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# Managing Clinical Risk and Measuring Participants' Perceptions of the Clinical Research Process

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## IDENTIFYING AND MANAGING CLINICAL RISK IN THE CLINICAL RESEARCH ENVIRONMENT

Clinical research most often is conducted in an environment that is part of a larger health care system. Both the conduct of clinical research and the practice of clinical medicine involve risk. The extent to which risk is present in the hospital environment has been well documented in recent years. The Institute of Medicine's groundbreaking report "To Err is Human" characterized the magnitude of the occurrence of medical errors in the United States, estimating that between 44,000 and 98,000 hospital-based deaths per year could be attributed to medical errors.<sup>1</sup> Even using the lower rate, 44,000 annual iatrogenic deaths eclipse the annual number of deaths associated with motor vehicles (43,458), breast cancer (42,297), and AIDS (16,516). Preventable medication errors account for two in every 100 hospital admissions, with the average increased cost associated with these medication errors estimated to be \$4,700 per event. Generalizing from this estimate, medication errors add nearly \$2 billion annually to the nation's health care bill. According to data from the Centers for

Disease Control and Prevention, nearly two million health care-associated infections occur each year; costing the nation an estimated \$20 billion dollars.<sup>2</sup> Whereas these figures are unquestionably daunting, they do not include either the scores of near misses or latent errors (errors that never reach the patient or result in harm) or the system failures that influence a patient's health care experience negatively. Clearly, the health care environment is fraught with risks and potential errors that must be identified and deftly managed if patients are to be cared for safely and appropriately.

Most clinical research is conducted in the context of these health care risks. As is the case for clinical care, and as noted by several authors in this text, the conduct of clinical research is inherently associated with risk. During both the scientific and human subjects protection review processes great effort is expended to estimate, calculate, and articulate the relative risk associated with each study drug, device, and intervention. This intense scrutiny at the protocol level works to improve the safety of subjects relative to the risks associated with the study question. Murff et al. describe additional risks that rarely are considered formally during the review of a clinical research protocol, including the

clinical environment in which the research will be conducted, as well as the system failures that are inherently associated with clinical medicine.<sup>3</sup> The health care environment—whether an inpatient unit, an ambulatory care clinic, or a community health center—is a complex system that is influenced by multiple factors that contribute to or mitigate risk in the conduct of clinical research.

Nolan describes a system as “a collection of interdependent elements that interact to achieve a common purpose.”<sup>4</sup> If one applies this definition to the clinical care environment, examples of interdependent elements that one might consider include such factors as the institution’s culture (especially with respect to safety), the competence of the staff, the availability of state-of-the-art equipment, and the quality of information systems, to name but a few. The health care literature is rife with examples of system failures resulting in harm to patients; for example, significant medication errors (e.g., the most public death of the *Boston Globe* reporter who died of a massive chemotherapy overdose),<sup>5,6,7</sup> wrong site surgeries that often top the Joint Commission’s list of reported sentinel events,<sup>8</sup> and the relative epidemic of health care associated infections.<sup>9,10,11,12</sup> Whereas any one of these events could be considered an error resulting from an individual provider’s negligence, systems thinking compels us to consider these adverse events as failures in a series of inter-related and/or co-dependent processes or systems. In truth, in the complex health care environment that exists in 2011 such events almost invariably involve a series of missed opportunities to correct the error—hence they truly represent system failures.<sup>13</sup> This shift in focus—from the individual to the system—forces organizations to broaden its analysis of incidents and, thereby, broaden the impact of any improvements. Because of the endemic nature of errors and system failures in clinical care, investigators and review bodies must collaborate with the health care practitioners with whom they entrust their participants’ safety to assure that the system/environment in which clinical research is conducted is safe, and has the necessary infrastructure in place to support the study. Further, the research team must have strategies in place to monitor the clinical research environment in order to identify risks and clinical events that could contribute to adverse events and/or protocol deviations, and to assure that processes are in place to prevent, mitigate, and manage risks.

