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Can Clinical Research Learn from the Patient Safety Movement?

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Abstract: *Since 1999, the patient safety movement in the United States has made important advances in preventing patient harm through three strategies: learning from its mistakes; identifying the quality gap between best practices and care as it is commonly given; and developing systems that track and analyze risk, harm, and potential harm. These three strategies from the patient safety movement could be adopted and implemented in clinical research to decrease the risk of preventable harm to subjects, improve compliance, and improve the overall conduct of responsible research.*

Introduction

In clinical practice, the patient safety world has been significantly influenced by three landmark reports from the Institute of Medicine (IOM). In 1999, *To Err is Human* began to describe and raise awareness of clinical care problems that resulted in harm and death to patients. The Institute of Medicine followed this with Crossing the Quality Chasm (2001) and Patient Safety (2004). While these landmark reports helped reshape the concept of safety in clinical care, they did not mention safety in clinical research.

Clinical research produces amazing science and discoveries that have improved the lives of many people. These benefits stem primarily from the dedicated efforts of the clinical research professionals who hold together a very segmented, fragmented, and fragile enterprise.

Common perceptions about clinical research include that it is conducted in tightly-controlled environments by highly qualified people and with rigorous measures exerted to ensure that things are done correctly. These perceptions have a basis in truth, but scratching beneath the surface, opportunities for quality and safety improvement can be identified.

It is likely that most clinical research professionals are aware of subjects in clinical trials injured as a result of a mishap in the research. The ability to quantify the extent of this harm is hampered by the lack of systems to collect and analyze these events across clinical trials. As a surrogate for measures of possible harm, three publications have reported on the structural and process risks involved with unsafe practices with investigational drugs. Similar to clinical practice, these risks increase the probability of subject harm due to preventable errors.

Young L, Haakenson C, Weber J, Tosch T. *National survey of pharmacy-coordinated investigational drug services*. Am J Hosp Pharm. 1984;41:1792–6.

Cruz JL, Brown JN. *Safety risks with investigational drugs: pharmacy practices and perceptions in the veterans affairs health system.* Ther Adv Drug Saf. 2015;6:103–9.

TABLE 1
Exploring Six Big Questions in Patient Safety

- What is the patient safety movement?
- How is patient safety different from drug safety?
- How large is the problem of preventable harm?
- How does the patient safety movement learn?
- Why should the clinical research enterprise care?
- Can clinical research apply similar lessons?

Jamie N. Brown, Sara R. Britnell, Andrew P.Stivers, Jennifer L. Cruz. *Medication Safety in Clinical Trials: Role of the Pharmacist in Optimizing Practice, Collaboration, and Education to Reduce Errors*. YALE JOURNAL OF BIOLOGY AND MEDICINE 90 (2017), pp.125-133.

Advances Made by the Patient Safety Movement
The national patient safety movement has made important advances in preventing patient harm by implementing three key strategies:

- Learning from its mistakes
- Instilling a culture of safety in the way that clinical care is provided and in the way that clinical care teams work together
- Developing systems that track/analyze risk, harm, and potential harm as well as the actions taken following unwanted events in clinical care.

No similar national movement exists in the clinical research enterprise to reduce preventable harm due to unsafe practices in research, flawed design, flawed infrastructure, failures in leadership, and failures in the work culture. Thus, there is a tremendous opportunity to bring the lessons learned from clinical care into clinical research. This paper will address six questions exploring lessons from clinical care that can be applied to improving clinical research (Table 1).

Question #1: What is the Patient Safety Movement?
Historically, individual professions such as pharmacy, anesthesiology, pediatrics, and nursing have done remarkable work, within their silos, to improve safety of their practices for decades. Arguably, the modern national patient safety movement began in 1996, at a multi-disciplinary conference *(Examining Errors In Health Care: Developing a Prevention,. Education and Research Agenda* held October 13-15, 1996 at the Annenberg Center for Health Sciences, Rancho Mirage, CA). This author attended the first conference that established a national agenda for safety in clinical care. This was followed by a series of conferences through 2001 that subsequently became a convening of the National Patient Safety Foundation.

Conference participants determined that the way forward should involve developing tools for safe clinical care and then using those tools to change the belief system of the providers of clinical care. Only by changing beliefs could practices be changed. The changed practices would be goal-oriented and evidence-based. The path forward also began to dismantle the professional silos, enabling providers from different backgrounds to learn the practices, culture, and systems in which each of the others worked and how these differences affected the overall workflow.

