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### **The Importance of Protocol-Directed Patient Management for Research on Lung-Protective Ventilation**

**ALAN H. MORRIS**

Pulmonary and Critical Care Divisions, Department of Medicine,  
LDS Hospital and University of Utah School of Medicine  
Salt Lake City, Utah, U.S.A.

#### **I. Introduction**

Nothing in this chapter should be interpreted as a condemnation of clinicians or clinical practice. I have unlimited respect for clinicians who I believe do a remarkably good job under trying circumstances. My focus in the following comments is on methods that could enhance the performance of clinicians and clinical investigators.

Unnecessary variation in clinical practice was formally brought to the health care community's attention in the 1970s (1). Unnecessary variation in clinical care appears to be an unavoidable feature of modern medicine (1-3) and has likely played a role in our failure to resolve multiple important problems in critical care. Many clinicians think variability is desirable because of the importance of individualizing treatment to a patient's specific needs. While this is an intuitively attractive argument, it incorporates two assumptions.

First, we assume that clinicians can effectively tailor treatment, particularly when reliable evidence for preferable therapies is absent, and that the resultant nonuniformity of treatment decisions is desirable at a

community-wide scale. Clinicians can, of course, tailor treatment to individual patients successfully. However, they can also fail to deal correctly with the individualized needs of patients and can thereby cause harm (4–18). Clinicians' decision-making is limited (9,18,19) and clinicians cannot easily predict who will respond to a specific intervention (14,15). For many, if not most, medical interventions, the medical community and the community of patients can only draw conclusions about the balance between potential good and potential harm through examination of the results of systematic investigations.

Second, we assume that nonuniformity is itself desirable because it fosters insight and innovation. It is true that many advances in medicine have been introduced through observations by bright and clever clinicians. However, the many questions addressed in modern medicine frequently involve small improvements (odds ratios of 3 or less) that will escape the attention of most observers if not examined within systematic studies (20). This evokes the success of those who recognized the importance of standardization of processes in nonmedical domains as a means of stabilizing systems so that small improvements could be observed when the system was changed (21–25). Medical workers in the clinical process improvement movement have adopted this approach successfully (10,26–29). Some opponents might argue that standardization is fine in cases where we have compelling evidence to standardize (lung-protective ventilation, insulin, sedation). However, studies indicate that clinicians do not adopt such compelling evidence quickly or uniformly (30,31). Opponents might also argue about clinical domains in which we do not have compelling evidence, such as intravenous (IV) fluid management in patients with acute lung injury. Is standardization of clinician decisions under such clinical uncertainty a good idea? The health care quality improvement success with stabilization of process through standardization of decisions indicates that the response to this question should be "yes." Without standardization, our chances of detecting promising elements of clinical management are reduced and frequently low.

In general, variability is fostered by incorrect perceptions (32–35) and is associated with unwanted and widespread error (6,7,11,36–40). The mismatch between human decision-making ability (9,18,19) and the excess information clinicians routinely encounter probably contributes to both the variability of performance and to the high error rate of clinical decision-makers (41–52). The recent U.S. Institute of Medicine (National Academy of Science) publications have brought to wide notice the long known importance of medical error and its deleterious impact on patient outcome (6,7). Guidelines and protocols can reduce variation and increase compliance with evidence-based interventions, can effectively support clinical decision-making (53), and can influence clinician performance and patient outcome favorably (54–59). They likely reduce error (60), but this has not been formally studied. Simple protocols such as physician reminders for

a serum potassium measurement when a diuretic is prescribed are commonly employed (61). Similar protocols for serum potassium evaluation can be stratified for renal function level and have an intuitive appeal to clinicians, in part because of their simplicity. More complex protocols have the same potential to aid clinicians and reduce error, but they are more difficult to comprehend and can appear abstruse and intimidating. Such complex protocols are discussed below and include those for mechanical ventilation, IV fluid and hemodynamic support, and blood glucose control with insulin.

Justifiable clinical interventions must produce more good than harm. This requires evidence of efficacy, effectiveness, and safety. Evidence-based medicine is an outgrowth of efforts to meet these requirements. Unfortunately, much of clinical care does not meet this evidence-based standard (5). This includes intensive care unit (ICU) delivery of mechanical ventilation and IV fluid therapy, both of which are characterized by large variations (62–64). The history of medicine is littered with therapies once widely disseminated and enthusiastically embraced by experts, only to be abandoned when subjected to systematic evaluation and demonstrated to be harmful (65). The Cardiac Arrhythmia Suppression Trial (CAST) and the Ischemic Optic Neuropathy Decompression Trial provide examples of commonly delivered therapies that proved to be harmful or useless after systematic evaluation (66–69).

Medicine, like social science, likely enjoys an “ecology of science . . . in which there are available many more wrong responses than correct ones . . .” (70). In complex clinical circumstances, clinician decision-making when unsupported by outcome data is likely to be both variable and incorrect. Because patients are nonlinear complex biologic systems (71–73), one frequently cannot easily anticipate the changes that might occur following a decision. Furthermore, the number of combinations of the complex variables involved is staggering (71).

Human error and injury are inevitable (44,52,74,75). Clinical error rates vary from about 1% to 50% (5,6,44,45,47–52,76–93). This is due in part to the inaccuracy with which even well trained and highly skilled physicians perceive physiologic data while making clinical decisions (94). The use of ill-defined terms or statements, such as “. . . caution should be exercised when pulmonary artery balloon occlusion pressure (PAOP) becomes increased to the extent that pulmonary edema is a risk” (95,96) must contribute to this inaccuracy. Patients can be harmed when clinicians do not comply with standard practice (6,7,97–99). Errors are common (6,74). Errors with antibiotic administration (100,101) include prescribing the wrong drug or wrong dose (102), failing to correct the dose for renal failure, failing to comply with ICU admission policies, and failing to use recommended deep venous thrombosis (DVT) prophylaxis. Sites of error documentation include hospital wards (103), surgical units (92), and critical care units (44,45,48,49,51,93). Critical care errors include failure to use

recommended tidal volumes for mechanical ventilation of acute respiratory distress syndrome (ARDS) patients (30,31). Even when error rates in a carefully managed academic ICU were only 1%, every patient was subjected to an error that constituted a major threat to life or limb every other day (93). Persons in this ICU performing correctly 99% of the time cannot improve much with education programs. Much more improvement in performance can be realized through systems approaches (21–23,25,74). The reduction in quality and safety of care associated with clinical error is a major concern for the health care community (6,7). Evidence-based therapy protocols are decision-support tools that likely can reduce clinical error (60).

If clinicians wish to pursue the best evidence, accurate literature search techniques for systematic reviews (evidence-based information) are available (104). However, compliance of physicians with evidence-based treatments or guidelines is low across a broad range of health care topics (101,105–109) and persists even when guidelines based on reputable evidence are available (54,110). Many factors, including cultural issues and health beliefs influence compliance (111,112). Widespread distribution of evidence-based guidelines (113,114) and education programs (115–119) have had only limited impact on this low compliance. On a more positive note, both paper-based and computerized decision-support tools that provide explicit, point-of-care (point-of-decision-making) instructions to clinicians have overcome many of these problems and have achieved clinician compliance rates of 90% to 95% (35,58,120).

Our understanding of clinical management of ARDS has not kept pace with our understanding of the mechanisms of ventilator-associated lung injury. This is also true of the closely related problem of sepsis. Although occasional successes are highly touted (121), many promising therapeutic agents have failed to be established as therapeutic advances (122–127). Among these are cyclooxygenase inhibitors (corticosteroids and ibuprofen), a platelet-activating factor antagonist (BN 52021), an antioxidant (*N*-acetylcysteine), an opiate antagonist (naloxone), a bradykinin antagonist (CP-0127), a cyclic-guanosine monophosphate stimulant (inhaled NO), antiendotoxins (E5 and HA1A), anticytokines [interleukin-1 receptor antagonist and anti-tumor necrosis factor (TNF)], and extracorporeal gas exchange (low-frequency positive pressure ventilation-extracorporeal CO<sub>2</sub> removal). The absence of a clear benefit from this broad spectrum of tested interventions leads to a compelling question. Are these clinical problems insoluble, have the needed interventions not yet been tested, or is our clinical investigative strategy flawed? The significant reduction in mortality of ARDS patients between the 1970s (128,129) and recent years (120,130) suggests that these clinical problems are, at least in part, soluble and that effective interventions currently do exist. I develop the argument that our clinical investigative strategy is seriously flawed. I explore the reasons for the absence of compelling clinical outcome data

(131), and I propose a solution based on the use of bedside computerized protocols that aid clinical decision-makers (3). I use examples from other scientific domains because of the importance of interdisciplinary communication and collaboration in science (132) and to support the argument that clinical experimental requirements are not different from those in other scientific domains.

Currently conducted clinical trials, especially nonblinded trials, have serious limitations. This may explain in part why many critical care clinical trials have failed to produce evidence of clinical benefit in spite of large investments of resources (133). The disappointingly low quality of critical care clinical trials (124,127,134) could, in part, be due to the widespread use of suboptimal methods. Meta-analyses cannot overcome this low clinical trial quality because meta-analyses can only generate credible conclusions if the analyzed clinical trial results are credible (135,136). Meta-analyses focus on methodology at the trial design scale (e.g., were true randomization and effective blinding employed) but do not deal with the methodologic details of the patient–clinician encounter for either outpatient (137) or critical care (124,127,134) clinical trials. The medical community is thus challenged to develop new approaches to experimental clinical trials and to use them to produce more rigorous clinical experiments and results. Unfortunately, the medical community lacks the tools that might aid clinicians in making more consistent and appropriate decisions and thus produce more rigorous clinical trials. These deficiencies contribute to unnecessary variation in clinical care (7,60). They are barriers to both the consistent delivery of safe and high-quality clinical care and the conduct of rigorous clinical research at the holistic clinical trial scale (34). These deficiencies therefore limit clinical research on lung-protective ventilation and impede the implementation of changes requested by the National Institutes of Health (NIH) in its Roadmap program (138).

## **II. Experimental Scientific Principles**

### **A. Aim of Science**

The principal aim of all science is generally considered to be the ordering of the complex appearances detected by our senses or by instruments that extend our senses (139). Scientists explore the world around us to explain its behavior. Scientists extend their senses in this endeavor by using instruments that enable observers to detect otherwise hidden behaviors. Among these instruments one must include statistical analytic tools.

#### *Experimental Replicability*

New scientific advances that seem to correctly represent the behavior of the world eventually become incorporated in the body of knowledge of the

discipline and appear in reference works such as textbooks. The key requirement, here, is the phrase “correctly representing the behavior of the world.” It does not appear possible to ever know with absolute certainty that this requirement has been fulfilled (73,140) and many philosophers including Kant have explained and explored this impossibility. Nevertheless, the lack of absolute certainty does not prevent application of new knowledge and of the advances that follow therefrom (73,140). Rothman and Greenland have nicely summarized the philosophical contributions of many including Popper who has clarified some fundamental aspects of the scientific method (140). Human experimental (clinical trial) results are analogous to the probabilistic predictions of quantum mechanics. The Schrödinger wave function does not predict the exact position (outcome) of a particle but rather gives its location as a probability distribution that predicts the pattern of outcomes in repeated measurements [p. 198 in Ref. (141)].

Replicability of experimental results is the fundamental criterion by which general acceptance of new knowledge is gained in scientific circles (70, p. 196 in 141, 142–147). Scientists generally believe that an observation that accurately reflects the way the world behaves should be replicable by other investigators. Both in physical science (139,141) and in social science (70,148), two scientific domains that bracket the scale of clinical trials, the requirements for scientific rigor and for experimental replicability, are well accepted. Actual or potential replicability of results is a basic requirement of all rigorous scientific investigation, regardless of scale (70,139,148–154).

Replication of an experimental result requires, of course, a detailed knowledge of the experimental method. This is a major challenge for the holistic human experimentation in clinical trials for two reasons. First and foremost, most clinical trials are not conducted with adequately explicit methods (see Section “Adequately Explicit Methodology: Protocols vs. Guidelines”). Second, editorial policies severely restrict the methodologic detail in medical publications.

#### Ethical Considerations for Replicability

Some clinicians with strongly held opinions have raised ethical arguments against several features of clinical research. These include arguments for scientifically questionable “rescue therapy” in clinical trials, arguments against or resistance to randomization of subjects, or arguments against adherence to protocol rules. These arguments lack merit. Investigators have two responsibilities to their experimental subjects: Their first responsibility is to maximize the quality of clinical care delivered to the subjects. Their second important responsibility is to conduct credible clinical research. Reasonable people should not be expected to agree to participate as experimental subjects if the experiments are unlikely to lead to credible results. Investigators must seriously consider both of these responsibilities in the

resolution of perceived conflicts between the delivery of the best clinical care and the achievement of the most credible clinical trial result.

The complexity of ethical issues and the conflict between these two investigator responsibilities are brought into striking relief when treatments being evaluated in the intervention group of a randomized clinical trial are used as “rescue therapy” for deteriorating control group subjects (“rescue therapy” is a euphemism for “desperation therapy,” a more accurate but repellent appellation not likely to garner approval in the informed consent process). Such use of unproved treatments may violate study protocols. They may also be included within study protocols. In either case, “rescue therapy” use can destroy clinical trial result credibility. Administration of a study intervention (an unproved treatment) as “rescue therapy” requires the presumption that the intervention is efficacious before the results of the trial are known. This is logically difficult to defend. If the intervention is being evaluated because its effect is unknown, how can the intervention be offered as a benefit to a failing subject?

For example, a clinical trial of extracorporeal membrane oxygenation (ECMO) allowed the application of ECMO, the test intervention, as “rescue therapy” when control subjects seemed without hope of recovery and satisfied what were termed *de jure* death criteria (128). In the ECMO trial, conditions that defined “control failures” and allowed the use of ECMO as rescue therapy for control patients were  $\text{PaO}_2 < 45$  mmHg for more than 12 hours with  $\text{FiO}_2 = 1.0$  and with maximum tolerated positive end-expiratory pressure (PEEP), or  $\text{PaO}_2 < 35$  mmHg for more than six hours (128,129). Since then, it has become clear that such predictions are quite uncertain. Patients who met these criteria have survived in the control treatment arm of a more recent randomized controlled clinical trial of extracorporeal therapy (122). However, ECMO was a dangerous and unproved treatment with uncertain clinical effects. If ECMO were given as “rescue therapy” to a failing control patient, it would violate principles of sound experimental design by introducing a crossover effect (20,149). This violation of experimental design principles would risk the sacrificing of one of the investigator’s two obligations to the subject (the obligation to produce credible clinical trial results) for the other (the obligation to maximize the quality of clinical care). This sacrifice would be unquestioned and unassailable if it involved the administration of therapy known to be beneficial. However, it should be seriously questioned when it involves a potentially harmful intervention of unproved effect. Sacrifice of the credibility of the clinical trial results for a questionable and unproved anticipated benefit for the subject could be interpreted as exploitation of enrolled clinical trial subjects and therefore as a violation of the requirements of ethical research (146). This sacrifice appears to be too easily accepted by the clinical trial community, both by investigators delivering “rescue therapy” and by clinicians either providing clinical care in violation of protocol rules or

withdrawing subjects from clinical trials. In so doing, the clinical trial community risks exploiting subjects. It ultimately compromises the clinical care quality available to the health care community at large and thereby reduces societal benefit. Interestingly, this ethical implication of such questionable clinical care and clinical experimentation does not figure prominently in discussions of error, even though the reduction in quality and safety of care associated with clinical error is a major community concern (6,7).