Clinical research programs must, therefore, embrace a systems approach to managing risk associated with the conduct of clinical research. For the purposes of this chapter, the term “conduct of clinical research” refers both to activities outlined in the research study as well as those intrinsic clinical care activities that are essential to the successful implementation of a study but that may not be explicitly described in the research protocol. Examples of such clinical care activities include infection control

measures, medication management procedures, the design of the physical environment, and information management. These critical clinical care functions often are assumed to be present and functioning at an optimal level to support the investigator’s study; however, investigators and/or institutional review boards (IRBs) may lack formal processes to assess the capacity of the clinical environment to support the study under review. The research team must engage the clinical care organization proactively to assure that the appropriate infrastructure is in place to provide care safely and efficiently to study participants. In collaboration with the health care team, the research team should have processes in place to:

- identify clinical care functions that are critical to the success of the protocol;
- identify and assess critical risk points of the clinical care processes that might place participants at undue clinical risk and/or compromise the integrity of the study;
- monitor the clinical environment continually for adverse events, errors, near misses and process failures;
- assess systematically and thoroughly errors that occur; and
- establish an armamentarium of process improvement tools to use to manage process and system issues when they are identified.

These processes and the tools and techniques described in this chapter can be implemented and managed at a variety of levels of an organization. If the research program resides in a large health care system, many of these activities can be managed by the hospital’s patient safety and clinical quality enterprise, in collaboration with the research teams. However, these processes and tools effectively can be applied on a much smaller scale (i.e., an individual research unit) with the same degree of success. Regardless of where in the organizational structure these functions reside, the findings from these performance measure, risk mitigation and improvement strategies should be communicated directly to the leadership and across the organization.

### **Building a Roadmap to Safe Care: Use of Quality Improvement Techniques to Identify Clinical Care Requirements**

A first step in assuring that appropriate clinical care infrastructure is in place to support the planned study is to examine the research protocol to identify the clinical functions that will be required to support the conduct of the study safely. In addition, the team of investigators should identify, objectively and prospectively, steps in the research process that may place participants at risk. Health care performance improvement tools such as flowcharting,<sup>14,15</sup> failure mode and effects analysis

(FMEA),<sup>15,16,17,18,19,20,21,22</sup> and clinical quality performance measures<sup>15,23,24,25,26,27</sup> can be applied effectively to the analysis and management of risk in the context of clinical research.

We use these performance improvement tools for this purpose in our institution, the Clinical Center at the National Institutes of Health (NIH Clinical Center). The NIH Clinical Center occupies a unique position in the nation's biomedical research establishment. The NIH Clinical Center is a distinctive and complex hospital whose sole mission is the support of science. High-quality clinical care is provided at the NIH Clinical Center in the context of clinical research, but the primary driver of that care is science. The NIH Clinical Center provides clinical research support for, and clinical care to, the research participants enrolled in the more than 1,500 active clinical research protocols ongoing at the NIH Clinical Center. The NIH Clinical Center's research portfolio differs substantively from most academic medical centers. Of the NIH Clinical Center's approximately 1,500 studies nearly half of the protocols are designed to study the natural history and pathogenesis of rare, often genetically determined, diseases. The other half of the NIH Clinical Center's protocols is comprised of clinical trials. More than 90% of these clinical trials are Phase I or Phase II "proof-of-principle" translational science trials. This unique intersection of clinical care and clinical research has positioned the NIH Clinical Center to use myriad health care performance improvement tools creatively to manage the implementation of a broad spectrum of clinical research protocols effectively.

One example of how performance improvement tools have been used to enhance the conduct of clinical research occurred in our institution as the Severe Acute Respiratory Syndrome (SARS) epidemic evolved in 2004. At that time, investigators at the NIH Clinical Center authored two protocols designed to gain insight into the epidemiology and pathogenesis of this new disease, as well as to study strategies for the clinical evaluation and management of patients with SARS—perhaps positioning the NIH Clinical Center as one of the few health care facilities in the world actively recruiting patients with SARS. The research protocols received rigorous scientific and human subject protections vetting and approval, and the principal investigators were poised to enroll their first participant/patient. However, several circumstances caused the NIH Clinical Center, as an organization, to pause before the decision was made to open recruitment. Because of the nature of the studies conducted at the NIH Clinical Center, many of the patients/participants are highly immunocompromised, either as a direct result of their underlying disease or due to the interventions associated with the research studies in which they are enrolled. Further, at the time of the SARS outbreak, the NIH Clinical Center was housed in a clinical environment—built in the 1950s—that posed significant

