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Perspective

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Enabling a learning healthcare system with automated computer protocols that produce replicable and personalized clinician actions

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ABSTRACT

Clinical decision-making is based on knowledge, expertise, and authority, with clinicians approving almost every intervention—the starting point for delivery of "All the right care, but only the right care," an unachieved healthcare quality improvement goal. Unaided clinicians suffer from human cognitive limitations and biases when decisions are based only on their training, expertise, and experience. Electronic health records (EHRs) could improve healthcare with robust decision-support tools that reduce unwarranted variation of clinician decisions and actions. Current EHRs, focused on results review, documentation, and accounting, are awkward, time-consuming, and contribute to clinician stress and burnout. Decision-support tools could reduce clinician burden and enable replicable clinician decisions and actions that personalize patient care. Most current clinical decision-support tools or aids lack detail and neither reduce burden nor enable replicable actions. Clinicians must provide subjective interpretation and missing logic, thus introducing personal biases and mindless, unwarranted, variation from evidence-based practice. Replicability occurs when different clinicians, with the same patient information and context, come to the same decision and action. We propose a feasible subset of therapeutic decision-support tools based on credible clinical outcome evidence: *computer protocols leading to replicable clinician actions (eActions). eActions* enable different clinicians to make consistent decisions and actions when faced with the same patient input data. *eActions* embrace good everyday decision-making informed by evidence, experience, EHR data, and individual patient status. *eActions* can reduce unwarranted variation, increase quality of clinical care and research, reduce EHR noise, and could enable a learning healthcare system.

INTRODUCTION

Our healthcare culture blocks development of a learning healthcare system

The current decision-making model is based on clinician knowledge, expertise, and authority/autonomy, with clinicians approving almost every intervention. Healthcare culture is inexorably linked to this expert-based model ("Era 1"[1]). Culture has been described as the "software of the brain."[2] New information indicates that culture can also modify the structure of the brain, changing people's biology independent of genetics, thus adding a new dimension to cultural considerations.[3] However, this culture is only the starting point for delivery of credible evidence-based healthcare interventions. The

Table 1. Comparison of different clinician decision-support strategies

Strategy	Intervention (Transfer Function)	Automated Action?	Clinician Compliance[a]	Clinical Outcome Credibility	Variation		Outcome Replicability
					Warranted Mindful	Unwarranted Mindless	
Top-down, system focus	CQI, 6-σ, Zero patient harm, care process, guideline, protocol	① No	Low (15%–40%) (31, 32)	Low	Yes: default[b]	Common ~50%	Low (15%–40%)
Bottom-up, clinical problem focus	*eActions*→ Adaptive, personalized patient care decision/ action	② No ③ Yes	High (~95%) Highest (~100%)	High Highest	Yes: default[b] Yes: not default	Small (0.3%) No	High (~95%) Highest (~100%)

Abbreviation: CQI, continuous quality improvement.

[a]with best evidence-based care.

[b]Yes: possible; Default: deciding clinician must approve each decision/action.

expert-based model is necessary but not sufficient for delivery of "All the right care, but only the right care" (p. 1[4])—a healthcare quality improvement goal yet to be closely approached. In this paper we focus on treatment (similar to a management system[5]) not diagnosis, since replicable clinician actions are currently more easily achieved for treatment.

Decades of compelling evidence indicate unaided clinicians suffer from cognitive limitations and biases when decisions are based only on training, expertise, and experience.[3,5–12] Almost all resources for improving healthcare outcomes support ordinary guidelines and protocols and processes (eg, quality improvement,[4,13] education,[14–16] and training[17]) (Table 1, row 1). These produce improvements but fail to approach achieving "All the right care, but only the right care." The behavioral economics strategy of making it "easy to do it right," consistently and rationally linking action to best evidence, is in natural tension with healthcare culture and the clinician's concept of decision autonomy.[1,18–20] Healthcare culture is thus a barrier to implementation of many potentially useful computer applications.[12,21] We argue that surmounting the cultural barrier and generating a true learning healthcare system will require a "bottom-up"[22,23] clinical problem-focused redesign that virtually eliminates random and systematic noise *due to variable clinician decisions*. Such a system can produce almost noise-free clinical EHRs and replicable clinical outcome results.[24–27]

Clinician variability in treatment decisions/actions

Clinician treatment decisions/actions vary widely.[1,28–30] Adults and children only receive recommended care about 50% of the time,[31–33] reflecting a significant treatment gap.[12,34–39] Desired, mindful, clinician variation can contribute new insights in some situations, such as the COVID-19 pandemic.[11] However, individual clinician decision-making is commonly associated with mindless[11,12] or unwarranted variation (deviations from best practice, not based on evidence or patient preference),[40,41] and associated with waste, morbidity, and mortality.[4,28,42–47] Even specialists claiming to follow best evidence do not consistently do what they say.[5,8,48–52] Widespread overestimation of professional self-confidence seems to contribute to this variability in clinician decision-making,[9,10,53] for example "…professionals often make decisions that deviated significantly from… peers, from their…prior decisions, and from rules… they… claim to follow" (p. 40[10]). This variation increases with urgency or acuity and can result both from variable clinician responses to task and information overload and incentive misalignment.[54–56] These responses reflect undefined and unrecorded individual clinician beliefs, biases,[3,5–12,29,30] and decision rules that, while preserving limited cognitive resources,[56–59] impede deep attention required to address complex problems.[60] The responses lack underlying clinician decision rationales and confound assessment of clinical outcomes of trials, observations, and large data sets (big data).[55,61,62]

