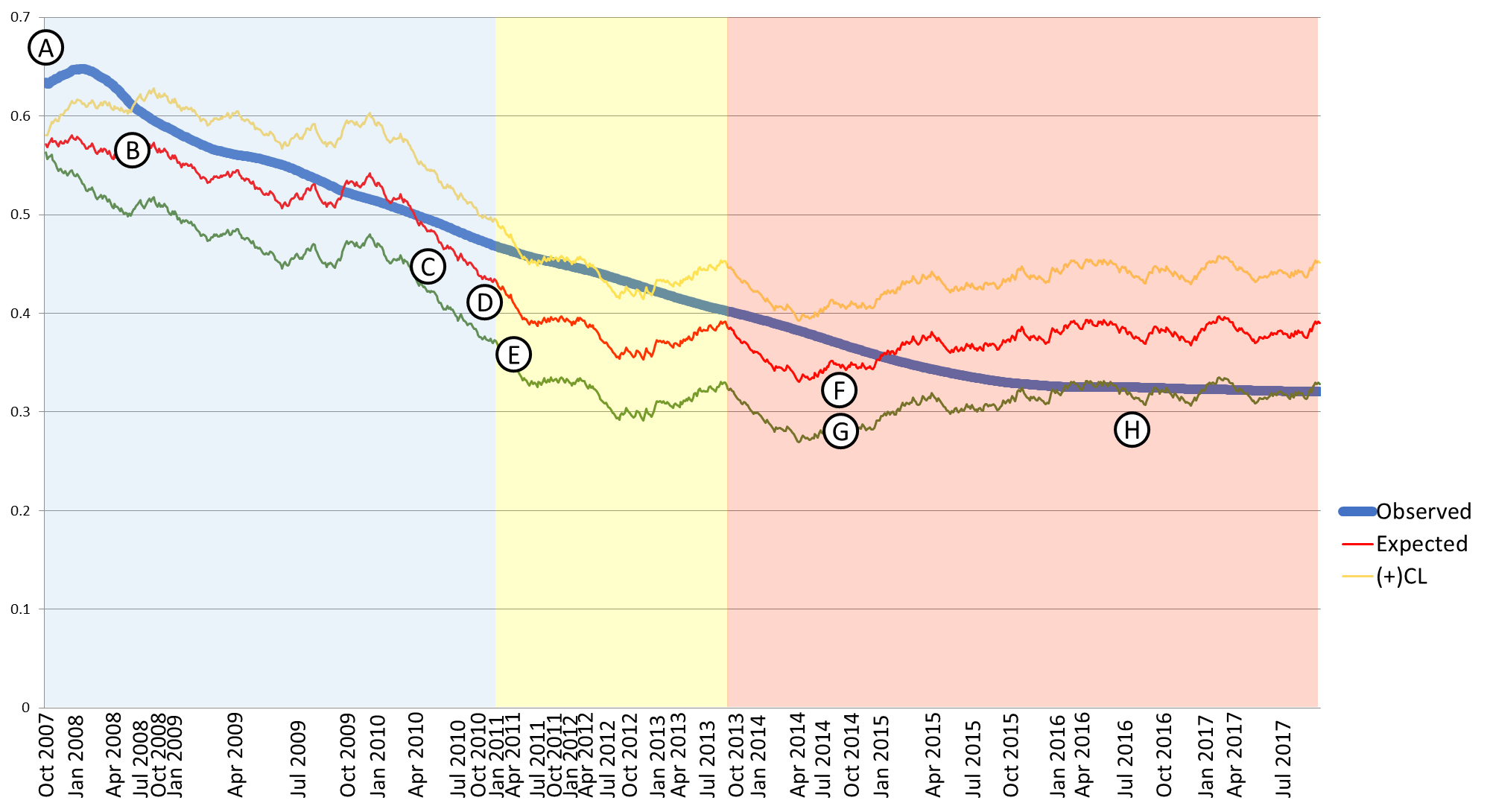
**II. Risk-Adjusted Exponentially Weighted Moving Averages Control Chart**

The RA-EWMA chart was derived using weighted average of sequential observations with most recent observations having the greatest weight12:

