Surrogate Measures of Patient-centered Outcomes in Critical Care

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"... a surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint." [1]

Introduction

The ultimate goal of medicine is to improve health in ways that matter to patients. A variety of outcomes are important to patients: symptoms, quality of life, duration of life, quality of dying, the effect of their health care on their loved ones, and the cost of medical care. Because of the importance of these outcomes to patients they are referred to as 'patient-centered' outcomes. Ideally, clinicians will offer, insurers will pay for, and patients will have the opportunity to use treatments that have been shown to improve patient-centered outcomes. Patient-centered outcomes are distinct from any number of chemical, physiologic, and radiographic variables that may be measured in clinical research. There are many reasons investigators choose to measure these important *alternate* or *auxiliary* measures. They often provide essential information about how a treatment works, about complications, and about the study population and subgroups. However, when one of these variables is used specifically as a substitute for a patient-centered outcome, it is referred to as a *surrogate* outcome variable. Other synonyms for these variables are *intermediate* or *proxy* outcome variables [2]. Common examples of surrogate outcomes are substituting blood pressure for survival in a study of antihypertensives, left ventricular function for quality of life in a study of therapy for congestive heart failure, and tumor size for survival in a study of cancer therapy.

Surrogate outcomes are usually proximal physiologic or laboratory effects of the treatment and therefore very sensitive to the treatment's effects. The surrogate outcome is a factor that is known (or highly suspected) to be in the causal pathway to the patient-centered outcome [3]. For example, sustained elevations in blood pressure cause atherosclerosis, congestive heart failure and stroke which lead to death and morbidity. The calcium channel blocking drug nifedipine dilates blood vessels and lowers blood pressure. If blood pressure is a valid surrogate for survival, then demonstrating the hypotensive effect of nifedipine is sufficient to prove its benefit in improving patient-centered outcome. A similar argument can be con-

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structed for cholesterol level. Elevated cholesterol causes coronary atherosclerosis leading to myocardial infarction and death. The cholesterol lowering drug clofibrate reduces blood lipid levels. Presumably, a study that demonstrates the effect of clofibrate on lipid levels is sufficient to demonstrate its beneficial effect on survival and quality of life.

There are enormous advantages to studying blood pressure and cholesterol level instead of survival, mortality* or quality of life. Surrogate outcomes hold out the promise of shorter studies of fewer patients to demonstrate the effectiveness of treatments [4, 5]. This is particularly desirable in chronic diseases where a treatment's effect on survival or quality of life may not be observed for years while its effect on a surrogate may be observed over weeks or months. Surrogate outcomes, by definition, are very sensitive to the treatment's direct effect and therefore are more responsive variables than patient-centered outcomes. Since surrogate outcomes are frequently laboratory or physiologic measures they can usually be measured reliably and precisely. By increasing the sensitivity, precision, and reliability of the outcome variable, surrogate outcomes can increase the statistical power of clinical studies requiring smaller numbers of patients to demonstrate a statistically significant effect [6].

Patient-centered Outcomes

While the definition of a patient-centered outcome offered above, 'how a patient feels, functions, or survives', has face validity, it allows for a spectrum of application in practice. At one end of the spectrum, physiologic and laboratory measures are clearly not patient centered since they do not directly measure feeling, function, or survival. Other measures, for example, validated quality of life instruments, are clearly patient-centered. In between these ends of the spectrum, there is room for debate about whether a given outcome is patient-centered or not. Frequently, decisions evolve through regulatory and peer review. When an outcome is measured can affect whether it is patient-centered or a surrogate. For example, mortality differences at 12 hours (if not sustained) are unlikely to matter to patients while differences at 5 years will matter. Questions about the exact timepoint when intensive care mortality should be measured continue. Twenty-eight day mortality has become an accepted standard, however, others have advocated longer timepoints [7]. If we know with confidence that the effect of the treatment or the mortality rate of the disease plateau after a specified timepoint, then this informa-

* The terms mortality and survival are used specifically throughout this chapter. Mortality as an outcome is the difference in the probability or odds of death **at a specific** time point (7 days, 28 days, hospital discharge, 5 years) expressed as a risk ratio, risk difference, or odds ratio. Survival as an outcome is the difference in **time until death** (truncated at some study observation end point) expressed as a difference in median survival time or as a hazard ratio (a ratio of rates of death). 'Survival' and 'mortality' should not be used interchangeably. Different statistical techniques are used to analyze survival and mortality data and they are subject to different study biases.

tion can help choose a window for observation. It is not unusual for critical care interventions to show a mortality difference at ICU discharge that disappears by hospital discharge [8]. Survival is a patient-centered outcome except when the study observation window is brief. For example, survival analysis of a critical care intervention that truncates patient observation at 28 days can find statistically significant differences in survival rates when the actual differences in survival time is hours or days [8, 9]. It is unlikely that these survival differences reflect meaningful differences to patients.