Unwarranted variation, for example, in transfusion or blood glucose targets,[29,30] impedes replicability and introduces systematic noise (bias) into clinician decision-making and thus into the EHR database. This noise, unlike random noise, cannot be overcome by increasing the number of observations. All noise impedes accurate machine learning[61,62] and thus impedes achievement of a sorely needed learning healthcare system. Limited availability of appropriately granular and interoperable EHR data is also an impediment. In addition, choice of machine learning strategy introduces variability.[63] Some computer applications can reduce a major source of both random and systematic (bias) EHR noise by almost eliminating variation in clinician decision-making called "unwarranted[40,41]" or "mindless[11,12]". This is a long-recognized problem.[28,64] We assert that reducing noise will increase the EHR signal-to-noise ratio[65,66] enabling a learning healthcare system[21,67–75] and improving important clinical outcomes.[52]

Replicability

Replication of results is a cornerstone of science and experimentation.[76–81] This is not always possible in clinical settings[82] but is generally recognized as an important goal even in settings difficult to control, like surgery.[83,84] In many clinical settings where evidence and heuristics are available, thoughtful and replicable detailed clinician decision-making methods produce more consistent evidence-based care across clinicians, time, and institutions.[5,24–27]

This construct began in earnest with paper-based protocols in clinical psychology[85,86] and automatic electroencephalographic control of general anesthesia[87] about 70 years ago, without broad adoption. Over forty years ago, closed-loop[66,88] computer protocols automatically controlled left atrial pressure post-operatively[89] with vasoactive drugs[90] and blood products.[91] *Replicability* occurs when the same patient information and context lead different clinicians to the same decision and action.[24,25,27,55,92–100] Such *replicability* of clinician actions (interventions) helps assure scientific validity of experimental and observational studies.[76,101–103] This replicability links interventions with evidence, increasing appropriate and effective care, enhancing research by reducing noise from unwarranted variation, supporting artificial intelligence utility, and perhaps in-

creasing teaching consistency.[104] Widely distributed replicability might also reduce racial and ethnic care disparities, as long as rules appropriately attend to racial differences.

Detailed computer protocols

In seeking benefits that outweigh risks, clinicians practice clinical "arts" through desired, mindful, clinician variation.[11,12] Absent guiding evidence or patient preferences, "artful" clinical decisions/actions must be determined exclusively by clinicians, usually during patient–clinician interactions, with contextual integration of clinician expertise and available information. However, complex healthcare challenges include diversity, quality, access, information overload, provider burnout, ethical dilemmas, and cost. Clinicians often make decisions and take actions without incorporating all available, and often overwhelming, evidence.[11,12,20,54,55,93,105,106] Well-designed computerized decision-support tools, based on comprehensive evidence and expert clinician logic/judgment, can help clinicians incorporate this evidence.[107,108] Expert clinician logic/judgment is captured through an iterative development process that includes elements of conflict resolution and enough comprehensive patient input detail to generate both patient and time-specific care instructions.[92,96] This overcomes the shortcomings of most decision-support attempts.[6] Decision-support rules are thus developed asynchronously, during tool generation before the patient–clinician encounter.[96] During the encounter, these tools function synchronously as a surrogate expert consultation and can unburden the overburdened clinician.[20] These tools generate *replicable*, detailed, patient and context-specific, evidence-based decisions/actions distributed across clinician roles and disciplines. Schwartz discussed, 50 years ago, the yet unrealized potential for computers to change medical practice. He claimed "…computer *as an intellectual tool* can reshape the present system of health care" (*italics* added, p. 1257[109]).

Unfortunately, current EHRs do not fulfill this vision. Indeed, by requiring many detailed, task-oriented interactions, they can be counterproductive and contribute to clinician burnout,[20] and impede experienced clinicians from deep clinical thinking and from applying clinical "arts."[20,110,111] Appropriate and automated tools can maximally relieve clinicians of this current EHR burden. We call these tools *eActions* to emphasize *replicable clinician actions* in contrast with decision aids that merely deliver replicable messages—an important distinction commonly overlooked.[112] *eActions* also enable rapid, detailed, and rigorous translation of clinical research results to usual clinical care[24] thus overcoming many barriers to diffusion of innovations that rely on learning and performance by individuals within complex institutions.[34,113–116] Translation of *eActions* from research studies to usual care is an extreme and effective version of the "make it happen" reengineering imperative for the spread of innovations in service organizations.[117] In addition, *eActions* operating automatically in a closed-loop manner[66,88] could diminish, or even eliminate, some important research strategy differences between detailed explanatory randomized controlled clinical trials (RCTs) and large simple, pragmatic, and comparative effectiveness trials. *eActions* could enable replicable methods to produce more robust explanatory trial results and enable more robust large multi-institutional trials with the same replicable method (replacing some pragmatic trials).[55] After completion of a trial, *eActions* can be immediately introduced into usual care and could become the basis of quasi-experimental or more rigorous comparative effectiveness trials[118–120] of modified *eActions*, thereby generating a learning healthcare system. A learning healthcare system could ameliorate the research uncertainties, and subsequent inappropriate care, associated with the use of biomarkers and other intermediate outcomes as surrogate endpoints for ultimate clinical outcomes.[121] *eActions* would be particularly helpful during difficult or novel situations that can overwhelm healthcare resources. Finally, automated *eActions* could extend automated computerized physician order entry,[122] respond to complexity[60] and decision-support challenges,[123] and maximally unburden clinicians during major threats like the COVID-19 pandemic.[124,125]