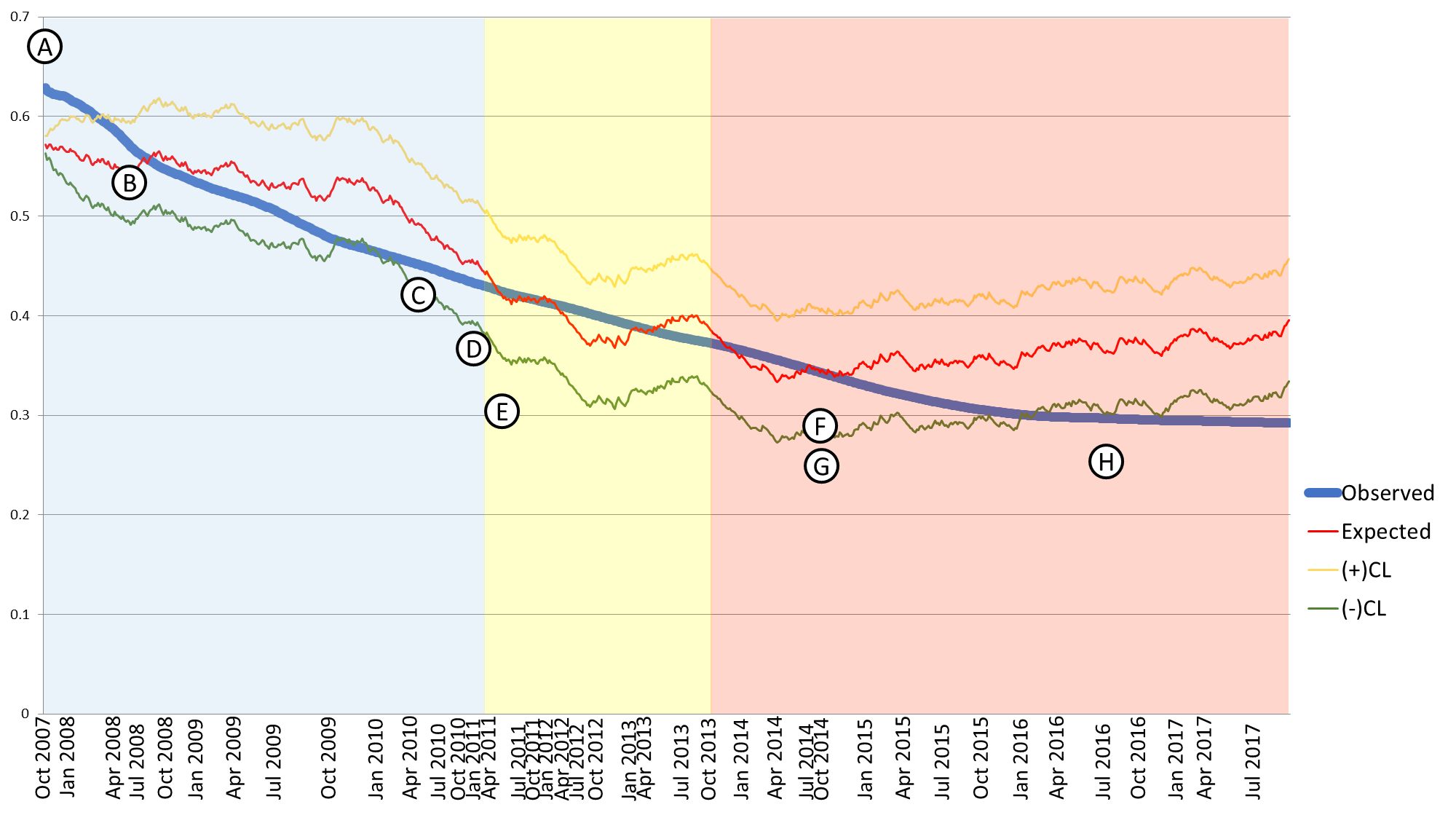
CL was estimated from the variance of the function, assuming that has a variance of zero12:

Ninety-five percent upper and lower CLs were estimated as follows:

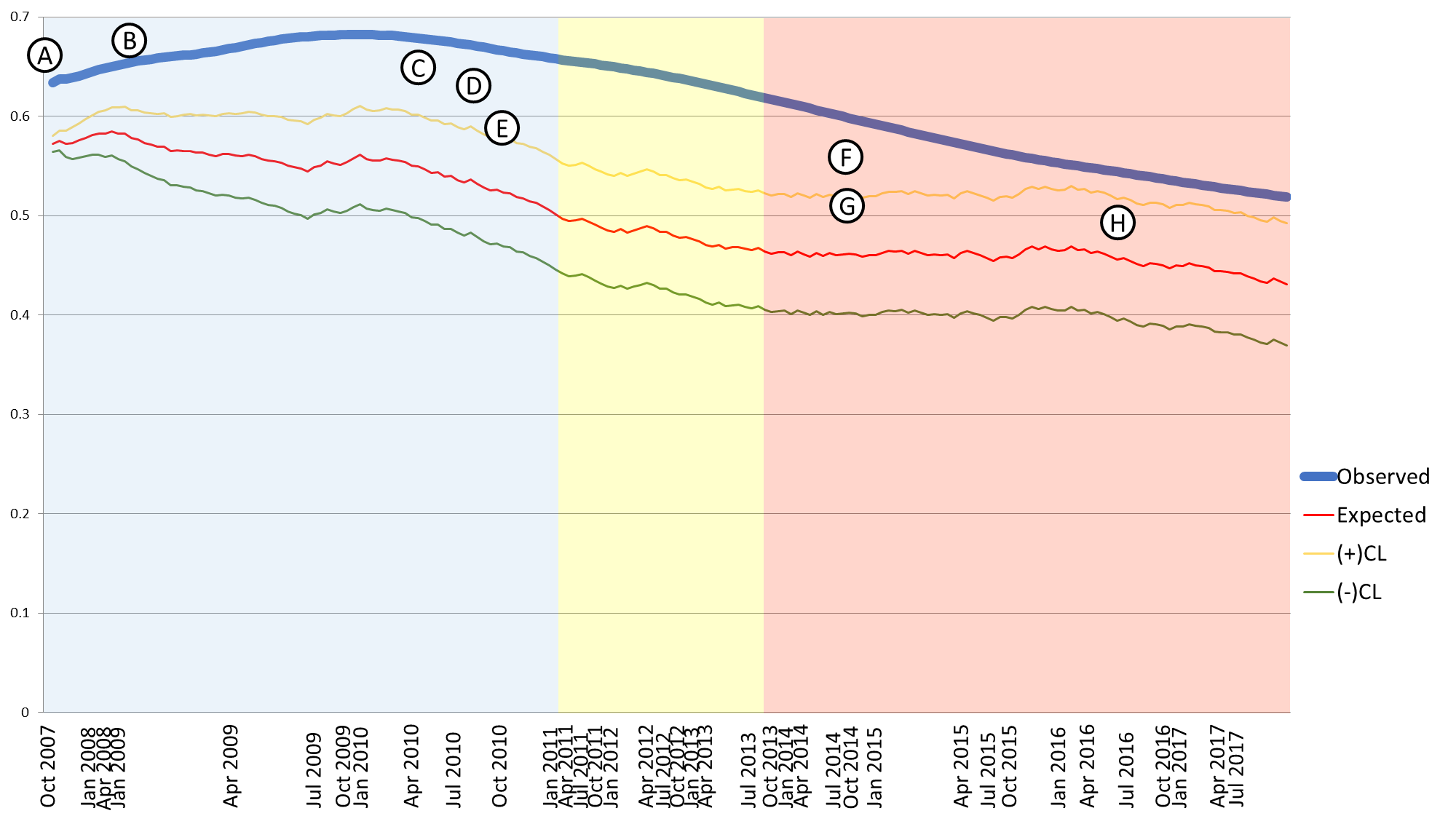
Width parameter is selected so that the in-control ARL (which corresponds to false positive rate) is suitably long while the out-of-control ARL (which corresponds to false negative rate) is suitably short13. Smoothing factor is used to attenuate noise in the data and smooth an erratic risk model while still being able to detect sudden trend changes. Application of EWMA in critical care13 showed that between 0.005 and 0.020 allow comparability of expected and observed outcomes. In this study, was set at 0.01, OR at 2.0, and at 2.07, hence having an in-control ARL of 1000 and an out-of-control ARL of 50 (approximately 5 months).