#### Clinician Resistance to Adequately Explicit Methods

Some clinicians claim that anything short of total freedom to make clinical decisions threatens the traditional expert approach to making and individualizing clinical decisions. Two paradigms of clinical decision-making—the expert or authoritarian paradigm and the actuarial or numerical paradigm—have been the subjects of an historical debate in medicine (155,156). Medicine has, since ancient times, traditionally employed the expert or authoritarian paradigm of decision-making. This relies on expert clinical judgment. The “best decision” for the individual patient at a particular time in this paradigm is based upon the expert’s background, experience, and training (clinician expertise). This clinician expertise has been described as intuitive, and therefore difficult to articulate and describe. In addition, it is also likely not reproducible because the expert’s background and experience are always changing. Clinicians may challenge an adequately explicit decision-support tool such as a computerized protocol by asking how they can be assured the rules are “right.” This is, however, an inappropriate question. We generally do not know what is right in any absolute sense. We only know, when we have good evidence, what works better than other approaches. All that should be required of a decision-support tool to justify its use or evaluation is that it be both a reasonable strategy of response and that it be safe. Generating the rules of such a decision-support tool requires effort and it requires attention to disagreements between clinicians (35). First, the best evidence is extracted from the literature. Next, domain experts contribute rules for which no published data exist. Finally, a consensus among the clinicians, followed by an iterative refinement process leads to robust protocol (35).

Adequately explicit methods are those that elicit the same clinical decision from different clinicians when they are faced with the same clinical information (see Section “Experimental Group Equation”). In complex clinical environments such as those in critical care, adequately explicit methods require sufficiently detailed protocols that provide clinician decision support (34,131). The use of decision-support tools such as adequately explicit computerized protocols incorporates an actuarial paradigm, one based on numerical analysis and on outcome data (157). The tension between these two paradigms in the clinical community dates back to at least the early 19th century (34,158). Then, it involved important clinicians

and scientists, for example, Poisson and Pinel (155,156). However, these two approaches to clinical decision-making are complementary, rather than mutually exclusive.

Notably, the bedside clinician is always in control when adequately explicit methods are used in an open-loop servocontrol manner (159). The protocols in the Utah Clinical Trial Toolbox generate adequately explicit instructions (Table 1) and lead different clinicians to the same action. We employ open-loop servocontrol with clinicians always examining the computerized protocol instructions before they are carried out. This forces the clinician to examine the patient and to evaluate if the patient still belongs to the set of subjects for which the protocol rules were developed [an evaluation of external validity or generalizability (153,160)]. The clinician always has the opportunity to judge whether the patient has changed and no longer belongs to the group for which the protocol was intended. This external validity-directed clinician judgment is appropriate. However, the tendency to reject a validated protocol instruction because of a clinician's opinion (an opinion often not founded on evidence) is frequently inappropriate and can threaten the internal validity of clinical trials (160). This error is fostered by the well-recognized overconfidence of physicians in the correctness of their beliefs and opinions (32,33,161).

Computerization forces attention to detail at a level not humanly possible with paper-based protocol development alone (34,35). Consequently, the depth of understanding of clinician decision-making is strikingly increased among the developers. The current Utah Clinical Trial Toolbox electronic tools include bedside screens for manual clinician data entry or for automatic data capture from electronic medical records (EMRs) (see section "Current Utah Clinical Trial Toolbox Electronic Tools"). The use of computerized protocols to standardize clinical decision-making in complex clinical settings has a sound ethical foundation (see above) (162,163).

There seems to be a widespread reluctance to accept rules for standardizing clinician decisions. (Many of us may be willing to acknowledge that explicit methods may produce better outcomes for "less expert" physicians,

**Table 1** One Iteration (Protocol Run) of Computerized Protocol Instructions for Mechanical Ventilation

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*Arterial oxygenation instructions*

Reduce inspired O<sub>2</sub> by 10% from 90% to 80%

Reassess oxygenation in 15 min

*Ventilation and arterial pH instructions*

Maintain tidal volume at 540 mL

Increase ventilatory rate by three breaths from 22 to 25 per minute

Sample arterial blood in 15 min at 15:40 hrs

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but not for ourselves.) Some authorities conclude that control with computerized protocols will not be widely distributable (160). Their association of detailed protocols with “complexity and rigidity” is a common expression of resistance to use of adequately explicit methods (160). It suggests acceptance of the expert paradigm as the ultimate reference for proper medical response (155,156). More importantly, it suggests an association of decision-support tools with “cookbook” (patient invariant) care. This is in fact an error, as described below (see section “Individualized, Patient-Specific Instructions”).

The reluctance of clinicians to accept rules (decision-support) for standardizing clinician decisions is an interesting challenge to a larger view in science that regards reductions of the possible number of system states to be the foundation of stability in natural systems. Both at the quantum level of atomic behavior [pp. 198–199 in Ref. (141)] and at the system statistical process control level (21–25), restriction of the innumerable possible states by application of rules results in stabilization of the system. Quantum restrictions provide the foundation for atomic and molecular stability and thus are fundamental to the generations of biologically important molecules [pp. 198–199 in Ref. (141)]. It seems ironic that, given the repeated criticism of unnecessary clinical variation (1,2) and its harmful consequences in medicine (6), many clinicians continue to defend the ultimate decision-making freedom (and reject efforts to standardize decisions) that contributes to this variation. Clinicians may forget to do intended actions and may make different decisions when faced with identical problems. Clinicians frequently seem to believe that the complexity of clinical problems cannot be captured by man-made sets of rules. This has an intuitive appeal, because clinicians understand how overwhelming clinical information can be. However, complex outcomes can be produced by simple rules. This appears to be the case in nature, when viewed from a cosmologist’s perspective [pp. 235–236 in Ref. (141)]. A similar relationship between complex and patient-specific treatment strategies and an underlying simple set of protocol rules has been observed for adequately explicit computerized critical care protocols (34,35,60,131,164,165). This reluctance to embrace adequately explicit methods is made more puzzling by the evidence of favorable benefit following their use.

#### Impact of Protocols

The impact of protocols including computer-based clinical decision-support systems on cost and efficacy appears to be favorable (56,57,166). Standardization of aspects of the clinical encounter appears to avoid vexing problems in many areas of clinical medicine (167,168). Computerized protocols have favorably impacted hospital pharmacy and infectious disease departments (100,101,169–171). Both outpatient and inpatient computerized

protocol use has favorable consequences (43,77,100,157,172–182). Computerized protocols for mechanical ventilation have controlled the intensity of care of patients with ARDS in both treatment arms of a randomized clinical trial (122). Three benefits follow the use of such specific computerized protocols: (i) precise description of the method (process) of patient care (the rules and logic for clinical decision making); (ii) assurance of equal intensity of care (experimental group equation or equivalence); and (iii) common intermediate (surrogate) end points (e.g., therapy regulated to produce the same PaO<sub>2</sub> and pHa). Because management of mechanical ventilation in severe ARDS is perceived as a complicated and intellectually demanding process, it is likely that many other facets of critical care can be successfully addressed with computerized protocols.

Patients with ARDS supported with computerized protocols experienced a higher survival than expected from historical control data (122). The impact of computerized protocols on patient outcome is favorable, when compared to the outcome of patients with ARDS treated without protocols (58). Limited data support a causal association between a computerized protocol and more favorable patient outcome, when compared with a paper-based protocol using the same decision-support rules for mechanical ventilation weaning (183). Other randomized clinical trials, using less detailed and manually applied paper-based protocols, have demonstrated clearly that protocol-guided care favorably affects the outcome of patients with thromboembolic disease (184–186).

### **B. Conceptual Paradigms**

Clinicians and clinical investigators think about problems in ways that depend on their perceptions of experiences and conceptual frames of reference. On an individual scale, these perceptions set the bounds for thinking and for posing questions. These perceptions are influenced by prevailing conceptual paradigms. Thomas Kuhn has argued that paradigms are a prerequisite for any science. He proposed that science is impossible in the absence of such paradigms (187). New paradigms introduce rapid changes in human intellectual behavior. This is analogous to both punctuated equilibrium in evolutionary biology contemplated by paleobiologists (188) and to changes in the basic forces of nature contemplated by cosmologists [p. 264 in Ref. (141)].

One of the most profound conceptual (paradigm) changes occurred as the middle ages were ending. Western societies adopted the numerical scheme introduced by Hindu mathematicians in India and brought to Europe through Spain by Arabic mathematicians. This decimal system that incorporated both the zero cipher and the concept of nullity has been described as "...one of the greatest discoveries that humanity has ever made (141)." It enabled major advances in thinking, calculation, and

recording. This, interestingly, is claimed to have led to separation of theological and scientific scholarship and to have opened the door to careful observation and experimentation (141). These advances fostered unparalleled developments in science and engineering with incalculable consequences on worldwide civilization.

On a professional community-wide scale, medical paradigms influence medical thinking, medical questions, and medical investigations. Galen's patently groundless view of the body held sway for 1400 years before William Harvey revolutionized medical thinking when he published "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus" in 1628. Several anatomists had for two centuries failed to find the interventricular septal communications demanded by Galen's theory. The Galenic view dominated so long, not because it was intellectually compelling, but, some argue, because there were no alternative conceptual paradigms available for organizing information about the world (189). Sir Isaac Newton, following in Sir Francis Bacon's footsteps, advanced a reductionist conceptual paradigm of science (71,190). This paradigm proposed that the behavior of complex systems could be constructed and fully understood from an understanding of the behavior of its component parts. This reductionist paradigm was fostered by Cartesian dualism (190). More recently, science has embraced a different and contrasting conceptual paradigm of "emergent properties" (71,72,189-200). In this recent conceptual paradigm, new properties emerge as parts or subsystems aggregate to form more complex systems. Consequently, laws or regularities that emerge at a higher scale cannot be expected to appear at lower scales. For example, the behavior of large and complex aggregates of elementary particles such as electrons cannot be understood in terms of simple extrapolation of the properties of a few particles. At each scale of complexity, entirely new properties appear [Philip Anderson, quoted in Ref. (192)]. Common sense supports this notion if one thinks of the behavior of a classroom of five year olds, or of a group of teenagers.

The emergence, with increasing scale, of new properties important to medicine is common (192,193,199,200). Medically pertinent examples abound. The behavior of two bacterial species in a bacterial biofilm cannot be predicted from an understanding of each of the bacteria independent of the other (195). Cardiac or circulatory function cannot be understood in terms of the heart and blood vessels alone (193). Adaptive biochemical responses of the heart to stress are usually interpreted to be favorable at the physiologic scale. However, when chronic they lead, at the medical scale, to dysregulation of cardiac intracellular molecules and ultimately to congestive heart failure (194). Other examples are discussed below (see section "Clinical Care Examples of the Importance of Scaling"). Interestingly, the emergence of new properties at higher scales of organization occurs even though common functional states and tasks can be identified

at different scales of organization (72). These two important concepts related to scale (emergent properties and common functional states or tasks) should not be confounded.

### C. Scale of Investigation

The scales of scientific inquiry vary from greater than  $10^{+20}$  m, the scales of astronomical studies, to less than  $10^{-20}$  m, the scales of atomic and subatomic particle studies [p. 241 in Ref. (141)]. This large range of scales of inquiry requires many different instruments, techniques, laboratories, and conceptual paradigms that must be matched to the scale of the item under study. Studies cannot be readily conducted with instruments that are matched to a different scale. One would not use a telescope to study bacteria, or an IR spectrophotometer to study gamma ray bursts. Mandelbrot illustrates this issue with a series of provocative answers to the question “what is the length of the coastline of Great Britain?” The answers form a set of responses, each of which is correct for the scale at which it was generated—but incorrect for other scales of inquiry (201). Penrose and Penrose, two eminent psychologists, discuss an interesting reflection of scaling in the “Waterfall” of the graphical artist Maurits Escher (202). Similar scale-specific answers are encountered in medical research (see section “Clinical Care Examples of the Importance of Scaling”).

The medical scales of inquiry (34), like those of the physical sciences (201), vary. They range from the reductionist focus on the behavior of the parts of a system to the holistic focus on the integrated behavior of the intact system. The parts of the patient system include biochemical, cellular, organ, and physiologic elements. For many medical questions, the intact system consists of the patient within the clinical environment, with all of the interactions and foibles that occur during the patient–clinician encounter (203–205). For medical decision-making, the concept of the scale of inquiry is important both to clinician decision-makers and to clinical researchers.

#### *Clinical Care Examples of the Importance of Scaling*

Three clinical examples illustrate the medical importance of the scale of inquiry: the use of vitamin C for the treatment and prevention of scurvy, the use of sodium channel–blocking agents for the prevention of sudden death following myocardial infarction, and a genetic deficiency of elastin (206).

#### Scurvy

The absence of a crucial enzyme (L-glucuronolactone oxidase) in humans (the result, apparently, of a genetic accident), which leads to an inability of cells to produce L-ascorbic acid, provides the foundation for scurvy. A deficiency of L-ascorbic acid leads to decreased peptidyl hydroxylation of procollagen. This leads to a failure to produce the normal triple collagen

helix. The deficiency of normal triple collagen helix leads to abnormal connective tissue. The abnormal connective tissue leads to clinical manifestations, including death.

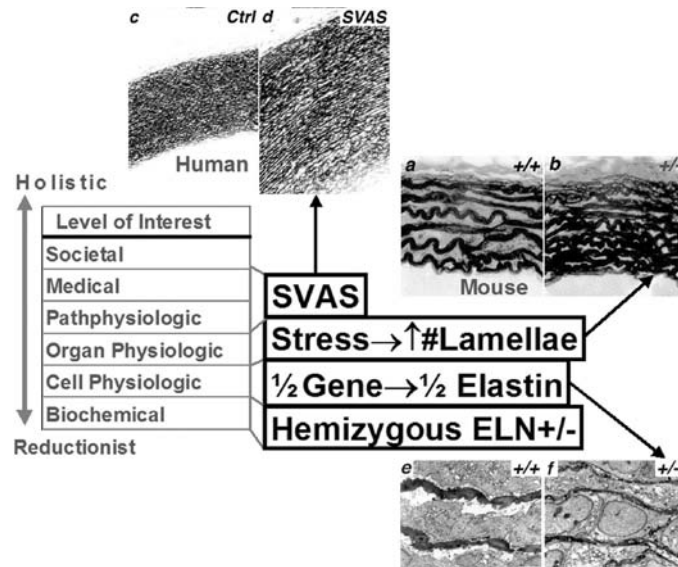
This fascinating story was delineated centuries after the cardinal clinical observation and the crucial medical intervention had been made. In the 18th century, long before any of the interesting reductionist information about enzymes or cell biology was available, Dr. James Lind, a Royal Navy surgeon, performed the first clinical trial of which I am aware (207). It was a cohort-controlled study of multiple agents including citrus fruit ingestion aboard ship, with only two subjects in each group (149). The signal-to-noise (S/N) ratio was so high, however, that the results were definitive even though the number of patients was small.

#### Sudden Death Following Myocardial Infarction

For decades, agents that suppress premature ventricular contractions (PVCs) in patients following myocardial infarction were commonly prescribed based on pathophysiologic and other reductionist research evidence (66,67). The rationale behind this therapy was well founded on electrophysiologic and cardiac physiologic data from animals and from humans. It was expected that suppression of PVCs would lead to increased survival, through interruption of the sequence: PVCs → ventricular tachycardia → ventricular fibrillation → sudden death. Subsequently, the results of the CAST, a large multicenter clinical trial, revealed that the agents—encainide, flecainide, and moricizine—effectively suppressed PVCs following myocardial infarction. They were, therefore, effective at the pathophysiologic scale. However, the death rate in the treatment group exceeded the death rate in the control group. The disparity between the results at the pathophysiologic scale (effective suppression of PVCs) and those at the holistic medical scale (reduced patient survival) is a sobering example of emergent properties of complex systems. This excess death rate following therapy that is effective at the pathophysiologic scale is a striking reminder of the need for holistic clinical outcome data from rigorously conducted clinical studies.