Human decision-making systems

Human decision-making involves 2 information processing systems: an automatic *effortless* cognitive system using large stores of knowledge and experience, and a deliberative conscious *effortful* system used for extreme decisions and requiring great attention.[56–59] The automatic effortless system often functions below awareness and resists change. The conscious effortful system is limited, more easily changed with information, and functions with full awareness. It is strictly conserved by avoiding deep rational thought whenever possible, a human behavior recognized for millennia.[126–130] Efforts to alter clinical context and improve decision-making generally address both systems and include: clinical guidelines and protocols; process improvement (eg, Continuous Quality Improvement,[13] Toyota Lean Methodology,[131] Zero patient harm,[132] 6-sigma[133,134]); ergonomic approaches like those pioneered by anesthesiologists to preclude incorrect device connections;[135] choice constraints (safe defaults requiring opting-out rather than opting-in); and team science studying organization, staffing, safety culture, and checklists.[11] "Nudging decision-makers toward default choices" is a common practice.[19,136,137] Many of these efforts (Table 1) are predominantly "top-down" *indirect* efforts that use marketing, training, and incentives to influence clinician decisions, but produce little change to internal motivation[20] because bedside decision-making remains largely done automatically with the effortless cognitive system. Conversely, rapid and large change can follow efforts that *directly* provide clinicians with evidence-based decisions/actions, but these require more strictly limited conscious cognitive clinician resources and require a change in the expert-based healthcare culture.[1,22,23] Removing some clinician task-focused decisions with decision-support tools would unburden clinicians and free cognitive resources to address higher-level complex situations and major therapeutic strategy decisions (the clinical "art"[20]). More simply, "bottom-up" *eActions*[23] that directly alter bedside clinician decision-making can lead to ~95% clinician compliance, even when not automated. *eActions* produce clinician actions tightly linked to credible evidence (Table 1, row 2).[24,25,27,55,92,96–100]

COMPUTER-PROTOCOLS LEADING TO REPLICABLE CLINICIAN ACTIONS

For *eActions* to be widely adopted they must be detailed, specific, and acceptable to clinicians. Acceptability depends primarily on demonstration of credible clinical outcomes and usability in practice. Unlike *eActions*, most clinical computer applications are difficult for clinicians to employ in practice.[138,139] Our previous publications labeled *eActions* with different names[25,27,55,92–94,96–99,140–142] (see Supplementary Materials for synonyms). *eActions* influence decisions/actions directly and indirectly by altering context (changing expectations, social motivation, administrative goals, etc).[24,25,27,55,92–94,96–100] *eActions* communicate specific decisions/actions based on the patient's current

state determined by multiple sources of data (eg, laboratory, imaging, the literature, patient trajectory, etc). Though they remain rare, we used *eActions* in multiple ways: as HELP system[143–145] embedded EHR rules or external EHR interfaced rules and as independent *eActions* computer applications.[24,25,27,55,92–100] *eActions* are usually activated by EHR data, avoiding double data entry. However, 1 independent *eActions* blood glucose management study required double,[25] and another required additional,[100] data entry. Remarkably, the bedside clinicians in 1 center[25] wanted to continue the double data entry for clinical care that they believed was improved, even though it increased their workload.

Usual guidelines, protocols, and most other decision-support tools or aids are not *eActions*. They encourage clinician decision independence with inadequately detailed messages (Table 1, row 1).[1,20,107,108] While these messages can be replicated, clinicians execute such messages differently except in simple circumstances.[11,146,147] Although commonly called medical algorithms,[107,148–159] a broad and loosely used term,[160] they are usually ambiguous flow-diagrams, tables, or rules and contain neither a precise list of steps, with temporal determinants, nor a clear stopping point (characteristics of mathematics and computer science algorithms).[107,108,161] For example, the declarative guideline message "achieve a normal hemoglobin A1c" is replicable but is insufficiently detailed to lead to replicable clinician actions. Similarly, an expert protocol goal for mechanical ventilation of acute respiratory distress syndrome (ARDS) patients (Supplementary Figure 1) is "… use the least PEEP and tidal volume necessary to achieve acceptable gas exchange while avoiding tidal collapse and reopening of unstable lung units."[162] This replicable statement can lead to many different specific interventions by different clinicians, or even by the same clinician at different times, because it lacks the detail required for the replicable clinician actions achieved by *eActions* (Figure 1). Replicable clinician actions are the target here. Replicability is more important than the specific clinical care *eActions* strategy chosen from the many available acceptable clinical care strategies.[164]