infrastructural hurdles to providing safe care to patients infected with highly infectious (and in this instance, potentially airborne) pathogens. In this complex clinical context, investigators from the National Institute of Allergy and Infectious Diseases submitted protocols requiring the provision of care for highly infectious SARS patients. Subsequently, these proposals were presented to the NIH community. As one might have anticipated, several investigators who provide care for patients who have severely compromised immune function were adamantly opposed to admitting patients with SARS or other highly contagious respiratory illnesses electively to the NIH Clinical Center. However, because of the clearly urgent public health need, as well as the potential unprecedented scientific opportunities, the leadership of the NIH Clinical Center approached the issue not by asking: "Can we safely provide care to patients with SARS?" but rather by asking the question, "How can we care safely for all of our patients?" As the protocols were being reviewed for human subjects protection, the leadership of the NIH Clinical Center set out to identify the critical clinical functions that they felt must be present and operating at an optimal level to admit and care for SARS patients safely. This assessment required the collaboration of the research team, the leadership of the NIH Clinical Center, and the active participation of key clinical departments such as hospital epidemiology, nursing, critical care medicine, pharmacy, and house-keeping. Using flowcharting techniques,<sup>14,15</sup> the team painstakingly cataloged each step in the research process, as designed, and identified clinical care functions necessary to support the research requirements. Clinical and operational functions that were identified as being essential to the successful care of these patients are outlined in [Table 39-1](#).

This exercise was eye-opening in that both the clinical care providers and the investigators were astounded by the breadth of hospital functions that required flawless orchestration to assure that the protocols could be implemented safely. Following the identification of the key clinical and operational requirements, a team was charged with assuring that appropriate policies, procedures, staff, equipment, and physical infrastructure were in place and functioning optimally and efficiently prior to the admission of the first SARS patient. The clinical care team worked closely with the research team as well as with the community of NIH investigators to assure alignment with the study requirements and to time, appropriately, the admission of the first protocol participant.

## Proactively Assessing Clinical and Operational Risk

The development of a complete listing of the essential clinical processes that need to be in place is a critical first

**TABLE 39-1 Critical Clinical and Operational Functions Required for the Safe and Effective Management of the Patient with Severe Acute Respiratory Syndrome (SARS)**

- Infection control
  - Isolation rooms
    - Availability
    - Capabilities
  - Appropriateness of current isolation precautions
  - Personal protective equipment (PPE)
    - Availability
    - Staff competence
- Critical care medicine
  - Intensive care unit capacity
  - Staff competence
- Respiratory therapy
  - Ventilator availability
  - Staff competence
- Staff, patient and family education
  - PPE
  - Isolation precautions
  - Managing containment/isolation/quarantine
- Laboratory medicine
  - Availability of tests/assays for clinical research and clinical care
- Medication management
  - Supply chain issues
- Equipment and supplies
  - Ventilators
  - Personal protective equipment
- Social work/emotional support
  - Participant and family support
- Patient transport
  - To the NIH Clinical Center
  - Within the NIH Clinical Center
- Security
  - Transportation assistance
  - Crowd control
- Housekeeping
  - Infection control training
- Code blue
  - Exposure/transmission mitigation
- Public relations/Communication
  - For staff, participants, families, public

step to prepare appropriately for the implementation of a new research protocol. As was the case with the SARS protocol, this process can be daunting. Focusing an organization's finite resources to assure that appropriate attention is paid to the most critical and potentially riskiest care processes is a challenge for most organizations. A variety of tools exist to guide the objective prioritization of what may ultimately be a very long list of critical issues that must be addressed. The failure mode and effects analysis (FMEA) is a powerful risk assessment tool that is used proactively, both to assess complex processes to identify potential vulnerabilities before errors occur as well as to guide development of interventions to mitigate identified risks.<sup>16,18,19,20,21,22,28,29,30</sup> Historically, FMEA has been used in the engineering environment to assess high risk processes associated with power generation in the commercial nuclear power industry; in aviation to assess the acceptability of aircraft designs; and in the automotive industry to establish manufacturing requirements for cars and trucks.<sup>16,19,22</sup> DeRosier and colleagues at the Veteran's Administration's Center for Patient Safety are credited with moving the techniques of FMEA to the bedside, applying the concept of prospective risk analysis to health care processes.<sup>31,32</sup> In 2002, the use of FMEA in health care further expanded with the issuance of a Joint Commission requirement that all health care organizations seeking accreditation conduct at least one proactive risk assessment on a high-risk clinical process every 18 months.<sup>33</sup> Clinical care practitioners as well as clinical research professionals can use FMEAs to identify risk and to avert adverse events, errors and other system failures in a variety of health care settings.<sup>16,17,19,20,21,22,30</sup>