#### Elastin Deficiency and Supravalvular Aortic Stenosis

Some animals and some humans are hemizygous for the elastin gene. This genetic deficiency information was obtained from research at the reductionist biochemical scale (Fig. 1) (206). This genetic deficiency leads to the anticipated reduction in elastin production at the cell physiology scale, with reduced elastin in each of the elastin lamellae of the aorta. However, this knowledge obtained at the biochemical and cell physiology scales does not permit one to anticipate the emergent property that appears at the organ physiology scale. The pulsatile stress sustained by the aorta in the intact organism leads to an emergent property, the unexpected production of an increased number of elastin lamellae, each one of which contains less



**Figure 1** Animals and humans can be hemizygous for the elastin gene. This condition provides a good example of the importance of scale of inquiry (level of interest). At the reductionist scale, the chemical knowledge of the presence of only half of the elastin gene complement allows accurate prediction of the production of elastin (half of that predicted for each elastin lamellum) at the cell physiology level. However, this reductionist-scale knowledge does not allow predictions of the emergent properties that appear at higher scales. At the organ physiology scale, an unexpected increase in elastin lamellae number is encountered. At the medical scale, an unexpected problem emerges: supravulvar aortic stenosis (SVAS) due to the thickened aortic wall that results from the increased number of elastin lamellae. *Source:* Modified from Ref. 198.

elastin than normal. More importantly for clinical decision-makers at the medical scale, the foreknowledge of biochemical and cell physiological information does not lead to anticipation of an emergent medical disease, supravulvar aortic stenosis, that results from increased aortic wall thickness due to the increased number of elastin lamellae (206).

#### Human Experimental Outcomes

Human experiments (clinical trials) provide many choices of outcome variables. Ultimately, patients, subjects, clinicians, and clinical investigators are most interested in the outcomes that should drive clinical decision making, such as survival, quality of life, and related variables. These are reasonably termed “ultimate outcomes.” For monitoring and experimental purposes, clinicians and investigators measure many other variables that reflect

intermediate physiologic states that precede, and may be linked mechanistically to, the ultimate outcome. These variables include body temperature, white blood cell count, serum sodium level, blood pressure, cardiac output, minute ventilation, urine output, creatinine clearance, sleep character, electrocardiographic variables, and many others. These are reasonably termed “intermediate outcomes” (also called physiologic variables, and surrogate outcomes). The different experimental outcomes that can be assessed belong to different scales (or subscales) within the medical scale of inquiry. The precise definition of outcome of interest is a crucial step in identifying the kinds of data required and the necessary tools that must be incorporated in study design at the medical scale.

#### Surrogate Outcomes

The settings appropriate for cell or organ physiology studies provide results that are frequently not directly applicable to clinical decision-making. The experimental results required for clinician decision-making in complex settings are best provided by rigorous studies at the holistic medical scale (34). Surrogate end points (intermediate outcomes) are variables that reflect outcomes at a reductionist scale, rather than at the holistic medical scale at which ultimate outcomes like survival and quality of life are sought. Surrogate end points may not reflect the ultimate outcomes and therefore can mislead clinicians and investigators (208,209).

High mechanical ventilator pressure applications to experimental subjects with acute lung injury have been evaluated with surrogate outcomes. Kirby et al. proposed that the care of patients with ARDS had become an easy exercise with the application of high PEEP (super PEEP, PEEP up to 50 cmH<sub>2</sub>O) (210). Lachmann and colleagues proposed “opening” the damaged lungs of ARDS patients, with a lung recruitment technique that was not, to my knowledge, ever adequately explicit (211–213). Both of these approaches focused on physiologic considerations and surrogate outcomes, principally levels of arterial oxygenation. They were subjected to a systematic evaluation at the scale of the intact patient in the clinical environment, using ultimate clinical outcomes (see below). Subsequent clinical trials, using different experimental strategies, failed to reveal benefit (120,130,214) from these approaches although they seemed appealing when physiologic scale (surrogate) outcomes were used.

#### *Reductionist Animal vs. Holistic Human Experiments*

I believe it informative to contrast the imperatives of reductionist animal experiments with those of human experiments. The arguments apply equally well to other reductionist research (e.g., organ physiologic, cell biologic, biochemical, genetic, etc.). I think it helpful to distinguish between those experimental attributes that focus on the experimental subjects from

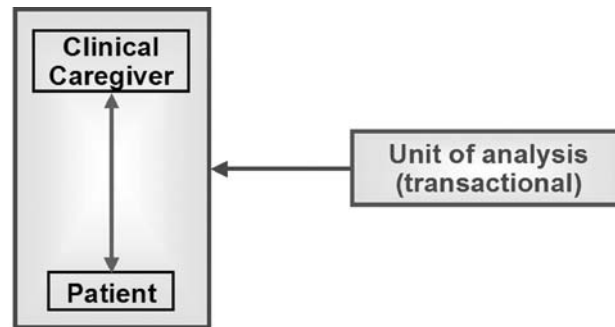
those that focus on the experimental design. Both animals and humans are sentient beings that require attention to and reduction of both pain and suffering during experimentation. However, self-determination is an attribute only assigned to humans. Therefore humans cannot, because of the ethical principle of autonomy (also called respect for persons), be asked to sacrifice their well-being for the good of others (other humans—also called the greater good). Animals, in contrast, are routinely forced to sacrifice their well being for the good of others.

The primary outcome focus for animal experiments is usually an intermediate outcome variable, because the goals of animal experiments usually are directed at uncovering mechanisms of injury or disease. In contrast, the primary outcome focus for holistic human experiments is usually an ultimate outcome. For human experiments, intermediate outcomes are usually secondary and frequently used to identify surrogate outcome variables that might substitute for ultimate outcomes, or to identify potential mechanisms compatible with the experimental results.

The level of experimental control for both investigator behavior and for experimental subjects is high in reductionist animal experiments, but low in holistic human experiments. Human subjects are usually more variable than animal subjects. Animals may be chosen with similar genetic background, identical age and comorbidities, and identical injuries. This conjunction of conditions is not possible in holistic human experiments. Consequently, the standardization both of interventions and of investigator decisions that characterize reductionist animal experiments cannot be expected in holistic human experiments. Clinical investigators and clinicians must tailor their decisions to the individual human subject's needs (identified by the subject's expressions of illness). Both the intervention and the cointerventions that the human subject receives are therefore difficult to standardize. Only the clinician decisions (responses to the subject's specific expressions of the disease) can be standardized.

#### *Transactional Unit of Analysis*

The appropriate unit of analysis in clinical experiments (clinical trials) is neither the patient nor the clinician (or the clinical environment). It is, rather, the combination of patient and clinician (or clinical environment). Environmental psychologists (203,204) identify the interacting patient and clinical environment, together, as a "transactional unit" (Fig. 2). For example, it is meaningless to inquire about the outcome of an infant born with cystic fibrosis, or of an adult with human immunodeficiency viral infection, without identifying their location. Both of these diseases will have different natural histories for patients in San Francisco and patients in rural sub-Saharan Africa. The same need to identify the clinical environment is present in ICU patient encounters. It makes little sense to ask about the



e.g.: 1- Response to PEEP (Patient + caregiver fluid therapy)  
2- Cystic fibrosis (GI, then pulmonary disease)

**Figure 2** The patient and the clinical caregiver (clinical environment) form a transactional unit that determines clinical outcomes. The patient expresses the disease or clinical problem with unique expressions and values of various quantified measurements. The clinical caregiver responds to these unique expressions. The iterative interaction of the patient and the clinical caregiver ultimately produce an outcome that can be examined by investigators. For example, the response of patients to PEEP is determined in part by the fluid administration chosen by the caregiver. One cannot define PEEP responsiveness unless the clinical setting and its therapies are identified. Likewise, one cannot describe the natural history of cystic fibrosis without identifying the clinical setting. In a rural area of a poor country, cystic fibrosis is a lethal gastrointestinal (GI) disease of infants. In a wealthy country with modern medicine, it is a pulmonary disorder of children and adults. *Abbreviation:* PEEP, positive end-expiratory pressure.

natural history of a patient with sepsis or acute lung injury without inquiring about the clinical response provided to patients with these conditions. The patient and the ICU clinicians, interacting iteratively and reciprocally, constitute the unit of analysis for which clinical outcome measures become meaningful. Therefore critical care researchers must be sensitive to the clinical care environment and the therapy it delivers when considering a patient or a group of patients with a critical care problem. Both the treatments and the decision-making of clinicians delivering these treatments to subjects are important elements in a rigorous critical care experiment.

Interestingly, this transactional unit concept is reminiscent of interactive systems at multiple scales. At the subatomic level, the Heisenberg uncertainty principle leads physicists to include the observer (and associated instrumentation) as part of the system, along with the particle being observed [p. 209 in Ref. (141)]. In philosophical discourse, the Hegelian dialectic is an accepted conceptual model. In biology, the new field of epigenetics formally acknowledges the interaction of the genome with its

environment, both local and macroscopic, as interactive determinants of phenotypic expression (215–219). The interaction of genotype and environment is also well illustrated by studies in microgravity. The accumulation of phosphate ions at the osteoblast surface under simulated microgravity conditions is higher by as much as a factor of three. This may explain the increased sensitivity of osteoblasts to apoptogens and provide a partial explanation for bone loss in the absence of gravity (220,221). The importance of gravity can only be explored, of course, when technological advances allow its elimination. The gastrointestinal tract is also influenced unfavorably by microgravity (222).

An interesting extension of the transactional unit concept might include experimental design and data collection as important components, much like the instrumentation used to “observe” subatomic phenomena. Then more than the patient, clinician and clinical environment need to be considered. Perhaps the experimental environment itself contributes to the outcomes and may lead to divergent results in seemingly similar clinical environments. This is one form of argument that might be raised against efficacy research and in favor of effectiveness research (160). However, in general, effectiveness research should only be conducted after the efficacy of the intervention has been established (see section “Efficacy vs. Effectiveness Clinical Trials”) (140,160).

#### *Multinational Critical Care Experimentation*

The requirement for hundreds of patients in many clinical trials of critical care issues frequently necessitates multicenter trials lasting several years. The multiple-year duration of many clinical trials introduces two serious limiting logistic problems: (i) unavoidable “secular” changes (changing cointerventions that occur as a result of the passage of time); and (ii) faltering enthusiasm and interest among participating clinicians (MD, RN, RRT, etc.). The use of bedside (point-of-care) computerized protocols to standardize clinician decision-making between institutions makes possible the conduct of clinical trials with explicit methodology in large numbers of institutions. The acquisition of the required number of patients could then be realized in a short period of time, perhaps a few months. For example, a consortium of 1000 hospitals configured to conduct clinical studies with computerized protocol standardization of clinical decision-making could likely enroll 8000 ARDS patients within six months. Other clinical trial tasks, in addition to bedside decision-support with computerized protocols, would also require electronic tool support and are discussed below (see section “Scalable Electronic Tools”).

Critical care medicine needs a robust experimental clinical outcomes laboratory in which to conduct rigorous human experiments (clinical trials). This laboratory must produce results that can be replicated. An adequately

explicit method is required for replication of results (34). Actual or potential replicability of results is a basic requirement of all scientific investigation (70,139,148–154). Standardization of clinician decision-making with computerized protocols can be a key to the development of the required adequately explicit clinical methodology. Cointerventions (see section “Confounders and Cointerventions”) in nonblinded randomized clinical trials are not well managed by randomization. Rather, adequately explicit protocols are the important tools for minimizing cointervention-induced differential bias in critical care randomized clinical trials. This is analogous to the use of protocols to minimize information bias in observational epidemiological studies [p. 279 in Ref. (223)].

Widespread efforts to introduce separate, institution-specific guideline or protocol decision support are under way in many institutions. While this may further standardization within each institution, the development of separate and institution-specific decision-support tools will have little impact on the interinstitutional variation in health care delivery. The potential of computerized protocols to effectively address the problems of secular trends and faltering enthusiasm of participating clinicians, through the conduct of large multicenter (including multinational) trials, will not be realized by such institution-specific protocols. The benefits of standardized explicit methodology in clinical trials and the experimental rigor that they will convey on clinical trials will only be realized by the standardization of clinician decision-making between large numbers of institutions. The development of separate, institution-specific, decision support tools is, in this regard, counterproductive and will merely formalize much of the unnecessary variation in medicine (1,2). While large simple trials can be done with paper-based tools (224) and large simple critical care trial in subjects with sepsis has been successfully executed (121), paper-based tools do not seem attractive. Critical care clinical trials will be improved if we can enroll large numbers of subjects quickly by engaging large numbers of hospitals, by employing the same adequately explicit method in all participating sites, and by acquiring a comprehensive set of data for each subject. Electronic tools should enable such clinical trials.

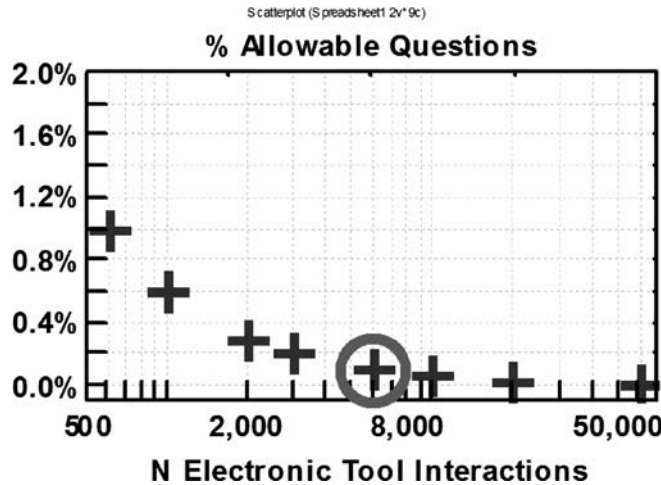
#### Large-Scale Critical Care Clinical Trials

*Scalable Electronic Tools.* Operational electronic tools are scalable and can catalyze the formation of a large-scale human clinical trial laboratory, linked through the Internet. This could support clinical trials with adequately explicit methodology and enable completion in months rather than years. Obstacles have been identified (35,225,226) but these have been overcome in the research clinical trial setting (58). The large enrolled subject number could allow multiple experimental groups and could produce dose–response curves (see section “Limitations of the Two-Experimental-Group Design”).

*Human Technical Support.* However, the human technical support staff are, in contrast to the electronic tools themselves, not scalable. The number of staff is limited and therefore they have a limited time to field questions from users. Each question or consultation is likely to take about half-an-hour of support staff time, because it is frequently necessary to acquire information about experimental subjects and clinical conditions to provide useful responses to queries. For example, consider the situation in which support staff could field six questions each day because they have only a fixed time of three hours available for consultation. If the support staff are limited to six questions daily, the fraction of electronic tool interactions that are unclear to clinicians and that generate clinician questions that require support must decrease hyperbolically as the number of clinical trial sites increase. According to Figure 3:

$$\% \text{ unclear interactions} = \left[ \frac{\text{six questions}}{\text{number of electronic tool interactions}} \right] \times 100\%$$

In a large-scale multicenter human laboratory, fewer than 500 enrolled patients could easily lead to 6000 protocol or other electronic tool interactions per day. If only 0.1% of these 6000 electronic tool interactions/day generated questions, the limit of six questions/day would be reached (Fig. 3). These considerations do not include the challenge of study start-up. Start-up should be



**Figure 3** Hyperbolic relationship between the percentage of electronic tool interactions that generate user questions that require support. Data are expressed as a function of the total daily number of electronic tool interactions for a human support team with three available hours daily to respond to questions.

expedited as well by carefully crafted electronic tools including tutorials and decision-support tools with embedded context-sensitive help.