The patient, clinician, and healthcare delivery system are all complex systems, each with modeling challenges.[60,165] The rules and logic of *eActions* address and model only the clinician decision-maker.[55,96] This does not require that we know the "truth," or even all the input variables that might ultimately be revealed important. It requires only that we extract from clinicians, using robust established techniques, the way they make their decisions based on the information at hand.[55,92,96] Clinicians, like all humans, are cognitively limited with average short-term (working) memory limited to 4 ± 1 psychological constructs before decisions become degraded.[56–59,166] While many seem unaware of this ubiquitous limitation, it is expressed in multiple human activities including slide preparation,[167] risk assessment,[168] and stock trades.[169] Most studied subjects overestimate their competence and inflate their self-assessments.[49,50] Even personal beliefs are not consistently reflected in decisions.[5,8,48–51] Paradoxically, these human cognitive limitations reduce the number of input variables developers need to consider for any single *eActions* decision and thus enable individual decisions (protocol branch points) to evolve from structured and focused clinician thinking.[92,96] Any single *eAction* decision usually requires only 1–3 data inputs.[55,96] Because *eActions* may contain thousands of single decision rules, the total *eActions* information for all of its rules includes detail and integration typically difficult for humans to access and utilize[11,12,20,55,93,96,98,104–106,166] (see mapping terms, drug classes, administration routes, equivalent doses, step changes, etc, and detailed rules, in Supplementary Table 1). For example, the first *eActions*, for management of arterial oxygenation in a clinical trial of extracorporeal support for ARDS, consisted of approximately 40 flow-diagram pages.[94] In addition to treatment decisions, *eActions* rules could also indicate evaluations for rare causes of common problems, like inherited metabolic causes of pediatric seizures.

eActions embrace the nuances of defensible clinician decision-making informed by evidence, experience, laboratory and other EHR data and by individual patient trajectory including treatment response. Because *eActions*, automated or not, can electronically capture clinician responses to instructions, the detailed clinician decision/action directed care method is clearly documented.[24,25,96–98,100,170] Such knowledge of detailed methods is rare.[56] *eActions* not only produce replicable clinician actions, they also produce replicable clinical outcomes (Figure 2a and 2b).[24–26,94,171] For example, *eActions* eliminated all variation in blood glucose management and blood glucose value distributions between 4 ICUs in 3 US states and Singapore (Figure 2b). Interestingly, systems that incorporate clinician decisions, like all second-order or higher systems, can oscillate and fail if not properly damped.[65,66] We incorporated 3 common clinician decision strategies to damp *eActions* and prevent failure due to oscillation: waiting times, dead zones, and fuzzy logic membership.[172]

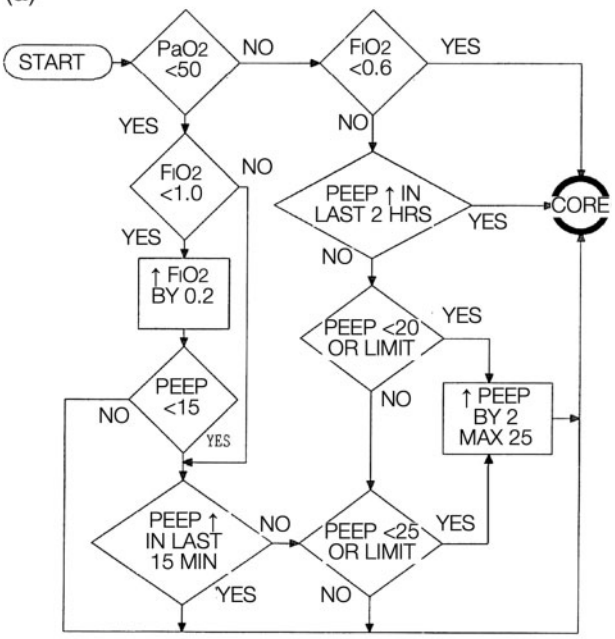
Understanding is a requirement for clinician acceptance of *eActions*.[140] Past work focused on *if–then* rule-based *eActions* because clinicians intuitively and easily understand *if–then* protocol rule logic. This was particularly important when *eActions* development began in 1986[173,174] and clinicians questioned *eActions*' ability to appropriately manage mechanical ventilation.[27,94,96,97,175] However, decision strategies other than *if–then* rules can also produce successful *eActions*. These include physiology-based computer models of bodily function for blood glucose homeostasis,[100,170] acid–base balance,[176–178] oxygenation,[179] and mechanical ventilation.[142,180] In fact, these computer model *eActions* may be easier to develop and more adaptable to changing clinical contexts than rule-based *eActions*.[100,141,142,170]

WHY HAVE *eACTIONS* LED TO REPLICABLE CLINICAL OUTCOMES?