Clancey C and Berwick D. The Science of Safety Improvement: Learning While Doing Ann Intern Med. 2011;154(10):699-701.

Perla R, Provost L, Perry G. Seven Propositions of the Science of Improvement: Exploring Foundations. Q Manage Health Care 2013 Vol. 22, No. 3, pp. 170–186

Table 2 provides an overview of key themes of the Annenberg conferences, which began with raising the visibility of errors and preventable harm that occur in healthcare and setting a national agenda for change. A proposed approach to this was to change the thinking/culture about error and to put a face to error, so that it is not simply a number on the spreadsheet. Error and preventable harm become a story describing what the patient and the provider experienced.

Another key goal of the national patient safety movement was to shift thinking from individual blame to system errors as the root cause of most problems in healthcare. By moving blame away from an individual and focusing on the system, reporting would be encouraged along with a shared investment and effort in addressing the causes. Follow-on goals were to use error identification and reduction strategies proven effective in non-healthcare industries. Annenberg conference participants benchmarked healthcare practices against industries such as aviation and nuclear power, which manage potentially dangerous practices within complex systems and do so in a highly reliable and safe manner.

With these themes in mind, the focus of error reporting and analysis was changed to emphasize systems errors and root causes of patient harm along with the respective patterns and trends. An emphasis was placed on identifying and managing high-alert medications and high-risk practices that use specialized procedures. Conference participants learned that error and risk do not randomly occur, nor is risk evenly distributed across healthcare interventions. Attendees were encouraged to recognize the inherently different levels of risk and focus on the most significant drivers of harm and risk in the system. These themes have

TABLE 2
Themes of the Annenberg Patient Safety Conferences (1996-2001)

- Raise the visibility of error and set a national agenda for change
- Change the thinking/culture about error and put a face to error
- Systems errors vs. individual blame
- Use error identification and reduction strategies proven effective in other industries
- Change the focus of reporting/analysis to emphasize systems errors and root causes
- Increase emphasis on patterns of errors and trends
- Increase emphasis on high-alert medications and high-risk practices
- Apply cognitive psychology and human factors engineering

been disseminated across the clinical care enterprise by the attendees and their colleagues over the last twenty years.

Today, the modern patient safety movement brings in expertise in cognitive psychology and human factors engineering to create the science of safety. The science of (patient) safety is a new way of looking at healthcare delivery. In other industries, the science of safety has been well established; however, it is relatively new to healthcare. The science of safety requires a deeper understanding of how complex healthcare systems contribute to its outcomes. These complex systems are each made up of sub-systems, which interact in ways that are generally predictable and yet at other times, can be entirely unpredictable.

Most importantly, the new science of safety recognizes that a *culture* of safety is critical to achieving positive outcomes. In a culture of safety, professionals continually aspire to achieve the best possible outcomes with the minimum degree of harm. Key elements of a robust safety culture include: 1) recognizing that routine activities carry high risk, 2) the pursuit of consistently safer processes, 3) creating an environment where individuals will report problems or potential safety concerns without fear of retaliation or retribution, 4) enabling individuals and teams to work across arbitrary organizational barriers in order to develop solutions to problems, and 5) assuring that the organization devotes necessary resources to address safety concerns.

The culture of safety is not an easy concept to understand or achieve in practice. Most healthcare professionals are not formally trained to recognize and support a positive safety culture. Furthermore, experience has shown that cultural change is only possible with leadership's strong support. If leaders do not embrace a culture of safety, outcomes are not likely to improve.

Question #2: How is Patient Safety Different from Drug Safety?

In clinical trials regulated by the U.S. Food and Drug Administration (FDA), drug safety has been the main focus. Drug safety focuses on the medicine's effects on the human body – the known or expected benefits and risks of the drug due to its pharmacology and mechanism of action once administered. This is very different from patient safety, which focuses on the safe use of the drug in the healthcare system, where "use" includes whether it is the best drug for that patient at that time, the preparation, dosing, and administration of the drug, the monitoring of the patient before and after the drug is administered, and the management of any adverse effects of the drug.