**Figure 4.** RA-EWMA chart of entire population. Blue series – Observed mortality. Red series – Predicted mortality. Yellow series – upper 95% confidence interval of control limit. Green series – lower 95% confidence interval of control limit. Implementation of Institutional changes and events are marked as follows: A. Pilot study of Sepsis Alert Pathway (Sept 2007), B. Hospital-wide launch of first version of the Sepsis Alert Pathway (May 2008), C. Start of fellowship in Critical Care Medicine (April 2010), D. Implementation of Rapid response system (Oct 2010), E. Implementation of RFID in ICU (Jan 2011), F. Start of residency in Emergency Medicine (September 2014), G. Purchase of ultrasound machine dedicated to the ICU (September 2014), I. Management directive regarding pathway activation (July 2016). Pathway version in implementation differentiated by the background: blue – version 1, yellow – version 2, red – version 3.



**Figure 5**. RA-EWMA chart of Protocol-based group only. Blue series – Observed mortality. Red series – Predicted mortality. Yellow series – upper 95% confidence interval of control limit. Green series – lower 95% confidence interval of control limit. Implementation of Institutional changes and events are marked as follows: A. Pilot study of Sepsis Alert Pathway (Sept 2007), B. Hospital-wide launch of first version of the Sepsis Alert Pathway (May 2008), C. Start of fellowship in Critical Care Medicine (April 2010), D. Implementation of Rapid response system (Oct 2010), E. Implementation of RFID in ICU (Jan 2011), F. Start of residency in Emergency Medicine (September 2014), G. Purchase of ultrasound machine dedicated to the ICU (September 2014), I. Management directive regarding pathway activation (July 2016). Pathway version in implementation differentiated by the background: blue – version 1, yellow – version 2, red – version 3.



**Figure 6**. RA-EWMA chart of non-protocolized management group only. Blue series – Observed mortality. Red series – Predicted mortality. Yellow series – upper 95% confidence interval of control limit. Green series – lower 95% confidence interval of control limit. Implementation of Institutional changes and events are marked as follows: A. Pilot study of Sepsis Alert Pathway (Sept 2007), B. Hospital-wide launch of first version of the Sepsis Alert Pathway (May 2008), C. Start of fellowship in Critical Care Medicine (April 2010), D. Implementation of Rapid response system (Oct 2010), E. Implementation of RFID in ICU (Jan 2011), F. Start of residency in Emergency Medicine (September 2014), G. Purchase of ultrasound machine dedicated to the ICU (September 2014), I. Management directive regarding pathway activation (July 2016). Pathway version in implementation differentiated by the background: blue – version 1, yellow – version 2, red – version 3.

