To: NQF's Patient Safety Standing Committee
NQF Consensus Standards Approval Committee (CSAC)

Re: Severe Sepsis and Septic Shock: Management Bundle (NQF measure #0500)

FM: Henry Ford Health Systems, The Measure Steward

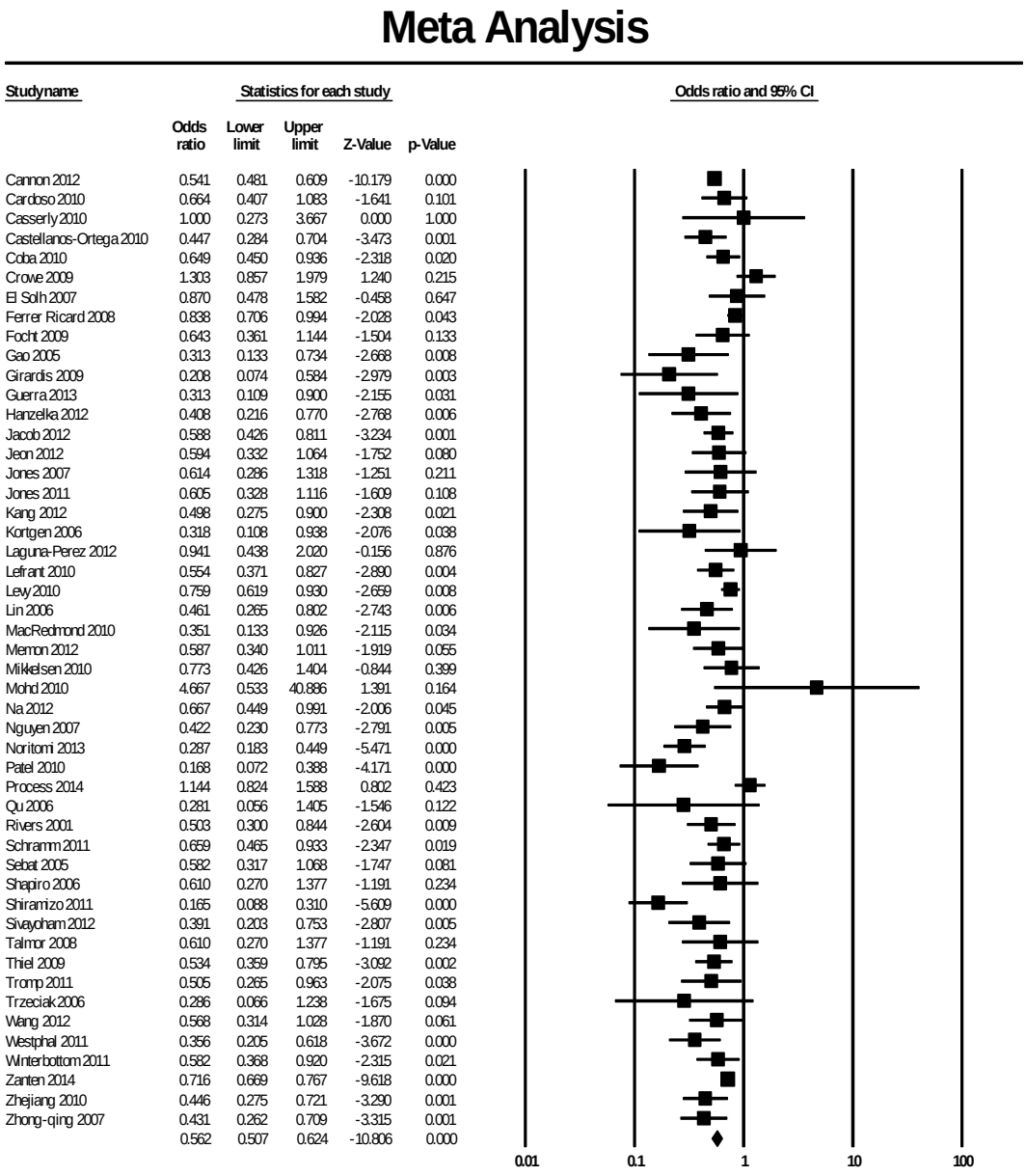
Date: 6-26-2014

The original NQF Sepsis Measure 0500 was submitted in 2007 and was approved in 2013 some 6 years after submission. Within a few months after this approval, a NQF Ad Hoc Committee's responded to a request to review the Protocolized Care for Early Septic Shock (ProCESS) trial which was published on March, 2014.[1] Less than 3 months after the ProCESS trial was published, the Ad Hoc Committee, by the most narrow margin voted to remove from it item 'F' or the central venous catheter (CVC) to measure central venous pressure (CVP) and oxygen saturation ($ScvO_2$) as measure goals.