Table 3 on the following page, provides an overview of drug safety as it is commonly described in the regulatory literature. The context for drug safety is: 1) pharmacology and 2) regulation. The Institute of Medicine report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (2007), is exclusively devoted to these two areas. The FDA's response to the IOM (https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM171627.pdf) notes the Agency's substantial agreement with the IOM report and also describes the emerging regulatory activities to support drug safety that include:

A. Strengthening the science that supports our medical product safety system at every stage of the product life cycle from premarket testing and development through postmarket surveillance and risk management
B. Improving communication and information flow among all stakeholders engaged in promoting the safe use of medical products.
C. Improving operations and management to ensure implementation of the review, analysis, consultation, and communication processes needed to strengthen the U.S. *drug* safety system

Safety in clinical research has been defined by unwanted and unexpected experiences of the past and with a focus almost exclusively on *drug* safety. Notable events that have driven "drug safety" include:

- Fetal harm from in-utero exposure to thalidomide from drugs given to the mother
- The poisoning and death of patients treated with sulfanilamide inappropriately formulated with diethylene glycol
- The delayed identification of increased cardiac mortality from non-steroidal anti-inflammatory drugs (NSAIDS), which had been viewed as cardio-protective

TABLE 3
Drug Safety

- Common context:
  - Pharmacology and regulation
- Past experiences:
  - Shaped beliefs, study design, and institutional policies
  - Persistent impact
- Lessons from past experiences with drug toxicity:
  - Codified into public policy, laws, and regulations
- Response to past events:
  - Created a form of tunnel vision about safety

The lessons learned from these experiences of drug toxicities were codified into public policy, laws, and regulations with the goal of doing everything possible to prevent drugs from causing harm.

These experiences have profoundly shaped beliefs, study design, laws, regulations, and policies. Nearly seventy years after the problems of in-utero thalidomide exposures occurred, "safety" in clinical research continues to be defined almost exclusively by how a drug affects the patient.

To some degree, this response to past events has created a form of tunnel vision that safety in clinical research means preventing the drug from doing something bad to people by designing a better drug or a safer molecule. This pursuit is obviously necessary. In the broader picture, however, that focus prevented researchers from seeing and defining patient (subject) safety beyond the harm caused solely by the drug.

FDA drug safety communications in 2016 (https://www.fda.gov/Drugs/DrugSafety/ucm479779.htm) focus predominantly on how the drug adversely affects patients. For example, the FDA made these statements:

> ". . . the risks of using the pain medicine tramadol in children aged 17 and younger due to rare but serious risk of slowed or difficult breathing."

> "….hepatitis C treatments Viekira Pak and Technivie can cause serious liver injury mostly in patients with underlying advanced liver disease. As a result, manufacturer must add new information about this safety risk to the drug labels."

> "…rare cases of underactive thyroid have been reported in infants following the use of iodinated contrast media (ICM) for X-rays and other medical imaging procedures."

These types of communications convey critical information, yet they can also reinforce the perception that a drug's pharmacology is a key focus of drug safety.
Fortunately, there have been important changes in public policy and regulation. The FDA now has a drug safety oversight group, the Office of Medication Error Prevention and Risk Management (https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm169536.htm) , which is using a broader lens to look at the way that drugs are used in patients in clinical research and clinical care, with the goal of preventing and managing the overall risks of medication use. This emerging part of the regulatory system offers encouragement that at some point in the future, there will be a broader national safety agenda for clinical research.

More recent drug safety communications from the FDA, for example, focus on dosing errors and contributing factors to those errors, such as confusing packaging and labeling design, different dosing regimens for two oral formulations of the same drug, and drug-drug interactions. Examples of these communications include:

> "...risk for dosing errors with Avycaz (ceftazidime and avibactam) due to confusion about the drug strength displayed on the vial and carton labels."

> "…differences in dosing regimens between the two oral formulations of the antifungal Noxafil (posaconazole) have resulted in dosing errors."

> "…investigate Kayexalate's potential to bind to other medications administered by mouth, drug interactions that could affect efficacy of concomitant medications."

Question #3: How Large is the Problem of Preventable Harm?
In 1999, the IOM report, *To Err is Human*, estimated the number of deaths due to preventable harm at 98,000 patients annually. A more recent paper suggests significantly higher estimates (James, Journal of Patient Safety: September 2013 - Volume 9 - Issue 3 - p 122–128). The accuracy of both the original estimates and more recent estimates have been critically questioned based on the methodologies used. From an ethical perspective, however, even a single death from preventable harm is unacceptable.