In addition, local clinical coordinators and the clinical coordinating center (data monitoring center) coordinators are not scalable. If we are to conduct large-scale clinical trials efficiently and without excessive cost, current levels of coordinator staff must be able to conduct large-scale trials. Tools that assist local and clinical coordinating center coordinators and web-based tools that expedite communication and allow “virtual site visits” by the clinical coordinating center coordinators are part of the effort my colleagues and I have engaged in during the past five years (see section “Computerized Protocol Experience”).

*Clarity of Electronic Tools for the User.* As the scale of the human laboratory increases, the clarity with which the protocols or other electronic tools communicate with clinician users must increase. The human computer interface must be clear and the messages displayed by the computerized tool must be unambiguous. If more than 0.1% of 6000 electronic tool interactions generated questions, they would overload the clinical trial support staff. With appropriate clarity of the electronic tools, their scalability could be realized without requiring a costly increase in the number of humans supporting the electronic tools, and their associated and difficult education and maintenance. The achievement of electronic tool interactions that are clear to the clinician 99.9% of the time and do not generate questions is a challenge—but it is achievable with proper attention to computer screen button labels, instruction texts, protocol instruction explanations, etc.

#### **D. Human Experiments (Clinical Trials)**

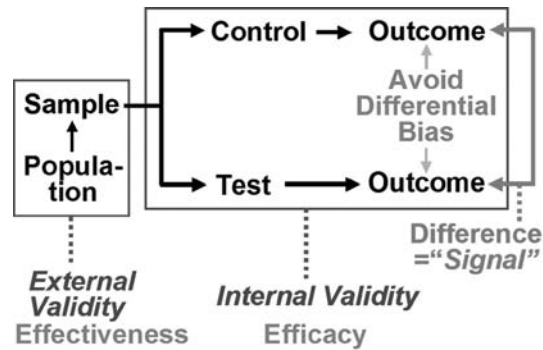
Among the several clinical study types described in epidemiology textbooks, the clinical experiment (clinical trial) is the source of the most credible information. Clinical trials are special cases of epidemiologic cohort studies. The fundamental difference between clinical experiments and other epidemiologic studies is that in clinical experiments the investigator determines the exposure of subjects to the test or experimental intervention. Clinical experiments (clinical trials) produce estimates or measurements of the effect size of the experimental intervention. Clinical experiments produce their most credible results when the experimental groups are comparable and differ only by chance, save for the exposure of subjects in the test group to the experimental intervention (140,227). The two major attributes of clinical experiments that assure, or at least increase confidence in, achievement of comparability between experimental groups are randomization and blinding (73,140,149,151,153,223,228,229).

Two sources of error can reduce the credibility of the measurement of effect size. Random error leads to imprecision. Systematic error leads to bias. Increasing the number of subjects in a clinical trial increases precision.

Bias, in contrast, is a more challenging source of error and requires careful attention to experimental design. The foundation of experimental design was derived from agricultural trials (228). They were designed so systematic error (bias) played little role. The randomized experimental design was believed to both assure random distribution of confounders to all experimental groups and allow statistical analytic correction for confounder imbalance between experimental groups (140). Randomized experiments stimulated development of statistical analysis tools (140,228). Unfortunately, evidence indicates that bias cannot be addressed and controlled by randomization alone for many critical care clinical experiments. Consequently, the conclusion that systematic error plays little role in clinical trials (140,228) is incorrect for many critical care experiments. In any case, the statistical approach to unmasking statistical or biological interactions is not satisfactory (140). The systematic error produced by postexperimental group allocation (post-randomization) bias due to confounders (better called cointerventions) can be antagonistic to, or synergistic with, the effect of the experimental intervention under study. Anticipation of either the direction or magnitude of such cointervention effects is hazardous (140,228).

Bias is expected and unavoidable in all clinical experiments because humans conduct these experiments on human subjects. Bias per se is not necessarily a problem if it appears equally in all experimental groups. Bias exerts its most pernicious effect when it is not equally expressed in the results of the different experimental groups. For example, IV nitroglycerine therapy, instead of a beta-blocking agent, for hypertension applied equally to both experimental groups might not eliminate the effect of a preferable mechanical ventilation–weaning strategy. Unequal administration of IV nitroglycerine will introduce a differential (between group) bias and might completely obscure the effect (230). Confounders that influence the different experimental groups unequally may produce a differential bias (Fig. 4). Differential bias threatens, and may invalidate, the assumptions of experimental group equation [Ref. (231) in Ref. (70)] or equivalence [Ref. (232) in Ref. (70)], (both early terms for comparability) necessary for the internal validity of a clinical trial (Fig. 4) (153).

Internal validity represents the extent to which the study results represent the true effect in the study subjects (see section “Efficacy vs. Effectiveness Clinical Trials”). External validity represents the extent to which the study results represent the true effect in the population of interest (140,153,160). Internal validity is emphasized in efficacy clinical trials and external validity in effectiveness clinical trials (153,160). Internal validity is a prerequisite for external validity. Consequently, efficacy clinical trials should precede effectiveness clinical trials (see section “Efficacy vs. Effectiveness Clinical Trials”) (140,160,223). Unfortunately, this requirement is frequently violated in critical care trials (131). Clinical trial design always involves striking a balance between the needs of internal and external

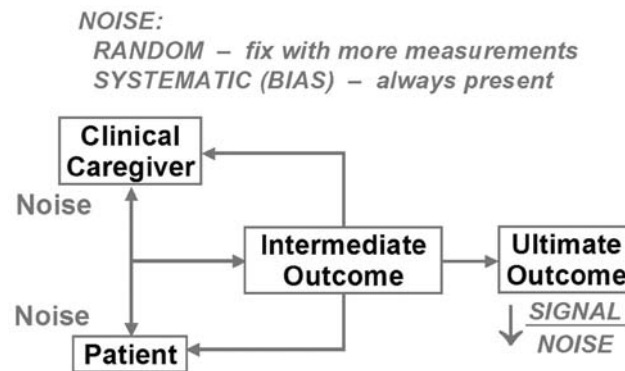


**Figure 4** The validity of clinical trial results can be assigned to two categories—internal and external validity. Internal validity is usually the focus of efficacy clinical trials and represents the validity with which the study results reflect the true effect in the experimental subjects. External validity is usually the focus of efficacy clinical trials and represents the validity with which the study results reflect the true effect in the population of interest (from which the study subjects were selected). The outcome “signal” that leads to inferences about the effect of the experimental intervention is the difference between the outcomes of the different experimental groups.

validity. The medical community has difficulty meeting the challenge of transferring the results of internally valid efficacy trials to the practicing clinical care community (7,233). Electronic tools have the potential of providing a replicable method that is used in efficacy trials but can be exported to practicing physicians and clinical care institutions (see section “Computerized Protocol Experience”).

#### *Noise and Signal-to-Noise (S/N) Ratio*

The detection of an association between an input signal of interest (Signal, S) and an outcome measure requires that the signal of interest be capable of separation from other unwanted signals (Noise, N) with which it may be confused or by which it may be obscured. A common measure of this capability is the S/N ratio (87). Unless the S/N ratio exceeds 1, the signal will be undetectable. The two major elements of the transactional patient–clinician unit (203), the patient and the clinical caregiver, determine the intensity of care and the outcome. Both the patient and the clinical caregiver are sources of random noise and of systematic noise (bias) (Fig. 5). The patient contributes noise because of uncontrollable host factors and because of variation in disease etiology, severity, extent, and duration. Local factors influence the patient’s disease and spectrum of clinical problems. The patient identification and selection process is quite imperfect and may incorporate much local bias due to the prejudices of individual clinicians and clinical



**Figure 5** Both random and systematic noise are introduced by both major elements of the transactional unit—the patient and the clinical caregiver (clinical environment). This noise decreases the S/N ratio and reduces the ability of investigators to detect the effect of experimental interventions. *Abbreviation:* S/N, signal-to-noise.

investigators. This bias is the result of many factors, among which are characteristics of local clinical environments and failure of the medical community to establish broadly accepted adequately explicit definitions of many diseases, including ARDS (234,235). The clinical caregiver contributes noise because of strongly held opinions based on many factors that influence behavior, including general and local cultural factors, local technical abilities, background, training, and experience. The effects of many experimental interventions on the outcome in complex clinical environments are likely to be small (20). They can easily be obscured by noise (Fig. 5).

The S/N ratio for random noise varies inversely with  $N^{1/2}$ . The impact of random noise can therefore be reduced by increasing the number ( $N$ ) of observations (224). In contrast, increasing  $N$  has no effect on systematic noise (bias). Techniques to minimize bias in randomized trials include allocation concealment (236), restriction of randomized subjects (140), blinding of patients, caregivers, and outcome assessors (236), using objective, reproducible criteria for assessing outcomes (143,144,154), assiduously screening all potential subjects, using adequately explicit inclusion and exclusion criteria, and assuring clinician and investigator compliance with all clinical trial protocol rules.

Clinical investigators have long recognized the importance of the uniform application of clinical interventions to comparable patients in clinical research (237). Existing large national databases lack this uniformity and they contain mixed groups of variable treatments labeled with the same procedure or treatment code. Variations of 60% to more than 400% for common process of care steps for Intermountain Health Care, Inc. patients with comparable presentation and outcomes were observed in a study of

practice pattern variation (238–242). Median procedure times for 16 surgeons performing transurethral prostate resection ranged from 40 to 95 minutes, while prostatic tissue removed ranged from an average of 11 to 42 g/patient (238). These variations had a strong statistical association with the occurrence of urethral strictures within one year of operation (the primary complication). Therefore, outcomes reported for treatments labeled using insurance data leave much uncertainty about the actual procedures employed (243–246). Similar variability due to noise in critical care databases is likely. For example, balloon flotation catheter use and IV fluid and electrolyte therapy (247) vary widely, with some physicians committed to conservative and others to liberal approaches.

#### *Clinical Trial Design Principles*

Advances at lower scales of inquiry cannot replace the study of integrated systems, such as sick patients in the clinical environment (34,192). Clinical trials will remain an important and the most credible source of information guiding clinical decision making. Attention to sources of nonuniformity between experimental groups is an essential part of experimental design (140,149,151,153,223,228,229). An epidemiologic investigative strategy requires investigators to assess the validity of a statistical association between a variable and an outcome of interest by excluding possible alternative explanations. These include chance, systematic errors in data collection or interpretation (bias), or effects of other variables (confounders) on the outcome (223). While this framework has been successful for observational epidemiological studies, the definition of confounders does not accommodate the needs of many nonblinded critical care clinical trials. For such clinical trials, it is important to distinguish between two categories of nonexperimental variables that can influence outcomes.

#### Confounders and Cointerventions

While the determinants of patient outcome may include the intervention under study, these determinants are multiple and complex. Among the multiple variables that may determine outcome (e.g., survival) are variables, called confounders. A confounder (confounding variable) is a variable that is associated with a predictor (input or test variable) and is also a cause of the outcome variable (153). For example, IV fluid can be a confounder in trials of mechanical ventilation strategies. Excessive fluid and salt infusions appear to harm patients (248,249) and may influence mediator levels in clinical trials (250,251). Conversely, PEEP can be a confounder in clinical trials of hemodynamic support strategies. Confounders can influence, alter, or reverse the results of clinical trials (140,149,153,223,252). Many experts claim that confounders can be addressed by randomization (see section “Experimental Group Equation”). However, confounders can be present

before or after random allocation of subjects (randomization) to the experimental groups of a clinical trial (140). Those confounders present before allocation are dealt with by randomization and by restriction of randomized subjects (140). They are commonly recognized and discussed in epidemiology texts (140). In critical care research, these variables should be called confounders because they correspond well to the traditional definition of confounding identified in epidemiology (223).

However, when confounders are introduced after subject assignment to the experimental groups, they are better termed “cointerventions” (153,154,252). This will distinguish them from those confounders present before subject allocation to the experimental groups. Cointervention is a good term because, like the experimental intervention, cointerventions are introduced after randomization and result from the interaction of the subject with the clinical environment (e.g., mechanical ventilation strategy, drug therapy for hypotension, IV fluid therapy, diagnostic strategies for suspected infection, monitoring intervals, laboratory tests, antibiotic therapy, sedation, etc.). Like the experimental intervention, they can alter the results of clinical trials. They can even invalidate the results of clinical trials. In addition, clinicians and investigators can easily overlook cointerventions. Unlike the experimental intervention, cointerventions rarely receive adequate attention in the protocols of randomized clinical trials. The Cochrane Collaboration proposed the following definition of cointerventions: “In a randomised controlled trial, the application of additional diagnostic or therapeutic procedures to members of either or both the experimental and the control groups” (252).

Cointervention is, however, not a widely accepted term. Horwitz et al. called cointerventions cotherapies in an analysis of clinical trial results that suggested that cointerventions reversed the effect of beta-blocking drugs following myocardial infarction (8). This observation was vigorously criticized in a vitriolic exchange because of the post hoc nature of their analysis (253–256). These arguments concern a longstanding debate among statisticians and epidemiologists. These publications focus attention on the importance of identifying and controlling, if possible, important cointerventions before a clinical trial is conducted. They emphasize the importance of including cointervention considerations in study design of efficacy trials and not, after the study is completed, in post hoc analysis (253–256).

Most texts do not mention cointervention and one reference defines cointerventions differently (as simultaneously applied experimental interventions) (257), a definition at odds with the use here and elsewhere (153,154,252). Even those who mention with authority the importance of cointerventions may not discuss the adequately explicit methods that could reduce the differential bias due to these cointerventions (153,154). Finally, a recent publication dealing with critical care clinical trials did not address the methodologic details needed to deal with cointerventions (160).

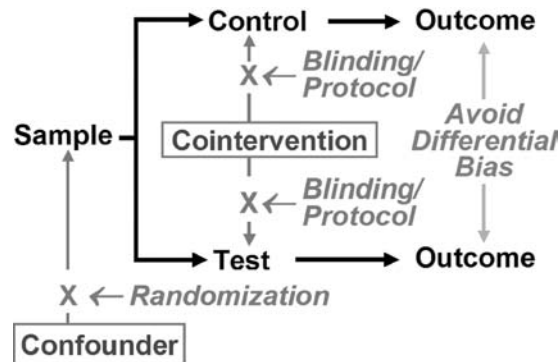
#### Experimental Group Equation

In the 1920s, experimental group equations [Ref. (231) in Ref. (70)] or equivalence [Ref. (232) in Ref. (70)] were identified as essential requirements for internal validity of an experiment (Fig. 4) (73,140,149,151,153,223,228,229). Two major attributes of clinical trials, randomization and blinding, reduce differences between groups and help assure experimental group equation. [Restriction of randomized subjects is also used to reduce differences due to confounders present before subject allocation to experimental groups (140).]

*Randomization.* Randomization, properly applied, can provide assurance that confounders, present among potential subjects before experimental group allocation, will be randomly (therefore almost uniformly) distributed among the experimental groups (140,149,151,153,229,258,259). Randomization assures that the experimental groups will differ only by chance. This allows application of statistical analysis in the interpretation of experimental outcome group differences (140,227). This technique is effective, especially when the number of subjects is large, and permits statistical analytic correction for such confounder imbalance. Randomization permits blinding as a tool to reduce unwanted differences between experimental groups (227).