Restricting the analysis of mortality and survival to deaths from a specific cause can also affect their patient-centeredness. Although some patients may have a strong preference for dying from a specific disease, a treatment that reduces death from a specific cause without affecting overall mortality provides small patient-centered benefits. In fact, well designed studies that show a reduction in cause specific mortality without a similar reduction in total mortality raise the possibility that the treatment actually increases mortality from causes other than the one specified as the outcome.

Are Surrogate Measures Valid?

The utility of surrogate outcomes relies entirely on the validity of the assumption that the surrogate outcome's response to therapy reflects the net effect of the treatment on patient-centered outcomes [3]. If surrogate measures reliably predict patient-centered outcomes, far more efficient clinical studies could be designed. This would lead to less expensive drug development and more rapid identification and distribution of effective treatments. Therefore, it is not surprising that an extensive literature has evolved to examine whether surrogate outcomes are valid predictors of patient-centered outcomes. Not surprisingly, the evaluation of surrogate outcomes is most advanced in the diseases where the causal pathways linking potential surrogate outcomes with patient-centered outcomes are best understood and where a sufficient quantity of studies with both surrogate and patient-centered outcome data exist. These areas of medicine include cardiovascular diseases, oncology, and human immunodeficiency virus (HIV) infection [2]. The literature evaluating the validity of surrogate outcomes speaks with a uniform voice: surrogate outcome measures are not reliable predictors of the effect of treatments on patient-centered outcomes and treatment decisions based solely on data from surrogate outcomes can be misguided [2, 10–13].

Perhaps the most frequently cited example is the Cardiac Arrhythmia Suppression Trial which explored a very reasonable hypothesis [14]. Sudden death after myocardial infarction from cardiac arrhythmia is strongly associated with the presence of premature ventricular contractions and other ventricular dysrhythmias in the post-myocardial infarction period. Suppression of these dysrhythmias should prevent sudden death after myocardial infarction which is presumed to be due to a cardiac rhythm disturbance. Effective drugs exist to suppress these dysrhythmias. However, in a large randomized clinical trial, drug therapy which was effective at suppressing the dysrhythmia was associated with increased mortality.

No hypothesis could make greater sense than the hypothesis that drugs that halt tumor growth would prolong survival in patients with cancer. The causal relation between tumor progression and cancer death is unquestioned. Tumor response as measured by reduction in size is an accepted surrogate endpoint for oncology trials. Again studies that measure both tumor response and survival repeatedly show that reductions in tumor size are not reliably translated into prolonged survival or quality of life [15].

The validity of blood pressure as a surrogate outcome is so entrenched that an abnormality in this surrogate measure is a disease – hypertension. The goal of treating hypertension turned into the goal of blood pressure reduction rather than the goal of preventing strokes, heart failure, and death. Here, too, the literature has shown that not all treatments that affect the surrogate outcome of blood pressure have similar effects on patient-centered outcomes [16, 17]. Specifically, diuretics and beta-blocker medication appear to be more effective at reducing mortality (or at least not increasing mortality) than calcium channel blockers.

The uniform failure of surrogate outcome measures is likely due to the many possible sources of error in extrapolating surrogate outcomes to patient-centered outcomes. The surrogate outcome may not fully capture the negative effects of the treatment on patient-centered outcomes. In this setting negative effects of the treatment on patient-centered outcomes may exceed any benefits of the treatment measured by the surrogate (Table 1). For example, the pro-arrhythmic effects of quinidine in causing ventricular tachycardia may obviate any benefit it provides in keeping patients out of atrial fibrillation [18]. The surrogate outcome may not reflect the long-term effects of the treatment. Short-term benefits may wane for a variety of reasons and long-term patient-centered benefits will be overestimated by the short-term surrogate. For example, the short-term effects of nucleoside analogs on CD4 counts may not reflect long-term effects on survival since HIV develops resistance to single drug therapy [12, 13, 19]. The surrogate outcome may only reflect one pathway the disease has for affecting patient-centered outcome. Measuring the response in the surrogate variable does not reflect the disease's effects via other pathways. For example, inotropic medication and fluids may improve the oxygen delivery problem in septic shock and increase blood pressure, but they do not affect its inflammatory and coagulation derangements. The surrogate outcome may only be associated with, but not part of the causal pathway of the disease. In this situation, surrogate measure response is irrelevant to the overall outcome of the disease. Frequently, more than one of these explain why a persuasive surrogate outcome fails to predict a treatment's effect on patient-centered outcome.