We implemented *eActions* in multiple clinical contexts and at multiple institutions (Table 1, Figure 2).[24,25,27,55,92,96–100] The 95% clinician compliance with *eActions* instructions seems explained by 2 linked factors: initial credible favorable clinical outcome evidence[24,25,27,55,96] and clinician beliefs.[140]

We obtained favorable clinical outcomes, in the *intended clinical care setting*, during the initial iterative refinement of *eActions*[96] for mechanical ventilation,[27,94] blood glucose control,[25] and sepsis management.[98] These results armed *eActions* developers with favorable outcome evidence.[24,25,55,96,98] This outcome evidence attracted colleagues to join randomized *eActions* clinical trials and to review and critique the readily available *eActions if–then* rule logic.[26,27] In contrast, well-conducted and important RCTs of other detailed *if–then* rule-based computer-protocols did not appear to have presented favorable initial clinical outcome evidence to participating clinicians.[181,182] These computer protocols used EHR data including vital signs, symptoms, and functional class to generate guideline-based cardiac care suggestions like "Treat systolic dysfunction with ACE inhibitor unless allergic—ORDER Lisinopril 10 mg PO qAM."[181,182] In the absence of favorable initial prestudy clinical outcome evidence, participating clinicians might have lacked helpful

(a)



(b)

```
NO CHANGE TO VENTILATORY RATE.  SETTING REMAINS AT 29 BREATHS/MIN.

DECREASE MINUTE VOLUME SETTING BY   .6 FROM 12.0 TO 11.4 LITERS/MIN.

NO CHANGE IN INSPIRATORY % : SET INSP. % = 25% (if not already %25)

                    PLEASE WAIT 5 MINUTES
                     from 15:26 to 15:31
                 then chart new patient measurements.
              HASN'T BEEN 5 MINUTES - Strike <RETURN>

          Confirm the adjustments made to the ventilator

                    Minute Volume Setting (VE):   11.4
```

Figure 1. (a) Replicable rules from a small section of an early mechanical ventilation *eActions*. CORE = Continuous Respiratory Evaluation protocol. **(b)** Computer displays of an early (1988) mechanical ventilation *eActions*.[94,163] **(c)** More complicated section of rules for Continuous Positive Pressure Ventilation (1992).

motivation and beliefs that enable compliance with computer protocol instructions.[140] This may explain their disappointing RCT results reported for both heart[181] and lung disease.[182] In spite of documented differences in clinician patient management styles,[29,30] clinician beliefs in self-efficacy (the ability to reach an intended goal) and in *eActions* information accuracy, timeliness and trustworthiness, were associated with high compliance with individual patient-specific decisions/actions.[20,140]

ELEMENTS FOR SUCCESS

Based on past successes, we believe broad dissemination of *eActions* will likely require 7 elements (Table 2). The first 4 are supported by evidence.[55,92,93,96,98,100,141] The remaining 3 need to be systematically evaluated. We believe that healthcare business leaders are good assessors of returns on investment for value-based medicine economies. The healthcare industry, itself, should invest in *eActions* as they currently do for care processes (Table 1).

