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Simulation for clinical research trials: A theoretical outline ☆

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Abstract Although medical simulation has not been shown to directly save lives, mounting evidence highlights its ability to decrease clinical protocol violations, increase adherence to guidelines, decrease time to competence, enhance team performance, and increase patient safety. These clinical insights suggest that simulation might offer similar improvements in the design, enrollment, and execution of complex phase 3 clinical research trials. This article provides a theoretical outline of why and how this could be done.

Matching the simulation technique with the specific trial uses well-established principles from adult education and process engineering. The goal is to give participants the experiential and emotional involvement that fosters complex thought. Simulation can facilitate "dry runs," role playing, analysis of videos, and "what-if" discussions. Simulated interviews with actors might help with obtaining informed consent and thereby boost enrollment. Simulated phone calls might help with reporting adverse outcomes. Full-body mannequins might be used to confirm that teams can coordinate multiple complex steps.

Overall, the goal of simulation in clinical trials is to maximize realism while minimizing logistics and cost. While increased study is needed, this technique has considerable potential to decrease the risk to enrolled patients and to increase the accuracy of study data. Simulation provides an effective tool for immersive, interactive and reflective experiences. Overall, if simulation represents a "revolution in healthcare" then clinicians, patients, and now researchers, all stand to gain.

1. Background

Medical simulation replicates clinical experiences in an interactive and immersive manner, ideally suited for adult learners [1]. Therefore, simulation is vigorously endorsed by many professional societies [2-6]. Much of its impetus has centered on offering realistic experiential learning without patient risk. However, evidence also highlights simulation's ability to decrease clinical protocol violations, increase adherence to guidelines, decrease time to competence, and enhance team performance when compared with traditional methods [7-13]. Therefore, simulation has been recommended as a key technique for decreasing error, creating safer patient care environments, and mitigating the human factors that greatly influence clinical outcome [11-15]. These insights suggest that, in theory, simulation offers similar opportunities to improve

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Table 1 Potential benefits of incorporation simulation into clinical research

- Decrease early protocol violations
- Decrease protocol learning-curve
- Improve study design
- Improve training
- Increase participant enrollment
- Increase participant safety
- Increase data safety
- Increase confidence for the coordination center
- Help with the production of teaching materials

the design and execution of complex phase 3 clinical research trials (Table 1). This article outlines why and how this could be done.

2. Sources of protocol violation in clinical trials

A requirement of phase 3 clinical trials is that all enrolled patients have the same likelihood of experiencing a beneficial effect from the investigational therapy [16]. However these trials are routinely conducted at many sites and in multiple countries with varying practice patterns. As such, protocol violations occur, especially with the first few patients enrolled. In fact, for some trials, results were substantially different based upon whether data from the first few patients enrolled at each site are included or excluded [16-18]. Furthermore, protocol violations have been identified as a key component in the high rate of negative phase 3 clinical trials [16-19]. These violations can be due to the learning curve associated with mastering complex study protocols. They can also be due to site-specific factors (eg, local protocol implementation, local practice patterns), protocol-specific factors (eg, complex steps required by a protocol, protocol amendments) and patient-specific factors (eg illness severity, comorbidities) [16]. If a study protocol is violated, it often means a patient's data cannot be used. This decreases the statistical power of the research, delays study completion, wastes resources, and contributes to equivocal conclusions. It can also mean that promising therapies are prematurely abandoned [18,19].

Current research coordinator training usually involves self-study, investigator meetings, and didactic lectures. However, these strategies represent passive learning, which, when examined, has less effect upon performance or behavior compared to active techniques [13]. In contrast, proponents of both adult learning theory and simulation argue for immersive, interactive, and reflective experiences [1,7-14]. Therefore, if the goal is to decrease protocol violations, then simulation might provide an effective tool.

3. Decreasing protocol violations using simulation

Simulation has been shown to decrease clinical-protocol violations and shorten the clinical learning-curve [1,7-10]. As such, it might also decrease clinical-study-protocol violations and shorten the protocol learning curve. The first strategy would by optimizing study design. For example, just as with the introduction of any clinical protocol, it is important to ensure that study protocols are practical, that cumbersome steps are minimized, and that appropriate "fail-safes" or "double-checks" exist. Simulation has also been shown to improve team performance and to unearth unexpected latent errors within complex health systems [1,7-10]. As such, it also offers a second strategy, namely, a vehicle to train each study site before study commencement. In short, simulation offers a realistic "patient safety laboratory" [7] where the benefits seem equally applicable for clinical care and clinical research.

4. Principles of simulation

Many associate simulation with the use of expensive computerized mannequins. However, simulation is a technique, not a technology [1]. It can be divided into subtypes: role-playing, standardized patient, task trainers, screen-based simulation, the electronic patient, and immersive environments. Regardless, the common goal must be to give participants the experiential and emotional involvement that fosters complex thought and self-reflection [20,21]. Rather than merely listening to or watching others, participants learn best when they actively participate [13].

For some phase 3 clinical trials, simulation would mean performing "dry runs." This can include identifying potential patients, reviewing contraindications, or preparing and administering the correct drug dose. In other cases, simulation could include role-playing, analysis of videos, and "what-if" discussions. Examples include determining whether clinicians understand how and what to report to central registries and what factors mandate (or, just as importantly for investigators eager not to lose enrolled patients, *do not mandate*) the unblinding of patients and their removal from the trial. Simulation can also include simulated interview with actors (to obtain proper informed consent) and simulated phone calls (to report adverse outcomes). For other situations, screen-based simulations or Web-based simulations might suffice. Full-body mannequin might only be necessary to confirm that side-effects can be recognized or that teams can coordinate multiple steps. In short, simulation need not be onerous, but it must target the type of reflective learning rarely achieved after didactic teaching or from passively "thinking through" a problem [1,13,20,21]. The goal is also to maximize realism while minimizing logistics and cost. Simulation experts therefore