In a complex care environment such as that of the NIH Clinical Center, where risk is compounded by the interplay of clinical medicine and clinical research, the FMEA is a useful tool to guide risk mitigation by identifying critical risk points in clinical care and clinical research processes. In the case of the SARS protocol described above, the FMEA was used as a compass to guide the work of the team charged with facilitating the implementation of the protocol. As mentioned previously, some investigators complained publicly about the prospect of the elective admission of highly infectious patients into an environment that housed patients with impaired host defenses. In discussions with both the practitioners who were adamantly opposed to admitting SARS patients and the investigators who supported the protocol implementation, one issue heightened the collective community's anxiety more than any other issue discussed—the safe transfer of the patients throughout the NIH Clinical Center. Practitioners, even those not enamored of the idea of admitting SARS patients, generally were comfortable that safe care could be delivered to the patient once the patient was safely ensconced in a functioning isolation room; however, the perceived risk

that an inadvertent exposure might easily occur while transporting the patient in the hospital was paralyzing to most practitioners. Not only would an exposure have a potentially catastrophic effect on a patient's health and well-being, but such an exposure could compromise the integrity of several research protocols (including the protocols in which the SARS patients were participating) and could pose a significant risk to the community.

In an effort to provide an objective assessment of the risks associated with the transportation of patients with SARS or other highly infectious respiratory syndromes, the NIH Clinical Center facilitated a formal FMEA of the process of patient transportation. Table 39-2 illustrates the analytical steps that are required to conduct such an FMEA.

This exercise resulted in the identification of over 25 failure modes and nearly 40 associated potential causes. The following critical process issues were identified as requiring immediate organizational attention prior to admitting patients with known or suspected SARS to the NIH Clinical Center:

- communication (among investigators, patient care staff, patients and families, and security staff);
- education about infection control procedures (investigators, clinic staff, patients, security staff);
- education regarding use of personal protection equipment (staff, patients, security); and
- availability of personal protection equipment.

More than 35 policies and procedures either were developed *de novo* or existing policies were revised to manage patients safely with known or suspected SARS.

Ultimately, no patients with SARS were admitted to the Clinical Center; however, this exercise provided the organization with a formal process for systematically and successfully assessing the risks associated with complex and high-intensity protocols involving patients infected with potentially airborne infectious diseases.

## Continually Monitoring the Clinical Research Environment for Risk

Using FMEA to identify the clinical risks points associated with the implementation of a clinical care or clinical research process is a critical first step in mitigating patient/participant risk. FMEAs or other risk assessments identify process points that are associated with increased risk to the patient/participant, to involved providers, and/or to the scientific integrity of the study. As illustrated in the example above, these risks can be addressed by myriad clinical and organizational interventions that are aimed at reducing those risks.

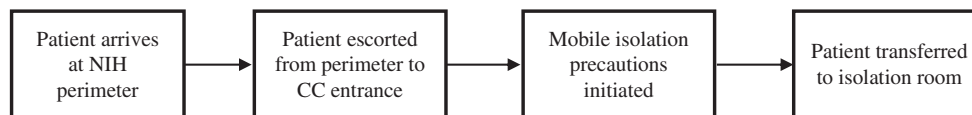
The next step in mitigating risk is the deployment of strategies to assess the effectiveness of interventions, and

to survey the research and care environments continually for other risks to the participants and to the study. Measurement is fundamental to assessment efforts and improvement in the quality of care. The history of health care quality improvement and measurement dates to Florence Nightingale's collection of mortality data and infection rates during the Crimean War, as well as to the work of Ernest Codman in establishing standards for hospitals in the early 1900s, including his provocative "end results hypothesis" that led to a Semmelweis-like estrangement from the health care establishment (see Chapter 1).<sup>34,35</sup>