*Blinding.* Blinding is a fundamental experimental mechanism for reducing inequality of care in experimental groups (20,143,149,260). Double-blind drug trials with a placebo or a routinely administered therapy control arm have been conducted successfully without protocols and have provided an important foundation for thinking about clinical trial design (140,149,151,153,223,228,229). Cointerventions are therefore traditionally dealt with by double blinding, as in drug studies (73,140,149,151,153,223,228,229). Differential bias will be reduced in double-blinded trials, but even with double blinding, differential bias may not be eliminated. If the experimental treatment has an effect that, on the average, changes the clinical expression of the disease between the experimental groups, clinicians may perceive (correctly or not) the group to which the subject had been allocated and thus violate the blinding (140,149,223,228). Clinicians might then apply cointerventions differently to the treatment groups.

Unfortunately the traditional double-blind drug trial (without protocols for cointerventions) has been frequently used as the model for randomized nonblinded critical care clinical trials. This presumes that all clinical trials can be managed with the same approach. This presumption is an error. Many interventional critical care studies, including those that incorporate mechanical ventilation techniques, cannot be double blinded. Comparability of experimental groups must be achieved by other means. Non-double-blinded clinical trial publications should be scrutinized and the clinical care carefully assessed for comparability of the cointerventions



**Figure 6** Confounders can be introduced into clinical experiments either before or after subject allocation to the experimental groups. Confounders present before allocation are addressed, and can usually be controlled, by true randomization that commonly distributes confounders equally among experimental groups and avoids differential bias. Confounders introduced after subject allocation to the experimental groups are called cointerventions. Cointerventions have been traditionally addressed by double blinding of clinical experiments. In nonblinded (open) clinical trials, blinding is not possible. Adequately explicit protocols can control or at least partially control cointerventions and reduce the chance of introducing differential bias.

in the experimental treatment arms. Cointerventions are frequently neither controlled nor measured and this deficiency threatens the internal validity of critical care clinical trials. In nonblinded (open) critical care clinical trials, all experimental arms require well-defined and detailed protocols (Fig. 6) (34,131,135).

Adequately Explicit Methodology: Protocols vs. Guidelines

Decision-support tools such as guidelines and protocols have been functionally categorized as reminders, consultants, or as educational (261). They are intended to enable clinicians to deliver evidence-based care consistently by standardizing some aspect of clinical care, thereby helping lead to uniform implementation of clinical interventions (182,262–265). However, many guidelines and protocols lack specific instructions for commonly encountered clinical practice scenarios, and are useful only in a conceptual sense (182,263,266–270). They neither standardize clinical decisions nor lead to uniform implementation of clinical interventions.

The medical subject headings in Ovid® define guideline as “A systematic statement of policy rules or principles” and protocol as “Precise and detailed plans for the study of a medical or biomedical problem and/or

for a regimen of therapy.” Guidelines are general statements with little instruction for making specific decisions (95). For example, “If the first drug is not tolerated, substitute a different drug from another class,” from a National Heart Lung and Blood Institute (NHLBI)/Hoescht Marion Roussel<sup>®</sup> guideline for controlling hypertension in older women, does not standardize specific clinical decisions. In contrast, protocols are more detailed and can provide specific instructions.

The explicitness of protocols varies continuously. An adequately explicit protocol is one that can generate specific instructions (patient-specific orders) without requiring judgments by the clinician and can elicit the same decision from different clinicians when they are faced with the same clinical information. There is no threshold beyond which protocols are adequately and below which they are inadequately explicit. My colleagues and I have concluded that our protocols are adequately explicit when clinicians accept and carry out over 90% of protocol instructions. This is clearly our choice and represents our judgment of the required level of acceptance of instructions by different clinicians. Adequately explicit computerized protocols can contain the greatest detail (271) and may lead to the upper limit of achievable uniformity of clinician decision-making with open-loop control (58,122,164,272) [closed-loop controllers automate processes and eliminate humans from the decision-making process (159,273–275)]. Paper-based versions can also contain enough detail to be adequately explicit (120,276). Inadequately explicit protocols omit important details (277–279) and elicit different clinical decisions from different clinicians. Clinician decision-makers must fill in the gaps in protocol logic. Judgment, background, and experience vary among clinicians and so will their choices of the rules and variables they use to fill in the gaps of inadequately explicit guidelines and protocols. In addition, because humans are inconsistent, any single clinician may produce different choices at different times, even though faced with the same patient data.

Unfortunately, even systematic and scholarly collections of flow diagrams commonly lack the necessary detail and cannot standardize clinical decisions (277–279). Protocols and flow diagrams are also called algorithms but this is an inappropriate use of the term (277,279). An algorithm in mathematics or engineering is a precise solution (71) although its definition allows the more liberal use common in medicine [“a set of rules for solving a problem in a finite number of steps” (280)]. The distinction between guidelines and protocols, particularly adequately explicit protocols, is crucial (34,35,281). Failure to make this distinction fosters confusion (131 265,281). The health care delivery community’s penchant to use guideline, protocol, and algorithm interchangeably (265,277–279,281–285) is more than a taxonomic error. It is a serious conceptual error that obscures the important distinction between adequately explicit and other methods. Adequately explicit protocols can serve as physician orders, and can function as

dynamic standing orders because they respond to changes in patient state, but guidelines cannot do so.

I chose the term “adequately explicit” with care. Any articulation of a method is explicit. For example, consider “. . . caution should be exercised when PAOP becomes increased to the extent that pulmonary edema is a risk” (95,96). While statements such as this are explicit, they do not elicit the same clinician decision when multiple clinicians are faced with the same clinical data. From the human experimentation perspective they do not establish a replicable experimental method. Most clinical investigators do not seem to recognize the difference between common ordinary protocols and guidelines and the uncommon adequately explicit methods that satisfy the scientific requirement of replication of experimental clinical trial results (20,34,35,131,149,237). For example, recent studies of high-frequency ventilation in neonates (286,287) have been described (288) as “. . . rigorously controlled conditions with well-defined protocols . . .” (286) even though the method includes the following statements: “. . . aggressive weaning if blood gases . . . remained . . . in range . . .”. This method will lead to different actions by different clinicians as they interpret “aggressive” and “remained.” These adult and pediatric critical care methods are not adequately explicit. Adequately explicit methods include rules such as “if [(last PaO<sub>2</sub>—current PaO<sub>2</sub>) > 10, and (current PaO<sub>2</sub> time—last PaO<sub>2</sub> time) < 2 hours, and FiO<sub>2</sub> > 0.8, and PEEP < 15 cmH<sub>2</sub>O], then increase PEEP by 2 cmH<sub>2</sub>O.” A rule such as this can lead to the same decision by multiple clinicians. A protocol composed of such rules can establish a replicable method that permits large-scale critical care trials within a network of many institutions. In continuous quality improvement terms, an adequately explicit method is part of the “stabilization of process” necessary to improve quality (21–23,25).

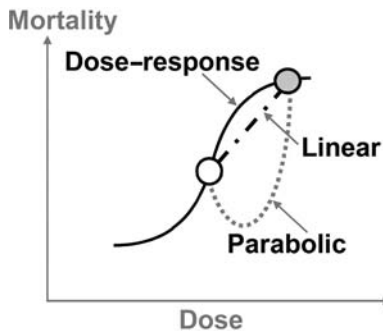
Protocols assure a reproducible level of care. For example, a brain edema protocol can support the performance of experienced as well as inexperienced colleagues such as new medical residents or nurses. Finally, it is important to point out that an adequately explicit method in the form of a computerized protocol has the potential to link efficacy trials with clinical practice, although this is a challenge. An adequately explicit protocol is a model of the clinician decision-maker. The method (computerized protocol) is exportable and could be used to replicate a study or to transfer a decision-support tool to clinical practice. It could provide a needed link between clinical research and clinical care.

*Individualized, Patient-Specific Instructions.* Clinicians and patients expect therapy to be tailored to the patient’s specific needs. All demand that clinicians respond to the patient’s individualized expression of disease. Therefore, adequately explicit decision-support tools must accommodate relevant variations among patients. If not, clinicians will reject them. Patients express their response to diseases in individual and variable ways,

including in their clinical data. These patient data lead to the instructions produced by adequately explicit protocols. Every single protocol instruction is based on patient data and leads to a standardized clinician decision according to the protocol rules. Every single protocol iteration yields at least one standardized decision (adequately explicit instruction) from the patient data. However, each patient expresses unique, patient-specific, clinical data that change over time. The patient's therapy regimen is the sum of all of the standardized decisions from the patient's unique clinical data from all protocol iterations over time. Therefore, the patient's therapy regimen is individualized (tailored to the patient). Preservation of individualized therapy with standardized decisions is a crucial attribute of adequately explicit protocols and a central element of their ethical foundation (34,35,131). Ethical obligations to deliver individualized clinical care to the research subject are thus discharged satisfactorily as the scientific requirement to reduce differential bias in the clinical trial experiment is met (34,162,163).

#### Limitations of the Two-Experimental-Group Design

The traditional common two-experimental-group limitation seriously limits the interpretation of clinical trial results, because two outcome estimates (e.g., event rates in the two groups) can fall on a straight line, a curvilinear function like a parabola, or a more complex function. While one group may have a more favorable outcome than the other, investigators cannot conclude that either experimental group intervention is an ideal therapy because what is frequently needed is a dose–response curve of outcome against multiple levels of the intervention. Such a dose–response curve is de rigueur in reductionist research such as in biochemistry, pharmacology, organ physiology, or in Phase II safety and dose-ranging human studies of new drugs. The limitation of the common two-experimental-group-design clinical trial was the foundation for the criticism by Eichacker et al. (289) of the NIH/NHLBI ARDS Network study of mechanical ventilation (120). This criticism precipitated the recent controversy between the Office of Human Research Protection and the NIH (282–284,290–293). The NIH/NHLBI ARDS Network investigators adopted the common practice of treating the two-experimental-group outcomes as if they belonged to a linear set (see linear curve in Fig. 7). Eichacker et al. argued that while the mortality of the higher tidal volume strategy (solid gray point in Fig. 7) was greater than that of the lower tidal volume strategy (open point in Fig. 7), an even lower mortality was possible at an intermediate, but not tested, tidal volume strategy (minimum of parabola in Fig. 7). They were articulating a systematic deficiency within the clinical trial community—the common use of a two-experimental-group design. A dose–response curve, constructed from multiple study group interventions (e.g., five groups), would have answered this appropriate criticism directly. A generic



**Figure 7** Theoretical dose-response curve for human experiments (clinical trials). Most clinical trials implicitly accept a linear curve. However, other curves are possible, two of which are depicted. Multiple group clinical trials (e.g., five) might enable investigators to define a curvilinear dose response, such as is commonly encountered in biochemical and pharmacologic studies.

drug dose-response curve is represented in Figure 7; however the true shape might be different and would require a Phase III clinical trial for its definition. It cannot be inferred with confidence from reductionist research results (e.g., cell biological, organ physiological, or animal safety study results).

While dose-response curves are generated in many traditional Phase II clinical trials of drugs, these Phase II trials use intermediate (or surrogate) outcome variables such as physiologic measures (e.g., blood pressure), inflammatory mediators (e.g., TNF $\alpha$ ), or routine laboratory analytes (e.g., serum creatinine). Such intermediate outcome variables are not necessarily linearly linked to the ultimate outcome variables (e.g., survival, days free of organ failure, recovery of function, quality of life) that are the important determinants of clinical decision making at the individual or societal level. The CAST results revealed an increase in mortality, even though the desired intermediate outcome (reduction of the number of PVCs) was achieved (66,294). In the NIH/NHLBI ARDS Network mechanical ventilation randomized clinical trial, mortality was decreased, even though the anticipated and desired increase in intermediate outcome, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, was not achieved and PaO<sub>2</sub>/FiO<sub>2</sub> actually decreased (120). These two examples indicate that intermediate outcome changes in Phase II dose-ranging trials cannot be mapped linearly to the important ultimate clinical outcomes in Phase III randomized clinical trials. The difficulty of establishing a dose-response curve in intact human subjects in the clinical environment of traditional Phase III trials has been so daunting that the health care community has become accustomed to abandoning this fundamental requirement of good scientific experiments when conducting many, if not most, Phase III

clinical trials. We should be able to achieve this goal with a new strategy based on electronic tools that enable large-scale participation of academic and community hospitals in studies using adequately explicit methods (computerized protocols) to generate Phase III randomized clinical trial dose-response curves.

#### Protection of Subjects

The claims by some that “rigid” protocols (160,264,265) expose patients and experimental subjects to risk and that computerized protocols will not be widely distributable because they are “rigid” (160) deserve a response. A common perception is that “Protocols should not represent rigid rules but, rather, guides to patient care” (264). This is a misperception propagated by confounding “adequately explicit protocols” with “guidelines,” a common mistake (see section “Adequately Explicit Methodology: Protocols vs. Guidelines”). The arguments above (see section “Individualized, Patient-Specific Instructions”) that adequately explicit protocols can generate therapy that is tailored to the individual patient or subject’s needs, while standardizing clinician decision making challenge the characterization of these protocols as “rigid.” One cannot argue with the claim that protocol use is associated with risks. Virtually nothing we do in health care delivery is risk free. However, the ample evidence that protocol use leads to more favorable patient and clinician behavior outcomes belies the claim that the balance of risks and benefits from the use of adequately explicit protocol is unfavorable to patients and experimental subjects (53–59). The ethical principles of beneficence and nonmaleficence (295) are thus respected when adequately explicit protocols are used for patients and experimental subjects. Finally, the claim that protocols endanger subjects (120,293) when they are used in clinical trials without an ordinary care (the misleading terms “usual” or “standard” care are more commonly used) experimental group is not an issue specific to adequately explicit protocols (see section “Adequately Explicit Methodology: Protocols vs. Guidelines”), but rather one that relates to experimental design (282–284,290–292) (see section “Limitations of the Two-Experimental-Group Design”).

#### *Efficacy vs. Effectiveness Clinical Trials*

Investigators should clearly identify the clinical trial goal before study design proceeds. Our a priori level of confidence in the ability of a clinical intervention to favorably alter patient outcome determines whether an intervention, after study results are available, will be accepted as part of routine clinical practice, or alternatively will be questioned (34,140,227). Efficacy and effectiveness studies have different goals (20,34,153,160).

“Efficacy” is the term assigned to human experiments conducted under most favorable circumstances such as those in an academic center with sizable resources committed to the experiment (160). Efficacy clinical trials provide the most compelling evidence and they should, whenever possible, precede the conduct of effectiveness trials (140,160). “Effectiveness” is the term assigned to a study conducted under more routine, and less favorable, clinical circumstances such as in community hospitals with more limited resources (20,153,160). Effectiveness studies can include experimental clinical trials such as the large simple trials advocated by Peto (224,296) or observational studies of the results of clinical practice. Some authors propose a hybrid approach, combining properties of efficacy and effectiveness clinical trials for critical care experiments (160). When planning clinical trials, investigators are always faced with challenges that require compromise between these two categories. The electronic tools discussed in this chapter may allow convergence of efficacy and effectiveness efforts (see sections “Clinical Care Examples of the Importance of Scaling,” “Multinational Critical Care Experimentation,” and “Computerized Protocol Experience”). [In contrast with efficacy and effectiveness research, continuous quality improvement (process improvement) studies focus on the efficiency with which one delivers a clinical intervention that is already accepted as part of ordinary clinical practice.]