The Agency for Healthcare Research and Quality reported in 2014 that for every 1,000 discharges, 121 patients were harmed by the healthcare system during their hospital stay. This is about 12% of patient discharges, another large number. The positive news is that this rate had been 145 patients per 1,000 discharges only 3 years prior. (2014 National Healthcare Quality and Disparities Report. Rockville, MD: Agency for Healthcare Research and

Quality; May 2015. AHRQ Pub. No. 15-0007). Nevertheless, in this author's opinion, most other high-reliability industries such as aviation and the nuclear industry could not survive with accidents occurring at these rates.

In contrast, the burden of close calls, errors (potential harm), preventable harm, and preventable death in clinical research is unknown and, if known, unpublished (Table 4). There is no national database nor a taxonomy where research-related problems can be organized and analyzed. There is no national monitoring system to assess risk across the clinical research enterprise. The current construct in clinical research today is driven by maintaining confidentiality and protecting proprietary information. There is no sharing of the lessons learned from past events and no sharing of preventive actions to minimize future problems. In contrast to what is known about errors and preventable harm in clinical practice, there is very little known about these outcomes in clinical research.

As a case in point, this author identified thousands of articles describing errors and preventable harm and the lessons learned in clinical practice, yet only a handful of publications about errors in clinical research, some focusing on process errors and others on study design flaws (errors) that led to harm. Examples of these research publications follow.

Process errors leading to preventable harm:
One article was about the GUSTO trial, an international study where about 12% of subjects experienced a known error in the delivery of the thrombolytic medication (Richards and Cannon: *Academic Emergency Medicine* 2000;7:1285-9). In another article, the author described the case of a subject who died in a peanut immunotherapy trial; however, this article focused more on the impact of the subject's death on those involved rather than on an analysis of the medication error and how it happened (Sanks RJ, American Journal of Health-System Pharmacy, 1999;56:907-9)

TABLE 4
Preventable Harm in Clinical Research

- No national database or taxonomy
- No system to assess risks of unsafe designs and practices
- Current construct in drug development is "confidential and proprietary"
- Medication error in the context of research is relatively an unexplored and unpublished topic

In one highly instructive but unpublished report involving a medication-error related death in a clinical trial, remarkably, the organization conducted a root cause analysis that identified many systems failures which contributed to a dosing error that led to the subject's death (*May 2005: Errors in the Media and Organizational Change PERSPECTIVE: Organizational Change in the Face of Highly Public Errors—I. The Dana-Farber Cancer Institute Experience*, James B. Conway; Saul N. Weingart, MD, PhD). As a result of the root cause analysis, among other significant findings, the organization gained new insight into the different ways that nurses, pharmacists, and physicians think about chemotherapy dosing. Physicians think about total treatment doses. Pharmacists think about the dose, diluent, and concentration that they need to prepare for a specific patient. Nurses think about the specific dose, rate, and route that they need to administer to the patient at a given time.

In retrospect, the prescribing, dispensing, and administration systems were not aligned to resist errors that can present along any part of this workflow. With a greater visibility and a deeper understanding of these and other system errors that led to the subject's death, the organization set out to correct these flaws (TABLE 7 on page 43) to prevent a similar future event – a process that would not have been possible without a systems approach or with a focus on drug safety alone.

Other systems failures identified in that report included:

- Trainee supervision
- Nursing competence
- Order execution
- Protocol violations
- Research leadership structure separate from hospital leadership structure
- Ineffective quality assurance leadership
- Poor error reporting/ management system.

Study design flaws leading to preventable harm
Two recent publications discussed preventable problems (harm) in research. The TeGenero trial was a first-in-human study of a new monoclonal antibody, FIH -TGN1412, given in a rapid sequential design. Six subjects were exposed to the drug over 70 minutes. Within 90 minutes, the subjects had serious systemic inflammatory responses, and between 12 and 16 hours, they became critically ill, but all survived.

An editorial in *The New England Journal of Medicine* published in 2006 looked at this event through the lens of a drug safety problem, i.e., a pharmacology problem. In this Editorial, Suntharalingam G, et al.