In a classic paper in 1968 Avedis Donabedian recommended measuring health care quality in three areas: structure (the characteristics of a health care setting); process (what is done in the health care setting); and outcomes (the status of the patient resulting from specific interventions).<sup>26</sup> This paradigm remains the mainstay of modern health care performance measurement programs and is the basis for the local, state and federal programs designed to measure the quality of clinical care and identify health care associated risks and adverse events. Clinical research programs, too, should implement processes to assess the performance of the clinical research enterprise systematically—primarily to assess for risks to the participants, investigators and care providers, as well as for threats to the integrity of the study. Collecting and reporting adverse events that occur during the course of a research study is a mandatory component of both the research process and the protection of human subjects. However, event reporting in clinical research focuses on individual protocols, not on how the system of clinical research is performing as a whole. This "protocol-centric" focus fails to identify clinical care and clinical research system failures that potentially might impact participant safety across multiple studies. Murff and his colleagues at Vanderbilt<sup>36,37</sup> have described the need for research teams to develop reporting systems that collect data about reportable adverse events, as well as "near misses" or "latent failures" in the clinical care and clinical research environments. Near misses or latent failures are errors that do not result in patient/participant harm; however, these events do have the potential to do harm if the circumstances of the event were somewhat different. Identifying and analyzing near misses or system failures provide the care and research teams the luxury of designing and implementing interventions to interrupt the error cycle prior to the occurrence of a serious error. Surveillance for errors, adverse events, and latent errors in the clinical care or research setting can be accomplished using a variety of strategies including: (1) event reporting systems; (2) electronic surveillance systems that utilize clinical triggers to identify errors; and (3) analysis of clinical performance measurement data.

**TABLE 39-2 Failure Mode and Effects Analysis: Transporting the Patient with Severe Acute Respiratory Syndrome (SARS)**

1. Convene an interdisciplinary team of stakeholders familiar with the involved processes  
The CC team included the study team, CC leadership, key clinical departments (e.g., hospital epidemiology, nursing, critical care medicine), transportation, security, hospital and the patient safety and clinical quality professional
2. Identify (and come to consensus about) the scope of the process to be analyzed. (Too diffuse a scope will result in a very broad but shallow analysis; too narrow a scope will result in missing or overlooking critical risk points)  
The NIH Clinical Center's process started with the patient entering NIH campus and ended with the patient arrival in an isolation room.
3. Construct a flow chart to map the process under study  
The success of this step is dependent on the experience of the person facilitating the flow charting process. A balance must be found regarding the level of detail that is mapped. The team needs to be certain that the process mapped has adequate granularity to facilitate the identification of risk points for which interventions can be crafted. The high level flow chart for the SARS protocol had only four process steps:



Each of these higher level steps were broken down further into approximately two to four additional process steps to narrow the focus to facilitate the identification of potential vulnerabilities more effectively.

4. Identify failure modes (potential vulnerabilities) and specific causes of the failure modes for each process step. Failure modes can include issues such as human factors, communication, the physical environment, staff competence, equipment design, and policies and procedures

Examples of failure modes identified in the SARS FMEA included:

Process Step #1: "Patient arrives at NIH perimeter"

- Security not aware of planned arrival and refuses passage
- Patient has not donned appropriate personal protective equipment

Process Step #3: "Mobile isolation precautions initiated"

- Transport equipment not available
- Equipment malfunction

5. Score each failure mode for probability (a measure of the likely frequency that the failure mode might occur) and severity (a measure of the potential effect of the failure mode).

The NIH Clinical Center's scoring scheme was adapted from the Veteran's Administration National Center for Patient Safety failure mode and effects analysis. Severity scoring was determined using the following scheme:

- Catastrophic - score of 4
- Major - score of 3
- Moderate - score of 2
- Minor - score of 1

Probability scores were determined using the scheme below:

- Frequent - score of 4
- Occasional - score of 3
- Uncommon - score of 2
- Remote - score of 1

6. Calculate a hazard score. A hazard score (the factor of the severity and probability measures) is calculated to prioritize the failure modes to guide improvement efforts

Probability	Severity of Effect			
	Catastrophic	Major	Moderate	Minor
Frequent	16	12	8	4
Occasional	12	9	6	3
Uncommon	8	6	4	2
Remote	4	3	2	1

Failure modes with hazard scores of six and above were determined to be of critical importance to the safe and effective transport of patients who have highly contagious respiratory syndromes and teams were charged to address each of those issues.