#### *Comparability of Experimental Groups in Critical Care Clinical Trials*

In the 1920s, experimental group comparability was identified as a goal for the internal validity of an experiment (Fig. 4). Comparability was termed “experimental group equation” [Ref. (231) in Ref. (70)] or equivalence [Ref. (232) in Ref. (70)]. Ideally, scientifically rigorous clinical trials strive for the delivery, to all patients in all experimental groups, of care that differs only by the random play of chance in every respect except for the experimental intervention itself (20,140,149,151,153,223,228,229,231,232,260,297). An infinite number of repetitions of a trial would achieve identical experimental groups, but any single trial can only approximate such comparability (227). Randomization assures the applicability of statistical analysis that enables the evaluation of experimental group outcome differences relative to those expected by chance alone (140,227). Comparability of study groups is less likely with nonexperimental studies or when experimental studies use historical controls, when patients are selected according to an individual’s judgment, or sequential subject assignment. The importance and the difficulty of establishing comparability of the experimental groups are widely acknowledged (140,149,151,153,223,228,229,237,258,259).

Two major attributes of clinical trials have been commonly used to achieve the experimental group equation or equivalence: randomization and blinding (140,149,151,153,223,228,229,258,259). These have been most

commonly used in double-blind drug trials, beginning with the British Medical Research Council clinical trials of streptomycin for treatment of tuberculosis in 1949 and of antihistamines for treatment of the common cold in 1950. Experts commonly recognize that confounders may be unevenly distributed among experimental groups both before and after allocation to experimental groups (140,149,151,153,223,228,229,258,259). The influence of drug trials with their emphasis on double blinding and on the outpatient setting has established common patterns of thinking about experimental design and its limitations. Most workers seem to have emphasized blinding to reduce, and analytic approaches to assess, the effect of confounders. While Friedman et al. discuss concomitant and compensatory treatment in non-double-blinded experiments (228), they and other workers have not carried this argument further. They did not identify these concomitant and compensatory treatments as postrandomization confounders (cointerventions)—a potent source of differential bias in critical care experiments. The fields of epidemiology and clinical trials do not yet seem to have adopted an approach matched to the needs of the critical care environment. Critical care involves such frequent and such diverse measures of bodily function that postrandomization confounders (cointerventions) loom large as sources of important differential bias. Even with double-blind experiments, the perception by clinicians that they know the subject allocation group is made more likely by the rich and recurrent source of data describing subject function in critical care trials (153). The fact that some of these numerous measurements will be accurate while some will be false-positive and false-negative results only compounds the problem. In addition, many critical care experiments cannot be double blinded, opening the door to the introduction of more postrandomization differential bias.

Friedman et al., like many authors, have accepted the common wisdom that precludes control over the variable treatments that characterize clinical care and clinical research (160,228). Some of these experts indicate that one can merely encourage clinicians to uniformly apply treatments, even though the widely recognized unnecessary variation in practice (1,2,96,298,299) makes success with this approach unlikely (30,31,300–312). In contrast, available tools have enabled clinical investigators to achieve advances in uniform application of treatments through clinician decision support (34,35,77,131,173,265,313–315).

#### *Confounders in Critical Care Clinical Trials*

Critically ill patients receive multiple interventions in the form of therapies, diagnostic tests, and monitoring. Patients who become research subjects are associated with confounders both before and after allocation to experimental groups. True randomization generally distributes uniformly those confounders present before experimental group allocation (140). However,

many therapeutic, diagnostic, and monitoring interventions continue to be applied to clinical trial subjects after allocation to the experimental groups. These postallocation interventions are not influenced by randomization and are potential confounders. Double blinding has been commonly used to assure uniform distribution of postexperimental-group-allocation confounders, especially in the double-blind drug trials that have constituted a major force in statistical development since 1949. Several workers recognize that even double-blind drug studies may not be able to preserve blinding. Therefore, postallocation confounders may not be evenly distributed between experimental groups (140,149,223,228). Blinding is not possible in many critical care trials (e.g., extracorporeal support, IV fluid and hemodynamic support, mechanical ventilation support, sedation and paralysis, positioning, blood sugar control, etc.). Postallocation confounders may strongly influence experimental outcomes in critical care clinical trials.

If confounding variable values are obtained during the clinical trial, an attempt can be made to account for their effect through stratified analysis. However, this is a complex issue that involves, among its several problems, the assumption of uniformity (that the effect of the confounder is homogeneous across strata) (140). I do not believe this assumption can be defended for IV fluid and hemodynamic support, antibiotic therapy, patient positioning, or other potential postallocation confounders (cointerventions). The reasons for which clinicians regulate or titrate these therapies may be unknown. In addition, patients are complex nonlinear biologic systems (71–73). It would be difficult to account for the sequential changes induced by any given confounders. Analytic attempts to correct confounder effects cannot adjust for the sequential dependence of each confounder on the previous confounder's effects. This is similar to the difficulty of separating, by statistical analysis, the effects of participation (selection bias) from those of disease determinants (140).

The three examples below are only a sample of the many postrandomization clinical interventions that could function as confounders (cointerventions) in critical care clinical trials. They serve to illustrate both the subtlety and the potential importance of confounders on experimental outcome. I am not aware of any mechanical ventilation experiment that attempted to control the differential bias that might result from these potential cointerventions. For all these cointerventions, a uniform clinician decision-making approach, using a protocol that embraces a reasonable set of rules, can minimize differential bias between experimental groups.

#### Antihypertensive Drugs (230)

Drugs can influence the duration of mechanical ventilation. While this seems almost axiomatic, the subtlety and magnitude of this effect is not widely appreciated. Some patients develop hypertension following thoracic surgery. Clinicians attempted to withdraw mechanical ventilation support

from these hypertensive patients when they met certain rules (a protocol) concerning arterial oxygenation (230). Thirty hypertensive patients, when treated with IV sodium nitroprusside or IV nitroglycerine failed to meet the criteria for initiating a trial of withdrawal of mechanical ventilation. When the therapy was changed to a beta receptor blocker, labetalol, to treat the hypertension, 28 of the 30 patients immediately met the criteria for a trial of withdrawal of mechanical ventilation. Should the type of antihypertensive drug employed in a mechanical ventilation clinical experiment be unevenly applied to the experimental groups, a large differential bias that could dramatically influence the duration of mechanical ventilation, or the number of mechanical ventilation-free days, could occur. Antihypertensive drug therapy is a cointervention.

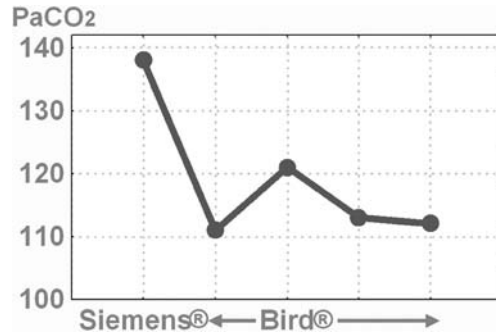
#### IV Fluids and Hemodynamic Support

Fluid and electrolyte therapy can influence patient outcome and obscure the effects of therapeutic interventions in clinical trials. Reliable evidence indicates that clinical management of the circulation with IV fluid and hemodynamic support can modulate lung injury (316–319), can alter mediator levels (250,251), and can harm patients (248,249). Although high intravascular pressures may worsen patient outcome (320) and induce alveolar collapse (321), low intravascular pressure may increase lung injury as well (318,319,322–325). The intravascular pressure is therefore likely an important determinant of the evolution of lung injury. This conclusion is supported by isolated lung experimental results (326). Variations in management of IV fluid and hemodynamic support can, if not uniformly applied to all patients in an experiment, alter the experimental outcome in unpredictable ways.

Uncertainty about proper IV fluid therapy comes at least in part from equivocal terminology. The terms used to evaluate body fluid status and its treatment are enveloped in confusion (327–337). This confusion precludes development of a systematic evidence-based practice (327–334). Contradictory terminology (96) probably contributes to the uncertainty surrounding fluid and electrolyte therapy for sepsis (338), shock (339–341), and acute lung injury and ARDS (320). Intravenous fluid and hemodynamic support therapy are cointerventions.

#### Body Temperature

The data of Figure 8 led experienced critical care clinicians to conclude that the mechanical ventilation support of a man with ARDS was better provided with a Bird<sup>®</sup> than with a Siemens<sup>®</sup> ventilator. In fact, the lower PaCO<sub>2</sub> measured during patient support with the Bird<sup>®</sup> ventilator was explained largely by a decrease in body temperature (Fig. 9), a variable frequently ignored in mechanical ventilation studies. Temperature, in this example, with its attendant reduction in metabolic rate, is a cointervention.

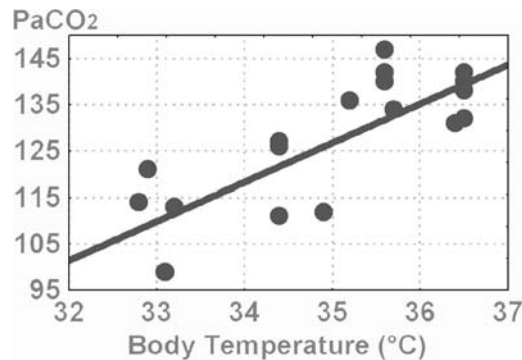


**Figure 8** PaCO<sub>2</sub> in a young man with ARDS while supported with a Siemens Servo 300 mechanical ventilator and thereafter with a Bird pressure-limited mechanical ventilator. *Abbreviation:* ARDS, acute respiratory distress syndrome.

### III. Computerized Protocol Experience

#### A. Experience with Computerized Protocols for Adults with Acute Lung Injury

The computerized protocols for mechanical ventilation of ARDS patients developed at the LDS Hospital (35,122,271,342) were exported in stand-alone PC versions (on Unix and Qnix platforms) to 10 other hospitals in five states (58). These 10 external hospitals were not involved in the development of the protocol or its rules. Clinician compliance with 38,546 protocol instructions in these 10 hospitals was 95% (58) and indistinguishable from that at the LDS Hospital (272); physicians objected to only 0.3% of the 38,546 instructions (58). The NIH/NHLBI ARDS Network clinician



**Figure 9** PaCO<sub>2</sub> in a young man with ARDS, as a function of body temperature. *Abbreviation:* ARDS, acute respiratory distress syndrome.

compliance with a paper protocol based in part on the LDS Hospital computerized protocol was 91% (120). These levels of clinician compliance with paper protocols far exceed the 20% to 50% characteristically associated with guidelines (101,105,115,314,343), but are lower than the 95% compliance experienced with our bedside computerized protocols (272). By the year 2000, this mechanical ventilation protocol had been used in computerized and paper-based versions for over 600,000 hours in over 1164 patients in 35 hospitals (Table 2). The NIH/NHLBI ARDS Network subsequently extended this explicit method approach to other successful randomized controlled clinical trials (120,276,344,345). It was associated with a 23% reduction in mortality of acute lung injury patients (120). These results indicate that an adequately explicit method of care can be effectively transferred for clinical trial use to many different geographically dispersed clinical settings, can reduce variation in clinical decisions, and can significantly reduce patient morbidity (58).

#### B. Current Utah Clinical Trial Toolbox Electronic Tools

My colleagues and I found our original rule-based flow-diagram protocols difficult to develop (164,346). We have now developed a more capable, efficient, and user-friendly software tool set built around a "frame-based" system for expressing clinical trial decisions (frames are lists of items necessary to make a decision with an associated logic statement relating the items). These current frame-based adequately explicit computerized protocols, used for bedside decision-support, are now part of the Utah Clinical Trial Toolbox, a comprehensive electronic tools system that brings many

**Table 2** Adequately Explicit Protocol Experience with Computerized and Paper-Based Mechanical Ventilation Protocol Rules Through Year 2000

Site	Protocol use (hr)	Patients
<i>Computerized version</i>		
LDS hospital (32,118)	>200,000	>200
10 other hospitals (55)	38,528	103
<i>Paper-based version</i>		
24 ARDS Network hospitals (116) <sup>a</sup>	350,880	861
Total (35 hospitals)	>600,000	>1164

Other hospitals are hospitals to which the LDS Hospital protocol was exported for a clinical trial. These other hospitals had no experience with or part in the development of the computerized mechanical ventilation protocol.

<sup>a</sup>Subsequent NIH/NHLBI ARDS Network clinical trials [higher vs. lower PEEP (352) and FACTT studies] have extended this use to more than another 1000 patients in about 44 participating adult hospitals.

*Abbreviations:* NIH, National Institutes of Health; FACTT, Fluid and Catheter Treatment Trial; ARDS, acute respiratory distress syndrome; NHLBI, National Heart Lung and Blood Institute.

advantages to clinical trials (347–351). We have also developed both paper bedside instruments (96,164) and computerized tools with which to capture the data necessary to calculate provider response (acceptance or rejection of protocol instructions). This is accomplished in part by software that captures provider compliance as the bedside protocol generates treatment instructions (164,347).

The Utah Toolbox is comprised of several desktop applications and a web application. The desktop portion was created with Microsoft (MS) Visual Basic 6.0 using MS Access<sup>©</sup> as the database (future versions will use the Microsoft.Net development environment or Java development tools). However the Visual Basic<sup>©</sup> applications will work with any relational DB via ODBC or OLE DB drivers (e.g., Oracle<sup>©</sup>, SqlServer<sup>©</sup>, and MySql<sup>©</sup>). The MS Access<sup>©</sup> Application itself does not need to be present on client machines.

There are two basic Utah Toolbox development tools: the FormBuilder for creating clinical coordinator applications such as data collection forms and the FrameBuilder for capturing the clinical decision-making logic and creating the bedside clinical decision-support applications. After an application is created with a FormBuilder or FrameBuilder template, the development functions are simply turned off, thereby creating the end-user application. Each application has its own MS Access<sup>©</sup> database. We currently use both a clinical coordinator application, built by the NIH/NHLBI ARDS Network Clinical Coordinating Center at the Massachusetts General Hospital, and a bedside clinical decision-support protocol for the NIH/NHLBI ARDS Network Fluid and Catheter Treatment Trial (FACTT) clinical trial.

We have also developed bedside clinical decision-support applications for blood glucose/IV insulin titration, and for the 6 mL/kg (predicted body weight) mechanical ventilation strategy used by the NIH/NHLBI ARDS Network for its mechanical ventilation and FACTT clinical trials (120,276 344,345).

We use two additional small applications for HL7 data capture from clinical laboratory computers: (i) A “socket application” (coded with C++), which listens for HL7 lab data at a specific IP address and saves it in a text file; (ii) A Visual Basic<sup>©</sup> Application that opens the file, filters only the patients of interest, translates the HL7, and puts the data into an observations table in the coordinator application database.

The web application is comprised of secure php pages that are served by an Apache Web server. Encrypted data are transferred to and accessed from MySql<sup>©</sup> and Oracle<sup>©</sup> databases on the server.

Electronic tools make possible the incorporation of much more complicated knowledge and logic (necessary to generate adequately explicit instructions) at the bedside. Time and effort is necessary to capture, represent, and process the logic. In the past, this has been an arduous process (and has, no doubt, contributed to the rarity of decision-support tools in clinical care) (34,35). The first phase involves a consensus process by

recognized experts in the field determining the decisions to be made, the component findings, and the logic relating the findings. The second phase involves computerization of the rules (in a database or even in ASCII or binary files). The third phase involves creating a computer application that will process the rules and generate actions in the clinical environment based on clinical data. The FrameAuthor tool of the Utah Clinical Trial Toolbox merges these phases into a single process by automating the second and third phases. The Utah Clinical Trial Toolbox uses methods developed at the LDS Hospital since 1985 and a validated frame-based knowledge engineering tool (164,271,347,353,354).

In addition, clinicians can create the knowledge “frames” themselves. A data entry form is automatically generated when a knowledge frame is developed. Frames can be tested at any time during the process with simulated or stored patient data (data can be accumulated and automatically rerun when changes are made in the frame structure). Database queries are created automatically as part of the frame-building process. When the clinicians are satisfied, they can turn off the development features and the data entry form becomes the decision-support application for the bedside clinician.