**Appendix F: Patient Characteristics at Baseline and 6-hours into Resuscitation**

|  |  |  |  |
| --- | --- | --- | --- |
| Patient Characteristics | Protocol-Based Group | Non-protocolized Group | p value |
| **N=750** | **N=190** |  |
| Demographics |  |  |  |
| Median Age | 69 (55-80) | 67 (56-79) | 0.84\* |
| <40 years old | 88 (11.7%) | 15 (7.9%) |  |
| 40-49 years old | 47 (6.3%) | 21 (11.1%) |  |
| 50-79 years old | 432 (57.6%) | 107 (56.3%) |  |
| >79 years old | 193 (25.7%) | 47 (24.7%) |  |
| Sex |  |  |  |
| Female | 433 (57%) | 81 (42.6%) | 0\*\* |
| Point of Entry |  |  |  |
| ER | 463 (60.9%) | 101 (53.2%) | 0.24\* |
| Ward | 287 (37.8%) | 85 (44.7%) |  |
| Operating Room | 6 (0.8%) | 2 (1.1%) |  |
| Delivery Room | 4 (0.5%) | 2 (1.1%) |  |
| Diagnosis |  |  |  |
| Severe Sepsis | 145 (19.1%) | 46 (24.2%) | 0.12\* |
| Septic Shock | 615 (80.9%) | 144 (75.8%) |  |
| Comorbidities |  |  |  |
| Hypertension | 339 (44.6%) | 89 (46.8%) | 0.58\* |
| Diabetes | 293 (38.6%) | 62 (32.6%) | 0.13\* |
| Asthma/COPD | 72 (9.5%) | 23 (12.1%) | 0.28\* |
| Stroke | 107 (14.1%) | 27 (14.2%) | 0.96\* |
| Atrial fibrillation | 97 (12.8%) | 31 (16.3%) | 0.20\* |
| Valvular Heart disease | 16 (2.1%) | 7 (3.7%) | 0.21\* |
| CAD | 95 (12.5%) | 23 (12.1%) | 0.88\* |
| Heart failure | 82 (10.8%) | 28 (14.7%) | 0.13\* |
| Malignancy | 158 (20.8%) | 51 (26.8%) | 0.07\* |
| CKD | 158 (20.8%) | 35 (18.4%) | 0.47\* |
| Cirrhosis | 19 (2.5%) | 14 (7.4%) | 0.001\* |
| HIV | 9 (1.2%) | 3 (1.6%) | 0.66\* |
| None | 112 (14.7%) | 15 (7.9%) | 0.01\* |
| Focus of infection |  |  |  |
| Respiratory | 501 (65.9%) | 121 (63.7%) | 0.56\* |
| Skin/Soft tissue | 107 (14.1%) | 17 8.9%) | 0.06\* |
| Genitourinary | 274 (36.1%) | 42 (22.1%) | 0.00\* |
| Blood | 53 (7%) | 17 (8.9%) | 0.35\* |
| Gastrointestinal | 109 (14.3%) | 45 (23.7%) | 0.002\* |
| Central Nervous System | 12 (1.6%) | 3 (1.6%) | 0.10\* |
| Clinical Parameters |  |  |  |
| White blood cell count (x 109 cells/mm3) | 14.5 (8.9-20.2) | 14.6 (8.9-22) | 0.56\*\* |
| Temperature (°C) | 38.0 (37.2-39.0) | 37.9 (36.9-38.8) | 0.01\*\* |
| Lactate (mmol/L) | 2.76 (1.66-4.30) | 2.82 (1.84-5.01) | 0.46\*\* |
| Lactate >4 | 195 (26%) | 43 (22.6%) | 0.15\*\* |
| Creatinine (mg/dL) | 1.36 (0.84-2.47) | 1.21 (0.71-2.6) | 0.08\*\* |
| Mean arterial pressure (mmHg) |  |  |  |
| Baseline | 63 (56-70) | 60 (55-71) | 0.76\*\* |
| 6 hours after resuscitation | 74 (67-83) | 76 (67-86) | 0.25\*\* |
| Heart rate (bpm) |  |  |  |
| Baseline | 105 (88-120) | 104 (88-121) | 0.80\*\* |
| 6 hours after resuscitation | 95 (84-110) | 94 (84-108) | 0.69\*\* |
| Total fluid resuscitation (liters) | 2.0 (1.0-2.0) | 1.0 (1.0-2.0) | 0.15\*\* |
| Antibiotic therapy within 30 minutes of diagnosis | 77.1% | 74.2% | 0.4 |
| APACHE-II Score | 20 (14-27) | 21 (16-28) | 0.13\*\* |
| Expected mortality | 36% (19%-57%) | 40% (24%-61%) | 0.15\*\* |

Values expressed as median with interquartile range

\*Chi-square

\*\* Mann-Whitney U test

**Appendix G – Propensity Matched Analysis**

**Variables entered into the equation:**

* Age
* Female gender
* Comorbid status (y/n)
  + DM
  + COPD
  + Cancer
  + CKD
  + HTN
  + CVD
  + Cirrhosis
  + HIV
  + Heart failure
  + Coronary artery disease
  + Connective Tissue Disease
* Origin: ER/Floors/OR/other ICUs
* Initial Mean Arterial Pressure
* Initial Heart Rate
* Suspected septic focus
  + central nervous system
  + cardiovascular
  + pulmonary
  + gastrointestinal
  + genitourinary
  + skin or soft tissue
  + blood

**Mortality x Pathway Cross-tabulation, Caliper = 0.2**

**(Pearson’s Chi-square Analysis)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Protocolized Management | Non-Protocolized Management | P value |
| n | 190 | 190 |  |
| Mortality (%) | 63 (43.4%) | 82 (56.6%) | 0.045 |