Is Critical Care Different?

A major goal of critical care is to restore and support physiology [20]. If this is true, then perhaps physiologic measures are the best outcome variables to study to decide whether the goal of critical care has been achieved. Given this rationale, it is possible that surrogate outcome variables may show better performance in critical care than their poor performance in other fields of medicine. Unfortunately,

Table 1. Validity of surrogate endpoints

Disease	Treatment	Effect on surrogate outcome	Effect on patient-centered outcome
Sudden death from cardiac arrhythmia	Encainide, flecanide, and moricizine [14]	Reduction in premature ventricular contractions	Increased mortality and suppression of arrhythmias
Atrial fibrillation	Quinidine [18]	Maintenance of sinus rhythm	Increased mortality
Acute myocardial infarction	Lidocaine [39]	Prevention of ventricular tachycardia	Increased mortality
Congestive heart failure	Milrinone [40]	Increased cardiac output, improved exercise tolerance	Increased mortality
Coronary heart disease	Fibrate lipid lowering drugs [41]	Reduced lipid levels, reduced mortality from coronary heart disease	No effect on total mortality, increased mortality from causes other than coronary heart disease
Colon cancer	5-fluorouracil plus leucovorin [15]	Reduced tumor size	No effect on mortality
HIV infection	Nucleoside analogs [19]	Increased CD4 count	No effect or increased mortality

adapted from [2]

experience with clinical research in critical care suggests that surrogate outcomes are no better at predicting patient centered outcomes in critical illness than they have proven to be in other fields (Table 2).

The treatment of acute respiratory distress syndrome (ARDS) provides a typical example. For over 20 years, investigators have explored therapies to reduce mortality from ARDS. Many treatments, including inhaled nitric oxide, inhaled prostacyclin, liposomal prostaglandin E1, prone positioning during mechanical ventilation, partial liquid ventilation, and tracheal gas insufflation have shown improvements in gas exchange in patients with ARDS. To date, none of these treatments have been shown to improve patient-centered outcomes despite, in the cases of inhaled nitric oxide and prone positioning, large multi-center clinical trials [21–23]. Contrary to the beneficial effects on gas exchange noted in these treatments, lung protective ventilation for ARDS, a treatment that uses low tidal volumes and allows carbon dioxide to 'permissively' build up, generally and intentionally worsens the surrogate outcome of gas exchange in patients with ARDS [7]. Despite its negative effect on patient physiology, mortality is significantly im-

proved. Therefore, gas exchange does not appear to be a valid surrogate outcome for mortality in ARDS.

Human growth hormone provides an even more cautionary tale about adopting treatments based on studies using surrogate endpoints. Critical illness is associated with a highly catabolic state reflected by a persistently negative nitrogen balance which is associated with mortality [24]. A number of studies demonstrated that negative nitrogen balance could be reduced or reversed with human growth hormone [25]. The clinical significance of improving nitrogen balance with human growth hormone was unknown. Two studies reported by Takala and colleagues were actually designed to explore the surrogate endpoints of duration of intensive care unit (ICU) stay, muscle strength, and organ failure [26]. Human growth hormone supplementation caused a doubling of mortality even though the patients' nitrogen balance improved. This lead to a "Dear Doctor" letter from the manufacturer warning about the risks of human growth hormone supplementation in critical illness. There are no data to indicate how many intensivists had adopted human growth hormone based on the surrogate outcome studies. If nitrogen balance alone had been used as an outcome measure in these studies, investigators would have concluded that human growth hormone was effective. If the effect on mortality had been smaller or if the study had enrolled fewer patients, the results may have demonstrated a 'benefit' in nitrogen balance and no effect on mortality.

Critical care does not differ from other fields of clinical investigation at least with regard to the performance of surrogate outcomes in predicting patient-centered outcome. In fact, as Table 2 shows, 'beneficial' surrogate outcome data are occasionally associated with increased mortality. Unfortunately, the failure of surrogate outcomes in critical care has been interpreted by some critics as a failure to identify the optimal surrogate outcome for studies of critical illness rather than a reason to reject surrogate outcomes in general [28, 29]. The overwhelming experience from clinical research outside of critical illness suggests that surrogate outcome measures frequently yield misleading information about patient centered treatment effects and reflect a failure of these measures in general rather than problems with their specific application in critical illness. In fact, there are several reasons to believe that surrogate outcome measures have less to offer and greater potential for misinformation than in other fields.