The Sepsis Measure #0500 was submitted as an integrated standard operating procedure (SOP) to improve outcomes in the early treatment of severe sepsis and septic shock when the mortality was approaching 50%. The core of this measure called early goal directed therapy (EGDT) was an assimilation of best practice provided at the most proximal presentation of hospital presentation. The measure includes early detection of infection, cultures, antibiotic administration, source control risk stratification and hemodynamic optimization (preload, after load, contractility, arterial oxygen content, while balancing systemic oxygen delivery and consumption). This measure was based on the pathogenesis of the disease which has not changed.

This measure has undergone the rigorous NQF evaluation process for over 6-7 years based on over 13 years of confirmatory studies. These studies provided the framework which allowed it to navigate the validity and reliability metrics as a whole measure including the CVC . This measure has been accompanied by the largest decrease in sepsis mortality in the last two decades both nationally[2,3] and internationally.[4] These results have been seen in large health care delivery systems such as Kaiser, California and in the community settings.[5] In multiple studies, the mortality benefits have been robust and striking similar to the initial EGDT trial. [6-9]

When the ProCESS trial is included in this data of 49 studies, its 1351 patients represents only a small fraction (3%) of the total body of evidence which includes 41,064 patients. Furthermore, ProCESS does not reflect practice in the community setting where the majority of patients are treated in the US. See figure below.



With this evidence, one questions the haste to change the measure 0500. Individuals comprising ProCESS trial investigators and some advocating for this measure change have long sought to "dissemble or unbundle EGDT".[10-12] Some view the measure as a hemodynamic intervention concentrating on the CVC catheter[13,14] instead of a SOP for early sepsis diagnosis and treatment. These components have been recommended by expert opinion for over 60 years.[15-18] As a whole this SOP has been proven to be highly effective in saving lives.

The first attempt to "dissemble and unbundle EGDT" was a non-inferior methodology which proposed lactate clearance as a substitute for $ScvO_2$.[10-12] A multi-center randomized trial using CONSORT guidelines concluded non-inferiority, however, the hypothesis proved flawed because lactate levels are not elevated in up to 30% of septic shock patients. [5,11,19] This important limitation was not even discussed in the publication but later acknowledged.[20] Furthermore, the event rate or mortality and the number of interventions were inadequate to support this conclusion. Even though this study concluded that one can eliminate $ScvO_2$, the validity and reliability by NQF standards was lacking. Furthermore, a CVC was still used. This trial was rendered a level 2 recommendation in spite being a multi-center randomized trial published in a major journal.[21]

This aforementioned study and its patient population was acknowledged as similar in the ProCESS trial discussion. The ProCESS trial found an event rate or mortality (20%) far below anticipated at less than half the historical mortality (46%).[22-26,40] Furthermore, over 56% of all the non-EGDT or control group patients received CVC line placement.[24] This reflects influence of the Surviving Sepsis Campaign (SSC) guidelines published in 2004, 2008 and 2012 during this trial's conduction. Although a randomized trial, the care was un-blinded and enrollment averaged only 8 patients per site per year over 5 years in "high volume centers".[21,27,28] As a result, these factors render this study underpowered and not translatable to make recommendations regard CVC use.

The CVC provides central venous pressure (CVP) and $ScvO_2$. These values can provide critical information about cardiac dysfunction[29-31] which is associated with improved outcome when treated.[5,32-34] As a result CVC placement has been shown to be one of the most important bundle elements[34-37] and independently associated with a 9% reduction in mortality.[38,39] Up to 15% of patients will have myocardial dysfunction which has been eliminated by the ProCESS trial.[40] Even delayed intervention up to 18 hours after diagnosis with the measure has been shown to be effective in reducing mortality.[41-43] This was not controlled for in the ProCESS trial.

Ironically, the concern for central line complications were not realized in the ProCESS study as complications were similar in all groups. Prospective randomized trials reveal CVC are associated with fewer complications then peripheral lines and can be put in as safely by nurses.[44,45] This procedure should be performed by the most qualified clinician as with any other disease. Are we concerned with the safety of a cardiac catheterization in the hands of a qualified cardiologist treating an acute myocardial infarction? It is the risk benefit, competence of the clinician and not the procedure itself.