The FormBuilder tool allows rapid construction of the administrative electronic forms (with built-in error checking), thereby generating a protocol-specific clinical coordinator tool. It is also integrated with the bedside tool so that it can automatically retrieve data from the bedside tool. Moreover, the coordinator tool can retrieve data directly from an electronic medical record (EMR). The Coordinator Application can provide automatic error checking and auditing of changed data and can facilitate data transfer to a Clinical Coordinating Center via our web-based communication application.

The clinical trial toolbox provides the foundation for an information exchange infrastructure. It is a hybrid system that can function as a stand-alone bedside decision-support or clinical coordinator tool, linking intermittently with a web server, or it can be attached to an EMR system. It provides common electronic tools for linking sites within a research network. We have mapped the knowledge-based dictionary to Logical Observation Identifiers and Codes (LOINC) for our current protocols and will also map to Systematized Nomenclature of Medicine (SNOMED) and International Classification of Diseases, Ninth Edition (ICD9) terms. In this way, these tools will be as compliant as possible with the evolving national medical informatics standards.

#### *IV Fluid and Hemodynamic Support Protocol for FACTT Patients*

The data entry screen for the NIH/NHLBI ARDS Network FACTT study requires bedside clinicians to enter only a few mandatory data elements (Fig. 10). The bedside clinician can, if needed, click on the instruction in the white box to read an explanation of the logic. If the bedside clinician

**FACTT PROTOCOL Patient Data Entry**

Patient Name: Test, Alice | Age: 32 | BWP: 65 | Location: 1 | Treatment Group: CVC | Treatment: Conservative | Protocol requires all data in yellow boxes | Demographics: | Last Doses: | Previous Meds: | Off protocol Rx: | Saved Instructions: | Fix Errors

Systolic BP: 120 | Diastolic BP: 67 | Mean BP: 95 | Heart Rate: 120

Urine [since last entered] | Volume (ml): 70 | Interval (minutes): 60 | mL/hr: 70 | mL/kg/hr: 1.08

Serum Creatinine: 1

Pright atrial or CVP: 17

Check here if Dialysis planned or done < 48hours

After Completing Data Entry CLICK here for Treatment INSTRUCTIONS

Dopamine: 0 mcg/kg/min | Norepinephrine: 0 mcg/kg/min | Epinephrine: 0 mcg/kg/min | Phenylephrine: 0 mcg/kg/min | Vasopressin: 0 units/min | Dobutamine: 0 mcg/kg/min

Lasix Routes:  Lasix bolus,  Lasix drip

Assessment date: 23-Oct-04 | Assessment time: 10:09 | Next assessment: 14:09

DATA EXPLANATION: UNITS

CONFIRM Accept or Decline Instructions	Accept	Decline	UNITS
<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Decline	KVO IV, Also, minimize as much as possible all other fluid volume (e.g., for	10.09
<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Decline	Increase Lasix Bolus to 40 mg. Reassess in 4 hours.	10.09

**Figure 10** Computerized FACTT protocol bedside screen. The shaded fields indicate mandatory data required for a protocol instruction to be generated. *Abbreviation:* FACTT, Fluid and Catheter Treatment Trial.

**FACTT PROTOCOL Patient Data Entry**

Patient Name: Test, Alice | Age: 32 | BWP: 65 | Location: 1 | Treatment Group: CVC | Treatment: Conservative | Protocol requires all data in yellow boxes | Demographics: | Last Doses: | Previous Meds: | Off protocol Rx: | Saved Instructions: | Fix Errors

Systolic BP: 120 | Diastolic BP: 67 | Mean BP: 95 | Heart Rate: 120

Urine [since last entered] | Volume (ml): 70 | Interval (minutes): 60 | mL/hr: 70 | mL/kg/hr: 1.08

Serum Creatinine: 1

Pright atrial or CVP: 17

Check here if Dialysis planned or done < 48hours

After Completing Data Entry CLICK here for Treatment INSTRUCTIONS

Dopamine: 0 mcg/kg/min | Norepinephrine: 0 mcg/kg/min | Epinephrine: 0 mcg/kg/min | Phenylephrine: 0 mcg/kg/min | Vasopressin: 0 units/min | Dobutamine: 0 mcg/kg/min

Lasix Routes:  Lasix bolus,  Lasix drip

Assessment date: 23-Oct-04 | Assessment time: 10:09 | Next assessment: 14:09

DATA EXPLANATION: UNITS

Intravascular Pressure				MAP < 60 or on dopamine > 5 or any dose of another vasopressor	MAP >= 60 mm Hg AND off vasopressors (Dopamine <= 5 mcg/kg/min is not a vasopressor)			
CVP		PAOP			Average UOP < 0.5		Average UOP >= 0.5	
Con	Lib	Con	Lib	Ineffective Circulation CI < 2.5 OR Skin Findings	Effective Circulation CI >= 2.5	Ineffective Circulation CI < 2.5 OR Skin Findings	Effective Circulation CI >= 2.5	
Range I				1	3	7	11	15
>13	>18	>18	>24	KVO, DOB Lasix	KVO, Lasix	KVO, DOB Lasix	KVO, Lasix	
Range II				2	4	8	12	16
8-13	15-18	13-18	19-24	KVO, DOB	KVO, Lasix	KVO, DOB	KVO, Lasix	
Range III				3	5	9	13	Liberal: 17 KVO
4-8	10-14	8-12	14-18	Fluid bolus	Fluid bolus	Fluid bolus	Conserv: 18 Lasix	
Range IV				4	6	10	14	Liberal: 19 Fluid bolus
<4	<10	<8	<14	Fluid bolus	Fluid bolus	Fluid bolus	Conserv: 20 KVO	

**Figure 11** Computerized FACTT protocol bedside screen display of the paper-based protocol with the appropriate cell circled. *Abbreviation:* FACTT, Fluid and Catheter Treatment Trial.

wants a visual display of the paper protocol used by the NIH/NHLBI ARDS Network for the FACTT study, a button click displays the paper-based protocol table with the cell in which the patient currently falls circled in red (Fig. 11). If the bedside clinician wants a display of the footnotes for that specific cell, a click on the cell reveals the cell-specific footnotes (Fig. 12). A clinician or knowledge engineer can examine the logic frames used in the generation of a specific instruction (Fig. 13). The logic on which any protocol table cell (Fig. 14) is based can also be viewed in the logic tree display, either as an overview (Fig. 15) or in detail (Fig. 16). Once the instructions are accepted by the bedside clinician, the screen displays a countdown timer indicating the time remaining until the next protocol-mandated subject evaluation (four hours in Fig. 17).

Computerized protocols avoid many bedside user errors of interpretation commonly made with paper-based protocols. For example, the first two or three FACTT clinical trial patients enrolled at each of 15 NIH/NHLBI ARDS Network hospitals received clinical interventions that deviated from the protocol instructed action 30% of the time (315 paper-based bedside protocol instructions in 20 patients). Ninety-three percent of these errors were due to misinterpretations of the complex protocol footnotes (Fig. 12), not to misidentification of the correct protocol table cell (Fig. 11). This was likely due to the complexity of the protocol instruction details. The footnote for Dobutamine administration in the FACTT protocol for Cell 3 (Fig. 11)

FACTT PROTOCOL Patient Data Entry

Patient Name: Test, Alice | Age: 72 | BWP: ES | Location: 1 | Treatment Group: CVC | Treatment: | Protocol requires all data in yellow boxes | Demographics: | Last Doses: | Previous Meds: | Off protocol Rx: | Saved Instructions: | Fix Errors

Systol	Intravascular Pressure		MAP < 60 or on: dopamine > 5 or any dose of another vasopressor	Average UOP < 0.5		Average UOP >= 0.5	
	DVP	PAP		Ineffective Circulation CI < 2.5 OR Skin Findings	Effective Circulation CI >= 2.5	Ineffective Circulation CI < 2.5 OR Skin Findings	Effective Circulation CI >= 2.5
Diastol							
Med							
Heart							
Pright atrial or							

**B. Furosemide (no diuretic substitution allowed):**  
 1. Withhold if:  
 a. vasopressor or a fluid bolus given last 12 hours OR  
 b. renal failure present (dialysis dependence) OR  
 c. oliguria with creatinine > 3 OR  
 d. oliguria with creatinine 0-3 and urinary studies indicative of acute renal failure

2. For cells 11, 15, 16, 18:  
 Begin continuous infusion of 3 mg/hour OR 20 mg bolus OR last known effective dose. Reassess in 4 hours; if still in a cell for which furosemide is indicated then:  
 a. If intravascular pressure has declined by one or more pressure ranges (rows) repeat the same dose as before, and then reassess in 4 hours.  
 b. If intravascular pressure range has not declined by one or more pressure ranges, and if average urine output over the preceding four hours < 3 ml/kg/hr, double the preceding dose and reassess in 4 hours. If average urine output over the preceding four hours > 3 ml/kg/hr, then give the same dose as before and reassess within 4 hours.  
 Maximum daily infusion dose = 24 mg/hour x 12 hrs (3 four hour cycles); maximum bolus dose = 160 mg x 4 hours x 3 doses.  
 If either the maximum daily infusion (24 mg/hr x 12 hrs) or maximum bolus dose sequence (160 mg x 3) is given, then do not give additional furosemide doses for 12 hours following the end of the 12 hour infusion or for 12 hours after the third 160 mg bolus.

DATA PLAN: | CONFIRM Access or Decline Instructions: | c4 | c10 | c8 | c14 | KVO

Protocol Table | Footnotes | Explanations

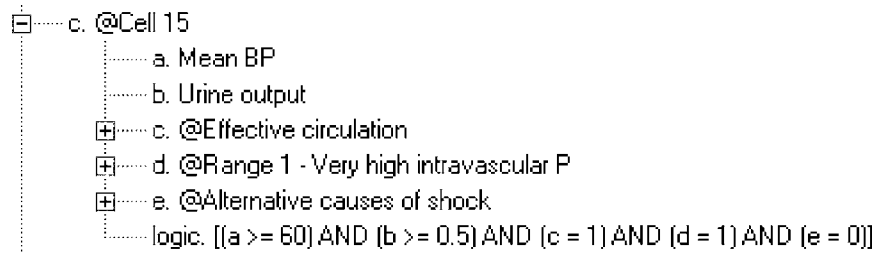
**Figure 12** Computerized FACTT protocol bedside screen display of the paper-based protocol with the appropriate cell footnote details after the bedside clinician taps on the circled cell. *Abbreviation:* FACTT, Fluid and Catheter Treatment Trial.

The screenshot shows the 'FACTT PROTOCOL Patient Data Entry' window. It is divided into several sections: Patient Information (Patient Name: Test, Bob; Age: 42; BWP: 65; Location: 1; Treatment Group: CVC), Vital Signs (Systolic BP: 100; Diastolic BP: 50; Mean BP: 67; Heart Rate: 120), and Laboratory/Other Data (Urine output, Serum Creatinine, Dopamine, Norepinephrine, Epinephrine, Phenylephrine, Vasopressin, Dobutamine). A central table lists protocol rules with columns for F# (Frame Number), Item Type, Finding, and Value. A 'CONFIRM or Decline Instructions' dialog box is open, showing options to 'Accept' or 'Decline' instructions like 'Give a Lasix Bolus of 40 mg (last effective dose)' and 'XVO IV: Also, minimize as much as possible all other fluids'. A 'DATA EXPLANATION' section at the bottom left provides details for the selected rule.

**Figure 13** Logic frame display that aids clinicians and knowledge engineers in evaluating and modifying protocol rules. Clinicians and engineers can examine the basis for a specific protocol instruction. Each logic frame used in the generation of the specific protocol instruction is highlighted.

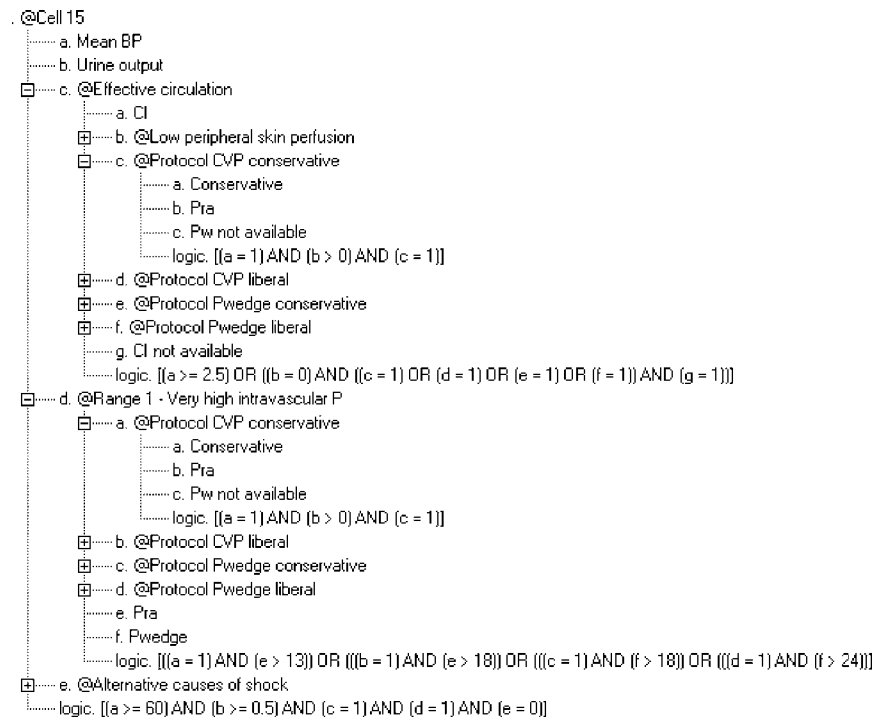
The screenshot shows the 'Frame Design' window. At the top, there are radio buttons for 'calculation', 'complex finding', 'boolean4', 'Frame Title', 'boolean3', 'boolean2', 'query2', and 'top'. Below this is a table with columns 'Frame#', 'Label', 'Finding', and 'Hiercode'. The table lists frames 234 through 238 with their respective labels and findings. Below the table is a logic expression:  $[(a > 60) \text{ AND } (b >= 0.5) \text{ AND } (c = 1) \text{ AND } (d = 1) \text{ AND } ((e >= 4) \text{ IAND } (e <= 8) \text{ IAND } (h = 1)) \text{ OR } ((f >= 8) \text{ IAND } (f <= 12))] \text{ AND } (g = 0)]$ . At the bottom, there is a small table with columns 'Frame#', 'Finding', 'Code', and 'Type', showing '222 Cell 15' with code '2472101837' and type 'boolean'.

**Figure 14** Logic tree partial detailed display for cell 15 of the FACTT protocol. Items with + sign have not been made more detailed for clarity. *Abbreviation:* FACTT, Fluid and Catheter Treatment Trial.



**Figure 15** Logic tree overview display for Cell 15 of the FACTT protocol. *Abbreviation:* FACTT, Fluid and Catheter Treatment Trial.

provides an example of the complexity that leads easily to incorrect bedside interpretations of the paper-based protocol. (The detailed footnotes are hidden and automatically interpreted correctly in the computerized protocol. They are available to view on command by the bedside clinician.



**Figure 16** Logic tree partial detailed display for cell 15 of the FACTT protocol. Items with + sign have not been made more detailed for clarity. *Abbreviation:* FACTT, Fluid and Catheter Treatment Trial.