Adapted from VA National Center for Patient Safety HFMEA: <http://www.va.gov/ncps/safetytopics.html#HFMEA>

## Occurrence Reporting Systems

Since the 1980s most health care patient safety and clinical quality programs have relied on voluntary or mandatory occurrence reporting systems as a critical source of data regarding clinical care errors and/or latent errors and near misses. These reporting systems are readily accessible and have the capacity to provide detailed information about these kinds of events.<sup>15,36,38,39,40,41,42</sup> The NIH Clinical Center has had a hospital-wide electronic occurrence reporting system (ORS) since the early 1980s. This voluntary electronic event reporting system captures more than 5,000 reports per year. Events entered into the ORS span the spectrum of clinical care and clinical research events—from serious harmful errors to reports of service quality. The NIH Clinical Center has found the ORS to be particularly useful as a surveillance tool for identifying trends in latent failures in clinical care and clinical research processes that otherwise would likely not be identified. The following is an example of a potentially harmful near miss or latent failure that could have had a negative impact on clinical research, had the issues not been identified by using data from the NIH Clinical Center ORS.

Upon review of data from the ORS, the Pharmacy Department Quality Officer noted a trend in administration events that was occurring associated with a specific investigational drug in a Phase I clinical trial. The reports indicated that drug delivery was delayed on several occasions because the infusion pumps had inexplicably suspended infusion. Each time the infusion would stop, the nursing staff would troubleshoot the problem, requiring the infusions to be restarted several times during a single delivery, potentially resulting in a delay of study drug administration, and potentially adversely affecting drug levels and pharmacokinetics. Alerted to these administration errors via the ORS, the Pharmacy Quality Officer met with the study investigators, the clinical care staff, the nursing staff, and staff from the Pharmaceutical Development Service (a section of the NIH Clinical Center Pharmacy Department that provides investigational drug development support to the investigators in the intramural program at the NIH). Collectively the group conducted an intensive review of the events. The common factor identified in each incident was that the infusion pumps stopped due to an “air in line” alert, although no air was noted in the tubing. All efforts to determine the cause of the alert generation were futile. Finally the team contacted the research team who had developed and conducted the initial laboratory testing of the drug in an effort to identify a reason for the alerts. Following the review of the current medication administration procedure for this study, the research team noted that the initial safety testing for the drug was performed using a different brand of intravenous tubing than the brand stocked and used in the NIH Clinical Center. The team changed the procedure for administering

the study drug, mandating a change in the brand of intravenous tubing used. No additional reports of mis-administrations were reported during the remainder of the study. Whereas these incidents do not appear to have caused any harm to the participant or the study, the potential for harm to the participant and the study are obvious, and any future potential adverse events or protocol deviations were averted as a result of identifying this series of events via the NIH Clinical Center's Occurrence Reporting System.

The success of voluntary event reporting is dependent on the organizational culture in which the reporting system is deployed, as well as on the manner in which the staff and leadership of the organization use the data to drive improvements in care and research. Establishing a non-punitive culture that encourages the reporting of events, free of reprisal, is essential to maintaining a robust and meaningful reporting system. Equally important is an organizational commitment to using the data provided by staff to understand system and process errors and failures and to develop strategies to mitigate risk and improve care. Finally, organizations should be committed to feeding back performance measurement data to the staff to keep them informed and aligned with institutional performance improvement strategies.

## Electronic Surveillance for Errors and System Failures

The nearly universal deployment of electronic clinical information systems in health care settings provides a robust platform for identifying adverse events in clinical care as well as in clinical research. Electronic surveillance for adverse events has proven effective in identifying, in real-time, events such as adverse drug toxicities and interactions, health care-associated infections, and other iatrogenic injuries or events. This technology uses clinical triggers to signal the presence of potential errors or adverse events. Clinical triggers can include high-risk medications, select abnormal laboratory values (e.g., serum potassium levels, microbiology culture results), treatment interventions such as antidotes (e.g., Naloxone (Narcan<sup>®</sup>), vitamin K), and corrective procedures (e.g., chest tube insertions, dialysis).<sup>6,43,44,45,46,47,48</sup> Electronic event surveillance for clinical care and clinical research errors and latent failures provides a tool that administrative institutional leadership, clinicians, and research investigators can use to identify, mitigate, and report these events in a much more timely manner than traditional voluntary incident reporting systems.