TABLE 5
Why Clinical Research Should Care About Patient/Subject Safety

- Clinical research often exists within a system of clinical care and must:
  - Fully coordinate with the clinical team and ensure that roles and responsibilities are clear
  - Minimize harm from overlapping care and research interventions
  - Optimize subject/patient experience to meet/exceed expectations
  - Abide by ethical duties to protect subjects
  - Exercise respect for persons and individual autonomy
- Clinical research is a business and should consider:
  - Compliance with FDA regulations and ICH guidelines
  - Data validity and scientific integrity
  - Business/economic case for safety: Direct and indirect costs
  - Business reputation and goodwill
  - Competitive recruitment and social networks

wrote that this experience provided insight into the immune-mediated cytokine system. (*N Engl J Med 2006*;355:1018-28).
However, a later analysis of this event attributed the incident "as much to the inappropriate design and conduct of the Phase I study as to the activity of TGN1412" (Horvath and Milton, *Toxicologic* Pathology, 37: 372-383, 2009). The latter article recognized and acknowledged that the safe use/safe design of the study was as important as understanding the drug's pharmacology.

The French study, which involved giving the fatty acid derivative BIA-10-2474 to healthy volunteers, is another example that has been analyzed extensively. One subject died, and three suffered serious potentially permanent neurological damage. The ANSM Comité Scientifique Spécialisé Temporaire concluded that there were major problems with the execution of the trial, including:

- Contract researchers who continued to administer the highest dose of the drug after the first volunteer fell ill
- Failure to notify the authorities promptly
- Keeping the incident from the remaining volunteers

Unsafe study design and execution and the apparent absence of a culture of safety contributed to this unwanted outcome (Essai clinique de Rennes - Rapport final du CSST inhibiteurs de la FAAH, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), 19 April 2016).

Question #4: How Does the Patient Safety Movement Learn?
In clinical care, there are many ways to learn and improve, with each approach effectively supported by committed leadership. Effective learning and improvement begins with looking at problems and designing new systems from a multi-disciplinary perspective. Learning and improvement can originate within an organization or from the experiences of others. From these internal and external sources, evidence-based safety practices are then designed into the clinical care protocol as well as into comprehensive unit-based care coordination practices. Care coordination goes beyond the individual role of each physician, nurse, and pharmacist. It includes an understanding of the importance of appropriate hand offs, communications, and assignment of roles and responsibilities. In addition to the above factors, learning is the result of:

- Providing tools and technical assistance to implement the available evidence and best practices
- Creating a culture of safety with concrete, evidence-based tactics
- Developing data and measures to assess the safety culture and the event rate

Question #5: Why Should the Clinical Research Enterprise Care About Patient Safety in Clinical Trials?
In the opinion of this author, there are three major reasons why the clinical research enterprise should care about patient safety in research: 1) Clinical research often exists within a system of clinical care, 2) regulation of clinical research is founded in part on ethical principles intended to protect subjects, and 3) clinical research is a competitive business (Table 5). Clinical research is often delivered within the overall healthcare system, but when it operates in a silo, artificially separated from the healthcare delivery side of the system, problems can occur that may have been preventable.

Coordinating clinical research and clinical care and ensuring that there is a clear delegation of roles and

TABLE 6
Applying Patient Safety Lessons to Clinical Research

- View safety in clinical research as a fully-integrated component of the healthcare system
- Modify perceptions so that patient safety is on par with the importance of drug safety
- Establish a strong culture of safety and engaged leadership
- View errors and preventable harm as events of special interest

responsibilities can be a challenging task, yet it is a primary responsibility of both clinical care managers and clinical research professionals to assure safety. The research team and the clinical care team must each know their designated responsibilities and communicate about their activities prior to and during the study.

The subject experience should be optimized to meet or exceed the expectations in the delivery of healthcare. Patient satisfaction is one of the healthcare quality measures used by the federal government as well as a major driver for quality and reimbursement in clinical care. Failure to satisfy patients can reduce quality scores and reimbursement.

Researchers similarly have the duty to ensure the ethical conduct of research by using evidence-based safe practices that minimize the risk of harm but have not historically been subjected to the same quality measures as clinical care providers. Researchers must also ensure respect for persons and individual autonomy by informing subjects of relevant problems that occur during a study that may affect the subject's willingness to continue participating.