FACTT PROTOCOL Patient Data Entry

Patient Name: Test, Alice | Age: 32 | BWP: 65 | Location: 1 | Treatment Group: CVC | Treatment: Conservative | Protocol requires all data in yellow boxes | Demographics: Toggle Timer | Last Doses: Previous Meds | Off protocol Rx | Saved Instructions: Fix Errors

Systolic BP: 120 | Diastolic BP: 57 | Mean BP: 85 | Heart Rate: 120

Urine (since last entered): Volume (ml): 70 | Interval (minutes): 60 | mL/hr: 70 | mL/kg/hr: 1.00

Serum Creatinine: [ ]

Pright atrial or CVP: 17

Check here if Dialysis planned or done < 48hours: [ ]

After Completing Data Entry CLICK here for Treatment INSTRUCTIONS

Dopamine: 0 mcg/kg/min | Norepinephrine: 0 mcg/kg/min | Epinephrine: 0 mcg/kg/min | Phenylephrine: 0 mcg/kg/min | Vasopressin: 0 units/min | Dobutamine: 0 mcg/kg/min

Lasix Routes:  Lasix bolus,  Lasix drip

Assessment date: 01-09-2005 | Assessment time: 15:28 | Next assessment: 19:28

DATA EXPLANATION: UNITS

CONFIRM Accept or Decline Instructions:  Accept,  Decline (Give a Lasix Bolus of 40 mg (last effective dose). Reassess in 4 hours. 15:28) |  Accept,  Decline (KVO IV. Also, minimize as much as possible all other fluid volume (e.g., for 15:28)

04:00:00

Protocol Table, Footnotes, Explanations

**Figure 17** Computerized FACTT protocol bedside screen display after the bedside clinician has confirmed acceptance of the protocol instructions. The countdown timer shows four hours remaining until the next FACTT protocol mandated patient assessment. This mandated assessment defines the longest allowed period between patient observations. Bedside evaluations are otherwise performed according to clinical need. If the patient is reassessed before the mandated maximum four-hour interval, the new data are entered in the bedside computer and the protocol rerun to obtain new instructions. *Abbreviation:* FACTT, Fluid and Catheter Treatment Trial.

Having captured this decision-making detail in an easily reviewed form at the bedside is an educational asset.) “Inotrope: If heart rate (HR) < 150/min for >12 hours and right atrial pressure (Pra) < 18 mmHg or echocardiography fails to reveal septal shift or right ventricle (RV) dysfunction, then give Dobutamine: start at 5 m/kg/min. ↑ by 5 q 30 to 60 minutes to 20 mg/kg/min max. If peripheral perfusion adequate for >4 hours ↓ 2 μg/kg/min q 1 to 2 hours as tolerated. Otherwise give Milrinone: loading dose 50 μ/kg undiluted IV over 10 min, then 0.375 μ/kg/min. ↑ by 0.125 q 30 to 60 minutes to 0.75 μg/kg/min max.”

The benefits of computerized protocols, compared with paper-based protocols, are clear. The computerized protocol incorporates all of this footnote complexity plus additional detail but it remains transparent to the bedside user (although the underlying logic and details are available upon demand). The user only enters a few data elements and then reads

the computer-generated patient-specific therapy instruction (see example in Table 1). The bedside clinician can always decline the instruction if there is a compelling reason to do so.

The bedside computerized protocols can standardize clinical decisions and can reduce noise associated with both the experimental intervention and with cointerventions (34,35,131,135). The use of explicit detailed methods for the experimental therapies and for the general care of the patient will increase the probability of finding clinically significant and relevant differences between the experimental groups.

#### *Blood Glucose/IV Insulin Protocol*

A computerized blood glucose/insulin protocol was developed, refined, and implemented using the Utah Clinical Trials Toolbox. The bedside computer screen (Fig. 18) is simpler than that for the FACTT trial (Fig. 10). The blood sugar and insulin IV infusion values are displayed with the resulting treatment instructions and a countdown timer that indicates the remaining time until the next scheduled blood sugar evaluation. If desired, the clinician can display the protocol instructions, whether accepted or declined, and the blood glucose values (Fig. 19). The clinician can choose a graphical display as well (Fig. 20).

The computerized protocols compute the insulin dose based on the deviation of measured blood glucose from the center of the target range, the rate of change of blood glucose, and the current insulin dose. The computerized blood glucose protocol has been used as a stand-alone bedside tool in a laptop PC. Through 2003, LDS Hospital clinicians encountered no blood glucose values less than 40 mg/dL in either higher (target range 121–180 mg/dL) or lower (target range 81–115 mg/dL) glucose protocols. Clinician compliance with protocol instructions was 85% with a paper-based and 97% with the computerized protocols (see clinician compliance in Table 3).

#### *Web-Based Tools*

Our current Web site functions (Fig. 21) include the Web screen for transfer of clinical coordinator data to the study monitors at the clinical coordinating center (Fig. 22). This is only one of the Web pages within a Web tool that facilitates (i) data transfer from the local site clinical coordinator to the Web server; (ii) data-field-specific query and answer exchanges between the local site clinical coordinator and the central Clinical Coordinating Center monitor; (iii) administrative functions that include document version tracking and archiving, meeting and conference call scheduling, etc.; and (iv) questionnaire functions that link the clinical sites with the central Clinical Coordinating Center (Massachusetts General Hospital, for our ARDS Network clinical trial).

**Test, HRW1**  
 Utilities Special Development

Patient Name	Glucose protocol	MRN
Test, HRW1	80-110	2222001

Assessment date: 26-Nov-04      Assessment time: 09:00

Serum glucose

Insulin drip       Feeds running     Feeds off

D50W

Insulin bolus

Click here if you're back charting

**Get Instructions (manual data entry)**

     **Next assessment:**

**Accept**    Start IV insulin at 1.5 Units/hour    09:00  
 **Decline**

**Trends**

Saved Instructions

**Patients**

Close

**Figure 18** Computerized glucose/insulin protocol bedside screen.

*Education and Training Tools*

These tools can minimize the training and technical skill needed to conduct a rigorous clinical study by using common electronic tools (Utah Clinical Trial Toolbox) to provide an interoperable information interchange infrastructure. We plan to expand the current “help-on-demand” and step-by-step

Recommendations Review						
Ascending						
Date	Time	Recommendation	Accept	Glu	Reason/Comment	User
25-Nov-04	13:00:00	In range. No change.	Yes	110		
25-Nov-04	14:00:00	Start IV insulin at 1.3 Units/hour	Yes	160		
25-Nov-04	15:00:00	Increase IV insulin to 2.6 Units/hour	Yes	240		
25-Nov-04	16:00:00	Increase IV insulin to 5.2 Units/hour	Yes	320		
25-Nov-04	17:00:00	Increase IV insulin to 10.4 Units/hour	Yes	400		
25-Nov-04	18:00:00	Increase IV insulin to 20 Units/hour	Yes	400		
26-Nov-04	01:00:00	Maintain IV insulin at 20 Units/hour. Alert physician of high insulin dose.	Yes	400		
26-Nov-04	02:00:00	Maintain IV insulin at 20 Units/hour. Alert physician of high insulin dose.	Yes	340		
26-Nov-04	03:00:00	Maintain IV insulin at 20 Units/hour. Alert physician of high insulin dose.	Yes	280		
26-Nov-04	04:00:00	Maintain IV insulin at 20 Units/hour. Alert physician of high insulin dose.	Yes	220		
26-Nov-04	05:00:00	Maintain IV insulin at 20 Units/hour. Alert physician of high insulin dose.	Yes	160		
26-Nov-04	06:00:00	In range. Stop insulin.	Yes	100		
26-Nov-04	07:00:00	In range. No change.	Yes	90		
26-Nov-04	08:00:00	In range. No change.	Yes	100		

Figure 19 Computerized glucose/insulin protocol instruction history.

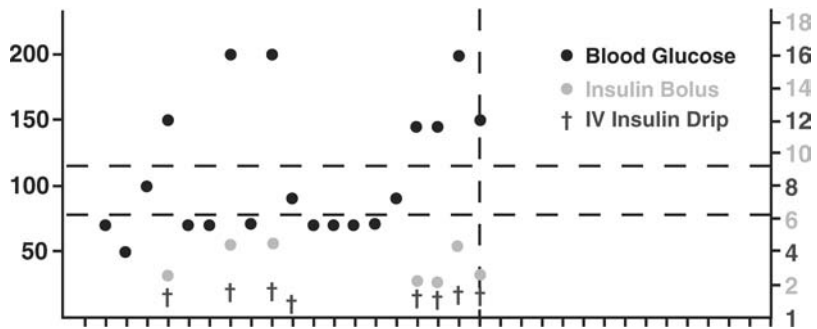


Figure 20 Computerized glucose/insulin protocol graphical data display.

**Table 3** Blood Glucose Experience Without and With Both Paper-Based and Computerized Protocols at LDS Hospital Shock-Trauma ICU from 1994 Through 2003

Year	Protocol type	Number of patients	Number of blood glucose measurements	Blood glucose (mg/dL)		% Blood glucose < 60 mg/dL	% Instructions accepted by clinicians
				Target range	Mean ± SD		
1994	None	~450	> 4,000	-	180 ± 68	0.8	-
1999-2002	Paper	~1600	> 16,000	121-180	145 ± 40	0.5	85
2002-2003	Computer	34	658	121-180	149 ± 31	0	97
2002-2003	Computer	26	1,105	81-115	120 ± 34	1	97

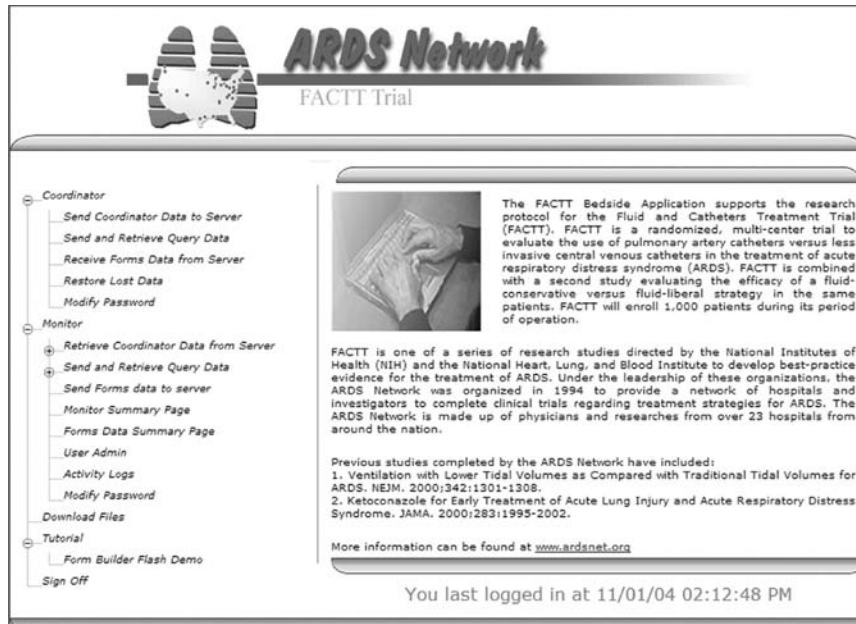


Figure 21 Utah Clinical Trial Toolbox Web site home page.

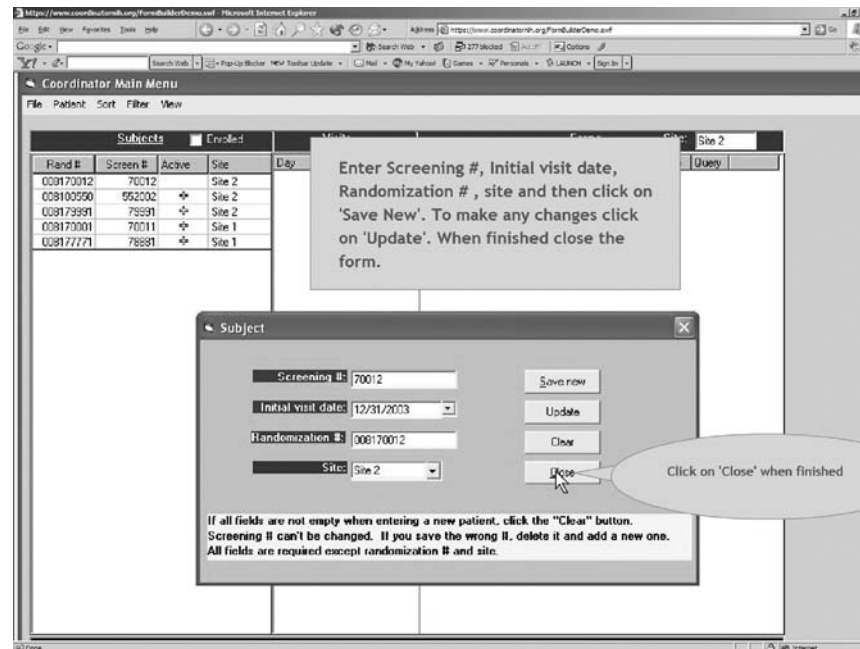
animated tutorials built with the Flash MX<sup>®</sup> application. We have developed a clinical coordinator tool step-by-step tutorial that replaces a personal educator (Fig. 23).

*Current Application of Bedside Protocols*

Computerized protocols are currently routinely used for clinical trials in the hospitals of the Utah Critical Care Treatment Group of the NIH/NHLBI



Figure 22 Utah Clinical Trial Toolbox clinical coordinator page for uploading data to the Web site server.



**Figure 23** Computerized FACTT clinical coordinator application tutorial. *Abbreviation:* FACTT, Fluid and Catheter Treatment Trial.

ARDS Network. Application of three computerized protocols in ICU patients and in subjects enrolled in NIH/NHLBI ARDS Network clinical trials from 15 June to 30 September 2004 is summarized in Table 4.

#### IV. Summary

Intensive care accounts for 20% of the total hospital health care expenditures in the United States. Although the majority of care occurs in adult ICUs, pediatric critical illness is a source of significant short- and long-term morbidity, and care of these children consumes significant health care resources. Currently, well-designed adequately powered clinical trials are uncommon in adult and rare in pediatric critical care.

Currently operational integrated electronic tools such as the Utah Clinical Trial Toolbox can expedite the conduct, improve the data and research quality, and increase the efficiency of ICU clinical research. This requires the medical community to adopt a new ICU clinical investigative strategy that utilizes electronic tools to link many different clinical sites into an extended human experimental research laboratory. Currently available

**Table 4** Computerized Bedside Protocol Experience with the Utah Clinical Trial Toolbox for FACTT (NIH/NHLBI FACTT) Subjects at the Utah Clinical Site from 15th June Through 30th September 2004

Hospital	Hospital care type	Total number of hospital beds	Protocol	# Patients	# Hrs protocol use	# Instructions	% Instructions followed by clinicians
Alta View Cottonwood	Primary	72	FACTT fluid	1	10	7	100
	Secondary	180	FACTT fluid	2	212	65	91
			FACTT mechanical ventilation	1	279	190	92
LDS	Tertiary	467	Glucose	70	8,823	3,695	94
			FACTT fluid	3	493	222	85
			FACTT mechanical ventilation	2	311	234	94
Total				79	10,128	4,413	93

*Abbreviations:* FACTT, Fluid and Catheter Treatment Trial; NIH, National Institutes of Health; NHLBI, National Heart Lung and Blood Institute.

decision-support tools can provide the adequately explicit methods needed for this extended laboratory. These adequately explicit methods can elicit identical responses from different clinicians when faced with identical clinical data. Importantly, the adequately explicit methods preserve individualized, patient-specific treatment. This large-scale clinical laboratory could more efficiently conduct clinical ICU studies and, with the same common electronic tools, could more rapidly extend ICU research results to clinical ICU practice than is currently possible. The use of adequately explicit detailed computerized bedside protocols should increase the probability of finding differences between experimental groups. This new strategy should enable investigators to uniformly implement and distribute knowledge-based ICU care and to address ICU clinical problems such as lung-protective ventilation that have defied resolution with traditional clinical investigation approaches.

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