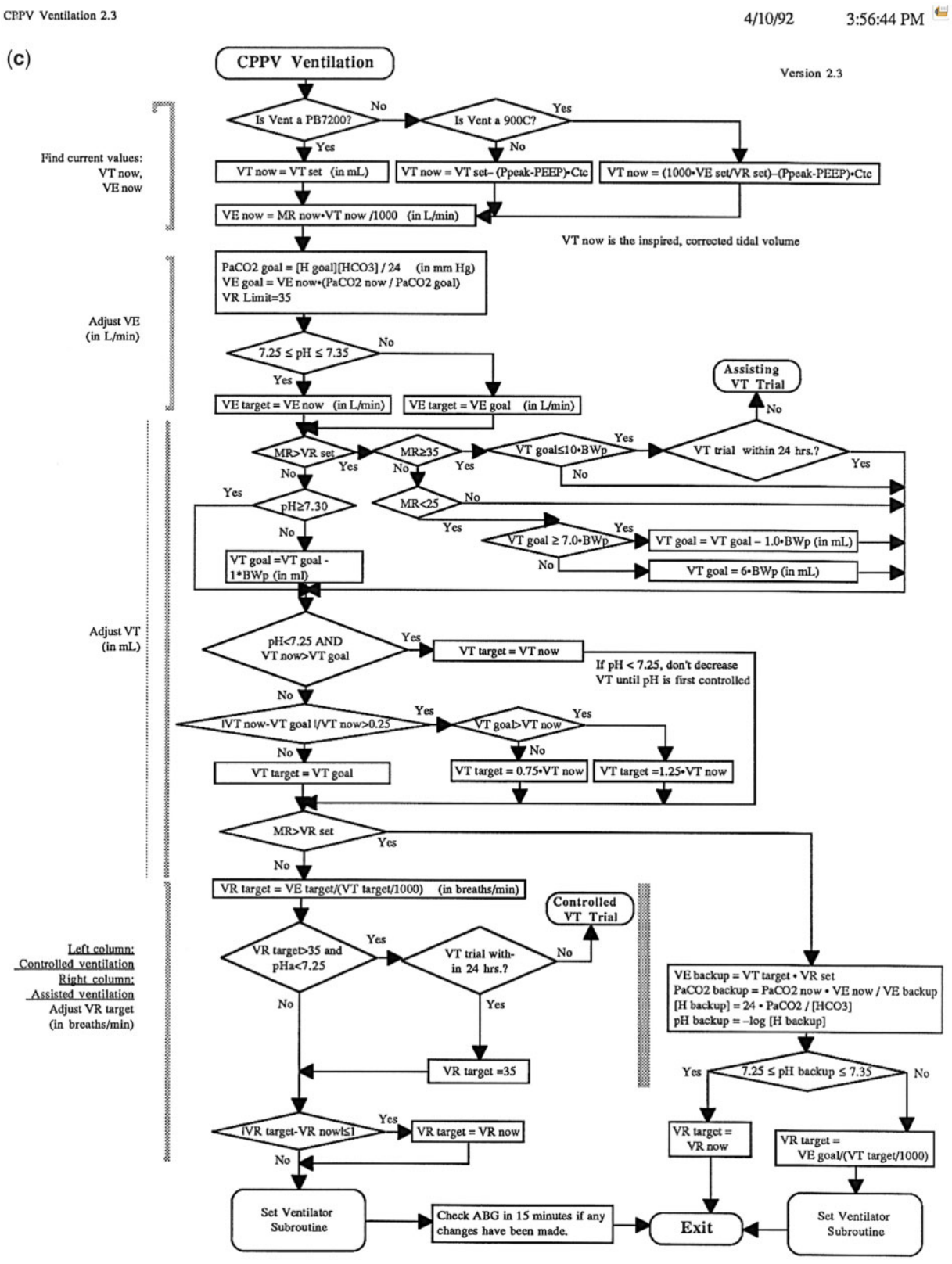


Figure 1. Continued.

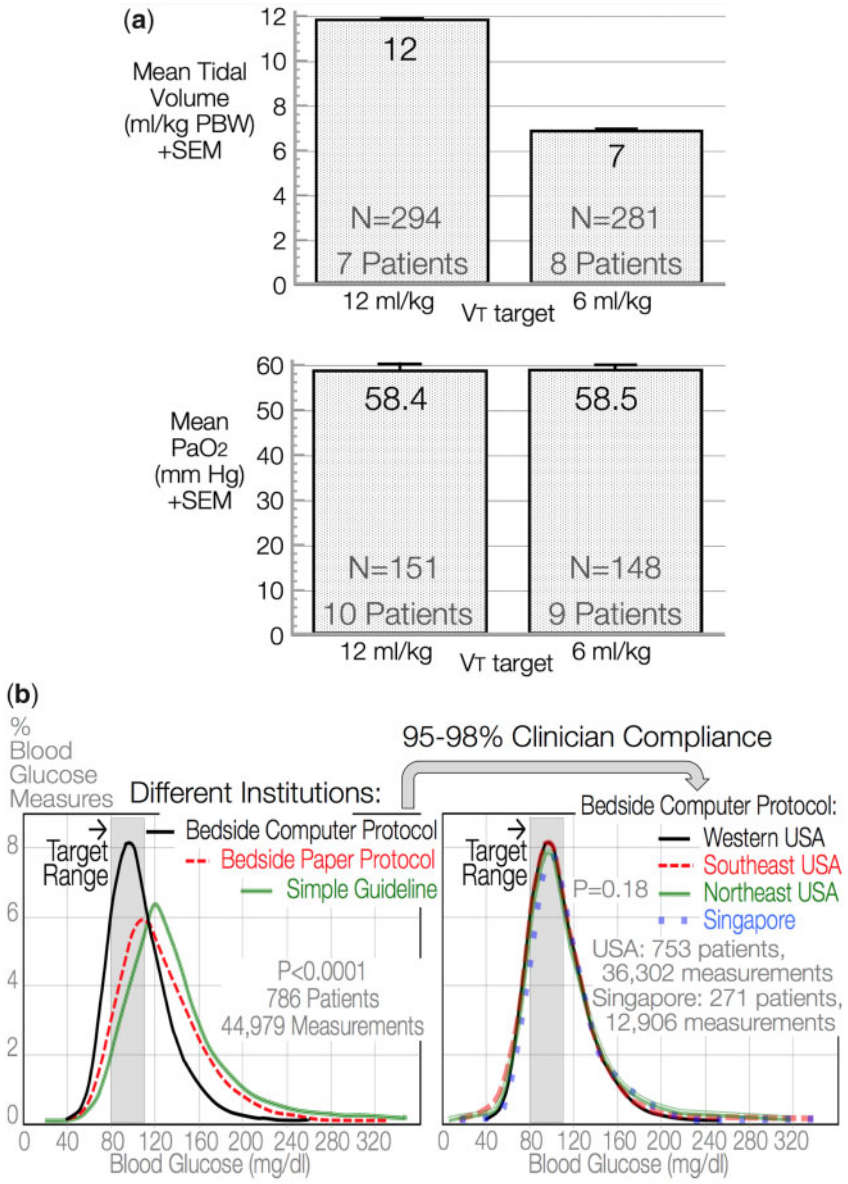


Figure 2. (a) Unpublished data (tidal volume, first 15, and PaO2, first 19 subjects) of an acute respiratory distress syndrome (ARDS) clinical trial[171] of mechanical ventilation *eActions*,[94] 72 hours after randomization in 6 and 12 ml/kg predicted body weight tidal volume target groups. VT = Tidal Volume, SEM = Standard Error of the Mean and N = measurement number. Replicable tidal volumes reflect rigorous control of the study intervention (VT targets not reached 100% of the time because of individual patient needs, although the *eActions* rules are identical except for the VT targets). Replicable PaO2 reflects rigorous control of this potential cointervention (a care element that can influence the study outcome and could obscure the impact of the study intervention). *eActions* PaO2 rules were identical for both tidal volume target group subjects. **(b)** Baseline distribution of ICU blood glucose values in multiple ICUs using different management strategies with an 80–110 mg/dl blood glucose target (left panel) and after exporting a bedside computer-protocol (*eActions*) to all US ICUs and to the National University Hospital of Singapore (right panel) with 95%–98% clinician compliance with *eActions* instructions—modified form.[25] This demonstrates replicability of clinician action (blood glucose value outcome), not correctness of blood glucose target.