One of the major advantages of surrogate outcomes is to increase the frequency of study outcomes. Investigators studying acute myocardial infarction, congestive heart failure, and even many cancers deal with short-term mortality rates between 0–15 %. Low event rates require large sample sizes to demonstrate statistically significant results. Shifting to an outcome like ejection fraction or tumor size provides significantly more patients with 'poor' outcomes than mortality. This is not a problem for investigators studying critical illness syndromes like ARDS, severe sepsis, and acute respiratory failure where short-term mortality rates of 30–60 % are common. Therefore, surrogate outcomes are unlikely to increase the statistical power of clinical studies by increasing the event rates. Clinical investigators studying chronic diseases like congestive heart failure, diabetes, and hypertension must observe cohorts of patients for years to identify patient-centered outcomes. Although the long-term effects of critical illness are just beginning to be appreciated, most studies indicate that the majority of deaths attributable to critical

Table 2. Validity of surrogate endpoints – examples from critical care

Disease	Treatment	Effect on surrogate outcome	Effect on patient-centered outcome
ARDS	Prone ventilation [23]	Improved oxygenation	No effect on mortality
ARDS	Inhaled nitric oxide [21, 22]	Improved oxygenation	No effect on mortality
ICU anemia	Blood transfusion [42]	Improved hematocrit	Increased mortality
Critical illness	Hemodynamic goal directed therapy [43, 44]	Increased oxygen delivery	No effect or increased mortality
Critical illness	Human growth hormone [26]	Improved nitrogen balance	Increased mortality, prolonged duration of intensive care
Sepsis	Ibuprofen [45]	Reduces levels of prostacyclin and thromboxane, decreases fever and lactic acidosis	No effect on mortality
Sepsis	Recombinant human interleukin-1-receptor antagonist [9, 46]	Improved survival time and reduced short-term mortality	No effect on mortality

illness occur within the first 60 days [30, 31]. Therefore, by chronic disease standards critical care studies already benefit from a brief time horizon. Finally, surrogate outcomes may have worse performance in critical illness because the causal pathways in critical illness syndromes are poorly understood. Current understandings of the body's response to injury, infection, and hypoperfusion stress the complexity of this response and the heterogeneity of the response depending on the age and comorbidity of the patient [32]. If surrogate outcomes fail in single organ diseases like cardiac dysrhythmia and cancer, it is difficult to imagine how they would perform better in the less well characterized critical illness syndromes.

Are Death, Cost, and Quality of Life the only Outcomes that Matter?

Even if surrogate measures are not valid predictors of patient-centered outcomes in studies of critical illness, variables other than death, cost, and quality of life are important in clinical research. Clinical research to understand mechanisms of critical illness requires a broad range of biochemical and physiologic as well as patient-centered variables. Phase II or hypothesis testing studies will continue to use surrogate variables to identify promising treatments to study in larger studies. When a class of treatments, for example beta blocking drugs, have been shown to

yield patient-centered benefits, surrogate outcome studies may be used to extend the results to a modified treatment that is a member of the same class without repeating patient-centered studies. Nevertheless, even within a class of drugs, some will confer risks that outweigh benefits and post-marketing surveillance is essential to detect these outcomes when a new treatment is adopted based on extending surrogate outcome data.

However, an important question remains, are there outcome variables besides death, cost, and quality of life that should affect treatment choices? There is no simple answer to this question. As one moves away from the fixed points of death, cost, and quality of life, outcomes are subject to increasingly difficult questions about their clinical relevance. Several important and arguably patient-centered outcomes are missed by studies of death, cost, and quality of life. These include major morbid events, process of care, quality of death and dying, and patient and family experience of intensive care.

Are there some major morbid outcomes in the ICU that are worth preventing as long as their prevention does not worsen patient-centered outcomes? If a treatment reduces ventilator-associated pneumonia (VAP) but has no effect on cost of care, mortality, or quality of life, should it be adopted? Is a treatment that prevents intubation worth adopting even if it offers no improvement in survival? Decubitus ulcers? Gastrointestinal bleeding? Delirium? If the answer is yes, how much information will we need to decide that the treatment is safe and how much would we be willing to pay for 'avoiding a catheter-related bacteremia' that may or may not affect patient-centered outcomes. These decisions will turn on an accurate understanding of the costs of the treatment, the risks of the treatment, the costs imposed by the morbid outcome, and some valuation of the outcome itself, either by patients, their families, or by clinicians. For example, we may think about preventing VAP differently if we can be virtually certain that the intervention is safe and cheap (semirecumbent bed positioning) than if the intervention has even theoretic costs and risk (rotational bed therapy, selective decontamination). We may choose to adopt semirecumbent bed positioning given the evidence of a reduction in VAP yet expect evidence of cost or mortality reduction to initiate selective decontamination.