**Appendix H – Logistic Regression Analysis**

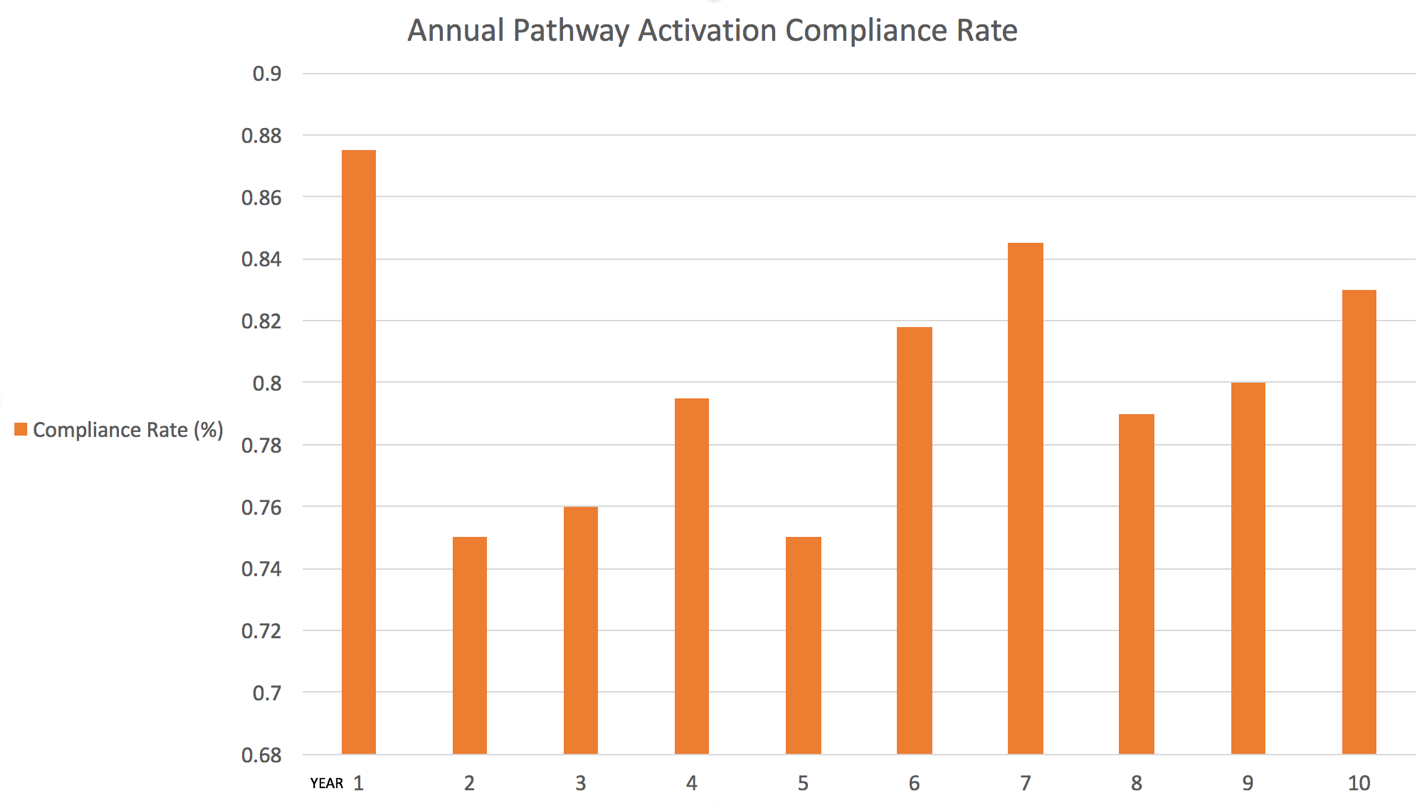
1. **Binomial Logistic Regression of Clinical Factors Affecting Mortality**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Odds Ratio | 95% CI | P value |
| Age > 60 years | 0.820 | 0.584-1.151 | .251 |
| Presence of any comorbidity | 0.749 | 0.476-1.178 | .211 |
| APACHE II score >25 | 5.487 | 4.010-7.508 | .000 |
| Lactate >4 mmol | 2.551 | 1.824-3.569 | .000 |
| Use of Protocol-Based Management | 0.497 | 0.345-0.716 | .000 |

1. **Multinomial Logistic Regression of Significant Clinical Factors Affecting Mortality**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Odds Ratio | 95% CI | P value |
| APACHE II score >25 | 5.306 | 3.894-7.228 | .000 |
| Lactate >4 mmol | 2.617 | 1.874-3.655 | .000 |
| Use of Protocol-Based Management | 0.509 | 0.354-0.732 | .000 |

**Appendix I – Annual Pathway Activation Compliance Rate**

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**Figure 7.** Pathway activation compliance rate by program year.