The ProCESS investigators admit that it was not a replication of EGDT. Thus, the subtraction of one of the measure components is not scientifically unacceptable. The validity, reliability and logistic issues of providing the alternative Protocol Based Standard Therapy used in ProCESS remain unanswered and untested outside of this study. This begs to question how the measure change can be recommended without knowing the performance under the rigors of the NQF process.

The NQF 0500 measure was originally submitted when there was little interest or resistance in early sepsis management. When the mortality was 40-50%, there was no call for national standards of care. This landscape has changed for the better regarding patient care for this disease. Creating an open ended measure by subtracting a proven component (CVC) could be deleterious in a setting outside the 31 centers in the ProCESS trial. These centers represent the minority of settings for the other 4500 hospitals where sepsis care is provided in the US.

An accompanying editorial of the ProCESS trial made a declaration of a "new era in sepsis management". What we do know is that 31 "high volume" hospitals who provided 8 patients per year over 5 years may not represent a national reflection of care.[46] The US health care system is the most expensive in the world, but comparative analysiss consistently show the U.S. underperforms relative to other countries on most dimensions of performance. Among the 11 nations studied in this report—Australia, Canada, France, Germany, the Netherlands, New Zealand, Norway, Sweden, Switzerland, the United Kingdom, and the United States—the U.S. ranks last.[47]

At a minimum, this disease still kills one out of every 5 patients. This is unacceptable and we should move forward with the original measure and not take a step backwards.

References

1. Pro CI, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683-93.
2. Kumar G, Kumar N, Taneja A, et al. Nationwide trends of severe sepsis in the 21st century (2000-2007). Chest 2011;140:1223-31.
3. Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis*. Crit Care Med 2014;42:625-31.
4. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012. JAMA 2014.
5. Cannon CM, Holthaus CV, Zubrow MT, et al. The GENESIS project (GENeralized Early Sepsis Intervention Strategies): a multicenter quality improvement collaborative. J Intensive Care Med 2013;28:355-68.
6. Wira CR, Dodge K, Sather J, Dziura J. Meta-analysis of Protocolized Goal-Directed Hemodynamic Optimization for the Management of Severe Sepsis and Septic Shock in the Emergency Department. Western Journal of Emergency Medicine 2014;15.
7. Jones AE, Brown MD, Trzeciak S, et al. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. Crit Care Med 2008;36:2734-9.
8. Wang AT, Liu F, Zhu X, Yao GQ. [The effect of an optimized resuscitation strategy on prognosis of patients with septic shock: a systematic review]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2012;24:13-7.
9. Barochia AV, Cui X, Vitberg D, et al. Bundled care for septic shock: an analysis of clinical trials. Crit Care Med 2010;38:668-78.

10. Lewis RJ. Disassembling goal-directed therapy for sepsis: a first step. Jama 2010;303:777-9.
11. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. Jama 2010;303:739-46.
12. Jones AE. Unbundling Early Sepsis Resuscitation. Ann Emerg Med;63:654-5.
13. Al-Khafaji A, Rivers E, Shoemaker W. The prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Article of Shoemaker et al with expert commentary by Dr. Emanuel Rivers. 1988. Journal of Critical Care 2008;23:603-6.
14. Gunn SR, Fink MP, Wallace B. Equipment review: the success of early goal-directed therapy for septic shock prompts evaluation of current approaches for monitoring the adequacy of resuscitation. Crit Care 2005;9:349-59.
15. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
16. Broder G, Weil MH. Excess lactate: an index of irreversibility of shock in human patients. Science 1964;143:1457-9.
17. Weil M, Shubin H, Rosoff L. Fluid repletion in circulatory shock: Central venous pressure and other practical guides. JAMA 1965;192:668-74.
18. Wilson JN. Rational approach to management of clinical shock: Utilizing light-reflection oximetry and central venous pressure monitoring. Archives of Surgery 1965;91:92-20.
19. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ, Group C. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006;295:1152-60.
20. Jones AE. Lactate Clearance for Assessing Response to Resuscitation in Severe Sepsis. Acad Emerg Med 2013.
21. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. Critical Care Medicine 2013;41:580-637.
22. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Critical Care Medicine 2010;38:367-74.
23. Cannon CM, for the Multicenter Severe S, Septic Shock Collaborative G. The GENESIS Project (GENeralization of Early Sepsis InterventionS): A Multicenter Quality Improvement Collaborative. Acad Emerg Med 2010;17:1258.
24. Shapiro NI, Howell MD, Talmor D, et al. Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. Crit Care Med 2006;34:1025-32.
25. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med 2009;37:1670-7.
26. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med 2007;33:970-7.
27. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858-73.

28. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.
29. Kirk JP, David M, Fiona W, et al. The Effect Of Pre-Existing Left Ventricular Dysfunction On Meeting Central Venous Oxygen Saturation (ScvO2) Goals In The Management Of Severe Sepsis And Septic Shock. D24 FLUID RESUSCITATION AND TRANSFUSIONS: American Thoracic Society; 2014:A5500-A.
30. Nakamura M, Coopersmith C, Greg M, et al. 1028: Difference in Lactate Levels and Cardiac Function Among Three Septic Patient Groups Stratified By Initial Central Venous Oxygen Saturation Levels. Critical Care Medicine 2012;40:1-328 10.1097/01.ccm.0000425241.67260.7c.
31. Ouellette DR, Shah SZ. Comparison of outcomes from sepsis between patients with and without pre-existing left ventricular dysfunction: a case-control analysis. Crit Care 2014;18:R79.
32. Grissom CK, Morris AH, Lanken PN, et al. Association of physical examination with pulmonary artery catheter parameters in acute lung injury. Crit Care Med 2009;37:2720-6.
33. Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki LM, Pettila V. Hemodynamic variables related to outcome in septic shock. Intensive Care Med 2005;31:1066-71.
34. Cannon C, Holthaus C, Rivers E, et al. Improving outcome in severe sepsis and septic shock: results of a prospective multicenter collaborative. The Journal of Emergency Medicine 2009;37:217–36.
35. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, et al. Impact of the surviving sepsis campaign protocols on hospital length of stay and mortality in septic shock patients: Results of a 3-year follow-up quasi-experimental study. Crit Care Med 2010.
36. Chamberlain DJ, Willis EM, Bersten AB. The severe sepsis bundles as processes of care: A meta-analysis. Aust Crit Care 2011.
37. Jeon K, Shin TG, Sim MS, et al. Improvements in Compliance of Resuscitation Bundles and Achievement of End Points After an Educational Program on the Management of Severe Sepsis and Septic Shock. Shock 2012.
38. Kashiouris M, Kashyap R, Jaffer-Sathick I, Gajic O, Cartin-Ceba R. Association between delays in central venous catherter utilization and organ dysfunction in patients with severe sepsis and septic shock. Critical Care Medicine 2011;39(12):142.
39. Walkey AJ, Wiener RS, Lindenauer PK. Utilization patterns and outcomes associated with central venous catheter in septic shock: a population-based study. Crit Care Med 2013;41:1450-7.
40. Kumar A, Haery C, Parrillo JE. Myocardial dysfunction in septic shock. Crit Care Clin 2000;16:251-87.
41. Coba V, Whitmill M, Mooney R, et al. Resuscitation Bundle Compliance in Severe Sepsis and Septic Shock: Improves Survival, Is Better Late than Never. J Intensive Care Med 2011.
42. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, Ortiz F, Llorca J, Delgado-Rodriguez M. Late compliance with the sepsis resuscitation bundle: impact on mortality. Shock 2011;36:542-7.

43. Sadaka F, Tannehill D, Trottier S, et al. 57: Resuscitation Bundle Compliance in Septic Shock: Better Late Than Never. Critical Care Medicine 2013;41:A16 0.1097/01.ccm.0000439241.94724.42.
44. Ricard JD, Salomon L, Boyer A, et al. Central or peripheral catheters for initial venous access of ICU patients: a randomized controlled trial. Crit Care Med 2013;41:2108-15.
45. Alexandrou E, Spencer TR, Frost SA, Mifflin N, Davidson PM, Hillman KM. Central venous catheter placement by advanced practice nurses demonstrates low procedural complication and infection rates-a report from 13 years of service*. Crit Care Med 2014;42:536-43.
46. Lilly CM. The ProCESS trial--a new era of sepsis management. N Engl J Med 2014;370:1750-1.
47. Davis K, Stremikis K, Squires D, Schoen C. Mirror, Mirror on the Wall, 2014 Update: How the U.S. Health Care System Compares Internationally. The Commonwealth Fund 2014.