Process of care variables may be important exceptions to some of the criticisms offered about surrogate outcomes. Investigators studying interventions to improve the quality of care can choose to study the *outcomes* of their quality improvement intervention (mortality, for example) or whether their intervention changes the *process* of care. When a treatment has been shown to improve patient-centered outcomes for a disease, for example, aspirin therapy for acute myocardial infarction, the treatment is known to be in the causal pathway for improving patient-centered outcomes. Studies of interventions to improve quality of care can gain considerable improvements in efficiency by studying process of care as a surrogate outcome rather than outcome [33]. There are three important assumptions in this analysis:

1. The treatment's efficacy regarding patient-centered outcomes is well defined.
2. The treatment's effectiveness in the study setting will be similar to its efficacy.
3. The intervention used to increase use of the treatment will not worsen patient-centered outcomes via other mechanisms.

It is the relative acceptability of this last assumption for quality improvement interventions that make process of care an acceptable surrogate for these studies.

The importance of end of life care in the ICU is increasingly recognized as are its inadequacies [34]. While efforts to identify a measure of the quality of death and dying proceed, it is important to recognize that none of the current patient-centered outcomes capture this important patient-centered outcome. In considering the design of studies that might improve the quality of death and dying in the ICU, it is interesting to consider the possibility that better end-of-life care and communication may actually increase mortality and worsen survival by early identification of patients who do not wish ongoing life sustaining treatments.

While long-term quality of life and functional status after intensive care are clearly patient-centered outcomes, the symptoms of patients in the ICU and the experience of families are also important. Outcome measures to capture these important domains and research into these fields are ongoing. The critical care nursing field has taken an early leadership role in this research. As the focus of weaning from mechanical ventilation shifts from optimizing exercise while weaning to optimizing comfort while evaluating for readiness, the patient's experience on mechanical ventilation takes on a central, and poorly understood, role [35]. Investigators face considerable barriers in studying patients' experiences in the ICU. Endotracheal tubes, delirium, and medication often preclude communication. Many patients have poor recollection of their ICU experiences and most studies of patients' symptoms rely on clinician assessment of level of sedation and discomfort.

Competing Mortality

Whenever an outcome other than mortality is studied, investigators must consider the potential that the outcome is not observed because patients die before developing the outcome. For example, duration of mechanical ventilation may be shorter in a treatment group because the patients have a higher mortality rate and shorter survival than controls rather than any effect from the treatment on the course of mechanical ventilation. This is a problem common to all clinical research and is not unique to critical care [36]. There are a number of solutions to the problem – none is perfect. One can ignore the problem and simply report the difference in the surrogate outcome. This is acceptable if the treatment is known not to affect mortality or if the mortality rate is negligible in both groups. One can compare the outcome in survivors and non-survivors separately but the results of this analysis can be misleading [37]. One can combine the mortality and non-mortality outcome(s) into a single outcome, for example, 'cardiac death, non-lethal myocardial infarction, or hospitalization due to progression of heart failure' is a common outcome in heart failure studies. Another solution is to weight survival by the non-mortality outcome into a single measure of mortality and morbidity [38]. A number of different outcomes use this option including: quality adjusted life year, relapse free survival, symptom-free days, and disability free survival. The 'ventilator-free day' and 'organ failure-free day' outcomes proposed for critical illness studies are versions of these weighted outcomes. These scores assign an

arbitrary weight of 1 to a day alive without organ failure and a weight of zero for days when the patient is dead, has the organ failure, or is alive with the organ failure beyond a window date. Finally, there are a number of statistical procedures for sequentially testing the mortality outcome first for evidence of harm followed by a test of the non-fatal outcome for effect [39]. Relatively little theoretic or simulation testing has been performed to explore the implications of competing mortality in surrogate outcome analysis or to identify the optimal solution in studies of critical illness. For example, there have been no empiric studies of the limitations, statistical power, or interpretation of the 'free-day' outcome in studies of critical illness.

Conclusion

Studies of surrogate outcomes have repeatedly provided misleading information about patient-centered treatment effects in many areas of clinical investigation. The appeal of surrogate outcomes, particularly in a physiologically oriented field like critical care, is understandable. Designing studies to address patient-centered outcomes requires larger, longer, and more expensive clinical trials than surrogate outcome studies. Nevertheless, ample evidence exists to make clinicians pause before adopting a therapy based on improvements in surrogate outcomes.

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