WHERE MIGHT *eACTIONS* BECOME SUCCESSFUL?

The guideline for management of extracellular fluid retention in heart failure patients is mature and widely accepted,[184] though inconsistently applied.[185] We developed an *eAction* for managing fluid retention that could be formally studied (Supplementary Table 1). It could populate EHRs with complete, valid, and almost noise-free clinician decision-making data. This *eAction* could be automated via telemedicine to manage patients at home, unburdening not only clinicians but also patients and clinics through reduced visits. *eActions* would enable rigorous comparative studies of alternative care strategies proposed by thoughtful clinicians. This future heart failure work could enhance, for example, the current groundbreaking comparative study achievements of the Learning Healthcare System at Vanderbilt University Medical Center.[186–189] A hint of comparative studies potential was provided by the reuse of EHR data populated by an *if–then* rule-based blood glucose and insulin *eAction*.[25] These EHR data were reused as input data for a competing physiology-based blood glucose homeostasis *eAction*.[170] The investigators concluded the results from the competing physiology-based *eAction* were likely preferable to the original

Table 2. Elements for development of computer protocols leading to replicable clinician actions *(eActions)*

Element	Explanation
SUPPORTED BY PUBLISHED RESULTS	
1."Bottom-up" clinician leadership[23] dedicated to solving a specific clinician decision-making challenge[55,93,96,98,100]	"Bottom-up" *eActions* leadership is a simpler, problem-focused strategy and complements the more complex "top-down" information technology efforts common in healthcare. *eActions* development, iterative refinement, validation, and safety assurance is resource intensive and enabled by clinicians with passion for solving a particular problem. It is this clinician focus on specific discrete problems that makes *eActions* challenges soluble.
2.Multidisciplinary team dedicated to development and validation in the intended clinical use setting[26,55,92,96,98,183]	This team requires frontline clinicians interested in solving the specific clinical problem, information scientists and technicians, multiple professional disciplines, and administrators.
3.Easily understood intuitive screens and messages, using 1 unique self-explanatory term and appearance for each protocol construct or button	Many proprietary EHR systems fail to achieve this requirement of self-explanation that is important for ease of use by clinicians. Past *eActions* have been initiated clinically with as little instruction as the following: "put the blood glucose value here and follow the displayed instructions." This reduces time-consuming, expensive, current clinician education as clinical unit staff members change.
4.Iterative refinement and validation in a well-supervised clinical setting functioning as a human outcomes research laboratory, and producing credible clinical outcome data during refinement and validation of *eActions* rules[25,55,93,96,98]	Clinical care environments that have adequate supervision and control to function as a human outcomes research laboratory are rare. Past myocardial infarction research units attempted to do this by complementing the clinical care units, but they did not reach the level necessary for *eActions*. It is the *intended clinical care delivery unit* that should be the human outcomes research laboratory.
NOT YET SUPPORTED BY PUBLISHED RESULTS	
5.EHR-platform-independent, public domain *eActions*	Future widespread distribution of *eActions* will not be achievable or capable of proper curation if applications are installed within proprietary EHR systems. These EHR systems are unlikely to achieve the level of interoperability necessary to allow rapid revision of *eActions* rules when new evidence appears. A single cloud-based application using SMART on FHIR and other strategies now seems a solution that would allow proper curation, like the Agency for Healthcare Research and Quality "CDS Connect" website (https://cds.ahrq.gov/cdsconnect).
6.Academic curation of the protocol	Academic curation requires constant vigilance of *eActions*, a requirement consistent with the concern raised by Schwartz regarding the danger of centralized clinical decision-making.[109] Such curation will likely require a change in current healthcare organizational culture and social pressure,[140] especially at academic sites.
7.Funding from healthcare industry sources	Funding from healthcare industry sources seem necessary since neither the initial rule development investment required for *eActions*[96,98] nor *eActions* curation needs are met by current research funding sources. The return on investment can justify the business decision by the healthcare industry. For example, the original *eActions* mechanical ventilation research protocol[27] was subsequently seamlessly translated to clinical care and consistently delivered lung-protective ventilation to Acute Respiratory Distress Syndrome patients.[24] This *eActions* generated about 2,000,000 protocol care instructions in about 22,000 patients during about 3 decades at the original development hospital[27,55,92] and at 1 of the collaborating research sites.[97]

results from the *if–then* rule-based *eAction*.[141] In addition, we were able to explore, with the same *eActions* rules, the impacts of 2 different blood glucose targets for ICU patients managed with intravenous insulin[190] and compare performance in diabetic with that in nondiabetic patients.[191,192]