Additionally, it would be an understatement to say that clinical research is a large business. Ensuring the integrity of the data requires compliance with the regulations and with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use *(ICH)* guidelines. There is a business case to be made for safety, such as lowering both direct and indirect costs. This is very poorly-documented in the literature, as much of this information is proprietary, but one study *(Emanuel EJ, et al, Journal of Clinical Oncology 2003, Vol 21, No 22 (November 15), 2003:4145-4150)* found that research teams spent 72 hours on average managing adverse events for the 20 subjects in a prostate cancer trial. While not specified in this paper, the costs of managing these events could include providing care, reporting, re-designing the trial, re-consenting subjects, re-training the staff, lost data, and delays.

Caring about the safety of subjects potentially improves the clinical research site's reputation and goodwill and may enhance competitive recruitment and the site's reputation on social networks. Social media carry messages about research studies and sites much further than clinical research professionals may realize. In a 2014 white paper from Tufts Center for the Study of Drug Development, the authors noted that only two research companies had social media listening initiatives. This was followed by a recommendation that listening should be started as close as possible to volunteer randomization, if not earlier, to monitor patient experiences in a given trial, participation concerns, and challenges that they face (https://csdd.tufts.edu/s/TCSDD_Social_Media_Final.pdf). In a 2014 paper (BMJ 2014;348:g368), the authors noted that a consumer-driven organization, PatientsLikeMe, was systematically gathering patient experiences from patients in more than 400 randomized trials with the premise that subjects hold unrealized power in clinical research.

Question #6: Can Clinical Research Apply Similar Lessons?

The language of patient safety differs between clinical care and clinical research. Clinicians use the term "error." Errors in clinical research, called protocol deviations or violations, are likely rooted in flawed system design similar to the underlying cause of errors in the clinical care setting. Experience and careful study has demonstrated that individuals are rarely the root cause of problems in healthcare, and this finding likely generalizes into clinical research.

Consider the complexity of clinical research today. Its subsystems include designing and implementing the protocol, site-based activities, the investigational product supply chain, subject management plans, study team selection and training, monitoring, and control of documents, data, and biological samples. Management of these subsystems is then delegated by the sponsor to contractors, vendors, and consultants, with the expectation that all groups work interdependently to achieve the study's goals. Flawed system design predictably leads to mistakes but at unpredictable times. When flawed designs are recognized using continuous quality improvement techniques, future mistakes can be minimized or prevented regardless of which practitioner or researcher is delivering the care or conducting the study.

The lessons from the patient safety movement can and should be applied to clinical research (Table 6). The first step is to view safety in clinical research as integrated with healthcare delivery. The silos between healthcare delivery and clinical research must be broken down to look at the greater system effect.

Perceptions must be modified so that

TABLE 7

Initial changes made subsequent to the root cause analysis

- New rules were adopted mandating close supervision of physicians in fellowship training.
- Nurses were required to double-check high-dose chemotherapy orders and to complete specialized training in new treatment protocols.
- Interdisciplinary clinical teams reviewed new protocols and reported adverse events and drug toxicities.
- A trustee-level quality committee was reorganized and strengthened.
- Discussions were begun regarding the transfer of inpatient beds to nearby Brigham and Women's Hospital.

Organizational lessons and changes to improve safety

- Safety is the responsibility of clinical and administrative leaders and of the trustees. Patient safety was and is the work of the organization, not an activity that could be compartmentalized.
- Error reporting systems were refined and expanded to detect risk, error and harm. A robust root cause analysis system was implemented to analyze critical incidents, report the results, and assign accountability for system improvements.
- System design and effective use of technology was recognized as paramount in the prevention of error – guided by direct input from front line providers.
- Partnerships with patient safety organizations and quality improvement organizations were developed to share information.
- Stakeholder engagement was established to increase transparency and improve decision making.
- Culture of safety was improved by recognizing that mistakes will happen and that the organization's responsibility is to recognize them quickly, mitigate the harm, disclose any errors to our patients, and look after the staff's psychological well-being. Accept the broad responsibility to learn from each mistake and to share the results of the learning.

patient safety is considered to be as important as *drug* safety. The largest and most durable changes will happen when leadership embraces a culture of safety. This includes leadership of research teams and the top leaders of the organization.