CHALLENGES AND LIMITATIONS

All decision-support tools, including *eActions*, incorporate beliefs, interpretations, and biases.[3,5–12,29,30,55,56,193,194] Consequently, rules must be defined wisely and consensually, be curated, incorporate clinical setting performance feedback, and deal with conflicts of interest and bias that may be present in guidelines adopted by prominent professional societies[195,196] or developed by commercial interests.[197] Credible clinically pertinent initial outcome data[24,25,55,96,98] provide important checks against suboptimal protocols that include improper bias and that may lead to incorrect instructions and patient harm.[195–197] Elimination of all clinician decision-making variation seems both impossible and undesirable.[11,20] Indeed, in situations where important uncertainty exists, alternative *eAction* designs that allow causal inference may be crucial to learning and reducing uncertainty. Circumstances outside the scope of *eActions*

rules and knowledge may suddenly emerge and be more easily captured with widespread use of *eActions*, than with current dependence on individual clinician recognition and reporting. The rules would subsequently, when appropriate, be modified through iterative refinement.[96] *eActions* would complement, not replace, other strategies currently employed in healthcare.

Complexity theory indicates that patient trajectories might, under some circumstances, be exquisitely sensitive to initial conditions, as in chaotic systems that sometimes make weather prediction difficult.[165] This exquisite sensitivity is imperceptible and hidden below measurement resolution. This theoretically might preclude patients with identical problems and the same comprehensive clinical input data from following the same trajectory.[60] We are unaware of any systematic clinical explorations of this potential complexity theory limitation. *eActions* would still enable different clinicians to achieve replicable actions and eliminate unwarranted variation. We believe that using the best available evidence to initiate therapy of even complex diseases, like glaucoma or insulin-dependent diabetes with multiorgan dysfunction and heart failure, is reasonable.[52] As long as we make relatively short-term decisions and use iterative refinement and intelligent decision-making rules to deal with those patients who do not respond in the expected manner to *eActions* instructions,[96] we assert this strategy will advance patient care.[60]

The totality of clinical problems amenable to *eActions* and to its widespread scaling both need exploration. Exploring more e*Actions* should help drive collection of more relevant and important clinical EHR data. We believe *eActions* will be widely applicable because human cognitive limitations[56–59,166] are ubiquitous and independent of healthcare discipline, disease, and clinical context complexity.[25,27,55,92–94,97,104] Both automated and nonautomated *eActions* are disruptive innovations not well addressed by mature businesses such as healthcare.[22,23,70] Funding for development, validation, implementation, and curation *of eActions* for multiple clinical problems will be important and should be provided by the healthcare industry. Not only will patient care quality increase (the face value imperative for moving ahead with this work) but profits might increase as well. One-quarter or more of clinical expenses are nonbeneficial wasted resources.[46,47,198–202] Broad application of *eActions* could reduce clinical waste. In addition to providing resources, healthcare industry acceptance will be key to providing environmental support, social pressure, and organizational cultural contributions that are important for clinician acceptance and compliance with *eActions* decisions/actions.[1,4,140] Admittedly, convincing the healthcare industry to fund work on *eActions* is challenging.[22,23]

Key to achieving healthcare culture change is not just individual compliance but also acceptance of the utility and value of our proposed *eActions* approach and linking it to clinician goals.[20,52,140] Clinicians will alter their behavior to comply with demands of employers, a widely recognized human response. Clinician deskilling[203,204] may occur and must be incorporated in assessment of risks and benefits of our proposed strategy. Although deskilling is declared an unavoidable consequence of civilization's advance (p. 42[205] and p. 29[206]), clinician deskilling does not have to occur.[207] Instructions for the use of our first *eActions* in the HELP computer system[144] clearly identified consistently applied principles and rules for mechanical ventilation of ARDS patients.[27,94,96,97] This enhanced our trainees' understanding, as was anticipated decades ago.[107,108]

CONCLUSION

Computer protocols leading to replicable clinician actions (eActions) reduce mindless, unwarranted variation in clinical care and research. *eActions* could improve both clinical care quality and research by unburdening overtasked clinicians and by reducing noise in clinical databases. Common current clinical decision-support tools or aids, including guidelines and protocols, neither enable replicable evidence-based actions, nor provide individual patient-specific care. *eActions* should be formally discussed and pursued, nationally and internationally, in our efforts to reduce clinician variation, improve care, and establish a learning healthcare system.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of this work, revised the drafts critically for important content, approved the final version, and are accountable for the arguments contained therein. AHM wrote the initial draft. The following authors participated as investigators in the past work discussed in this JAMIA Perspective: AHM, ML, JO, Jr, TPC, LKW, FT, CG, EH, TDE, CJW, MPY, DFS, MB, EB, KAS, SSP, GRB, BTT, RB, JDT, JS, RDH, DFW, JJZ, VMN, CJLN, JL, KHL, BPD, DKS, AW, PJH, UP, SR, DK, SA, DAS, DA, and MRP.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of the American Medical Informatics Association* online.

DATA AVAILABILITY

No new data were generated or analyzed in support of this perspective manuscript.

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CONFLICT OF INTEREST STATEMENT:

None declared.

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