Errors and preventable harm should be viewed as events of special interest similar to *adverse events of special interest*. They should be given dedicated review by sponsors, study teams, research organizations, and IRBs with the necessary steps taken to prevent future errors and preventable harm.

Medication safety as a component of the overall data and safety monitoring plan

One approach to improving subject safety is to increase the visibility and define the requirements for reporting medication errors as a specific type of protocol deviation. Defining medication errors in terms familiar to research teams increases their visibility by making these events an important part of the overall safety plan. Mandatory reporting of medication errors increases the sponsor's awareness of problems in the design or execution of the protocol. Sample language might include:

> "Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength."

Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product
- Potential medication errors or uses outside of what is specified in the protocol that do or do not involve the participating subject
- Whether or not a medication error is accompanied by an AE, as determined by the investigator, details of the medication error are captured on a specific section of the AE reporting form along with any associated AEs. "

Avoiding preventable harm should be on the list of priorities and characteristics for the infrastructure of clinical research. Identifying problems that are occurring is a good first step in developing this infrastructure. The next step is collaborating with patient safety expertise in the healthcare system, such as the patient safety officer and the medication safety officer. With effective collaboration, knowledge of safe designs and safe practices can be generalized from the clinical care enterprise to the clinical research enterprise.

Thinking and acting beyond the regulations, organizations and Institutional Review or Ethics Boards should consider policies that mandate that medical errors, medication errors, device-related or patient care-related problems are also reported to the institution's confidential Safety Reporting System or Risk Management Office. The FDA and the Office for Human Research Protections do not require this step; however, it is consistent with the science of safety, Good Clinical Practice, and ethical principles to minimize risk and prevent harm.

Corrective and preventive action plans must minimize the likelihood of recurrence of the event by focusing on the system failures that may have led to the problem, not the people involved. In the hierarchy of effectiveness, corrective action plans based primarily on education, counseling, discipline, posters, emails, and other temporal measures are insufficient to prevent future events. Stronger corrective action plans are system-based and modify the procedures, communication handoffs, equipment, environment, and culture, to create safety. Examples include: 1) the use of lean workplace design, forcing functions and constraints, 2) automation and computer feedback, 3) standardization and simplification, 4) independent verification and redundancy for high risk tasks, 5) clear and non-punitive conflict resolution mechanisms, and 6) safe communications/labeling that avoid dangerous nomenclature and abbreviations. (Chassin M, Loeb J. High-Reliability Health Care: Getting There from Here. The Milbank Quarterly, Vol. 91, No. 3, 2013 (pp. 459–490)) and (National Quality Forum (NQF). *Safe Practices for Better Healthcare–2010 Update: A Consensus Report.* Washington, DC: NQF; 2010.)

Conclusion

Eliminating errors and deviations by designing safer systems, establishing a culture of safety, and reducing the risk of human error are intermediate goals of a safety program, whether established in clinical care or clinical research. The primary goal, however, is to reduce the burden of preventable harm. The patient safety movement has several decades of experience in reducing preventable harm in healthcare. These lessons and strategies can be more fully adopted by the clinical research enterprise with a concerted national effort beginning with committed leaders in industry, research teams, Institutional Review/Ethics Boards, professional associations, and regulators. Until that happens, preventable subject harms will continue to occur.

It is not difficult to become desensitized to the operational risks and unsafe designs in conducting clinical research. As is the case in other complex and potentially dangerous industries, individuals understandably perceive the risks of their tasks in relative (incremental) terms rather than in the absolute. Small deviations, shortcuts, and work-arounds to overcome flawed systems become normalized behaviors, often to a degree that mis-perception of risk can be a significant contributor to events that result in preventable subject harm. In closing, James Reason, PhD, notes in his seminal paper Human error: models and management (BMJ 2000;320;768-770) that:

> "Perhaps the most important distinguishing characteristic of high-reliability organisations is a collective preoccupation with the possibility of failure."

Self Study Answers

1. d. b. and c. (Section C. (1))
2. e. all of the above (Section C. (1))
3. a. true (Section C. (1))
4. b. 21 CFR 812.28(c) (Section C.)
5. c. waiver (Section C.)
6. a. for at least 2 years (Section D.)
7. b. false (Section C. (1))
8. d. Section 814.15 (Section E.)
9. b. Declaration of Helsinki (Section E.)
10. a. true (Section C. (1))