## Patient Safety and Clinical Quality Measures

Another excellent source of information about the capacity of a hospital or other health care organization to provide a safe environment in which to conduct clinical research is



the organization's patient safety and clinical quality performance measurement program. These measurement programs collect data that are used to assess the quality of the care and services provided to patients. All hospitals and other health care facilities accredited by the Joint Commission must have systems in place to measure, continually, a proscribed list of clinical activities.<sup>49</sup> Most hospitals also participate in a variety of national and/or state clinical performance measurement activities, often as a condition of funding and certification.<sup>50</sup> Regardless of the type of performance indicators used by an organization to monitor patient care processes, these measures, if well designed and appropriately implemented, provide valuable insight into the health care organization's management of critical patient care processes. Table 39-3 provides a list of frequently monitored processes of care.

Data from performance measurement indicators provide investigators with critical information to guide study planning and preparation. For instance, if a clinical research study intervention will result in a highly immunocompromised patient population, the effectiveness of the hospital's infection control processes becomes highly relevant. Quantitative and objective data about the

organization's health care-associated infection rates and hand hygiene practices provide valuable information about system and process issues that might need to be addressed prior to recruiting and enrolling patients/participants.

Assuring that the clinical care environment in which clinical research participants will be managed and cared for is safe and capable of supporting high-quality care and clinical research support is a shared responsibility of the health care organization's leadership, the care providers and the research team. Basic quality improvement tools such as flowcharting, prospective risk assessment methodologies (e.g., FMEA), and clinical quality and patient safety performance measures provide objective data to guide protocol planning and implementation strategies.

### ASSESSING CLINICAL RESEARCH PARTICIPANTS' PERCEPTIONS OF THE CLINICAL RESEARCH EXPERIENCE

One aspect of quality that has been far less intensely addressed in the literature is the assessment of the quality of the care and services provided to research participants. In particular, few studies have addressed participants' *perceptions* of their experiences with clinical research processes. In this section, we focus on the assessment of participants' perceptions of their clinical research experiences.

Understanding the factors that influence potential subjects' willingness to participate in studies is critical to the success of the research enterprise. A substantial number of studies have been conducted to understand the factors that influence study participation. Factors such as altruism, financial incentives, access to otherwise unavailable health care, and expanded treatment options have been identified as important to subjects when making a decision regarding study participation.<sup>51,52,53,54</sup> Conversely, factors such as intrinsic public distrust of clinical research, fear of discomfort, time commitments, and a lack of access to, and lack of awareness of, the availability of clinical research studies have been described as barriers to recruitment and participation.<sup>55,56</sup>

Studies that have focused on what participants understand about their involvement in a research project have contributed further to understanding the impact that the design of a clinical research has on both patient recruitment and retention, as well as on the provision of informed consent.<sup>57,58,59,60,61</sup> Strategies that encourage study participation include offering participants a greater voice in the research process by seeking participant input in setting the research agenda, by seeking their input in identifying study outcome measures, and by understanding recruitment requirements.<sup>62,63,64</sup>

Whereas the studies cited in the prior paragraph offer incipient insight into participants' views of the clinical research experience, they raise more questions than they answer. Do the participants' perceptions of the process

**TABLE 39-3** Examples of Clinical Care Performance Indicators

- Medication management
  - Medication errors
- Pain management
  - Reassessment for pain post-intervention
- Treatment delivery
  - Delays in treatment
  - Patient wait times
- Invasive procedures
  - Complication rates
  - Returns to the operating
  - Re-admissions following outpatient procedures
  - Wrong site/person surgery
- Infection control
  - Infection rates
  - Hand hygiene compliance
  - Timing of surgical antimicrobial prophylaxis
  - Health care worker vaccination rates
- Patient falls
- Transfusion management
- Disease/diagnosis-specific measures
  - Acute myocardial infarction
  - Pneumonia
  - Heart failure
  - Stroke

change once the recruitment honeymoon is over? Do investigators have any insight into how participants perceive their experiences during the course of their involvement in a clinical research study? Why should the research team care about their study participants' experiences? In our view, this latter question must be considered carefully if investigators wish to continue to recruit and retain research participants who are both engaged and invested in the clinical research process—clearly a critical step in the process of translating scientific discovery into clinical medicine. However, actively eliciting information from participants about their clinical research experiences represents essentially unexplored territory for the clinical research professional. Whereas many aspects of the experience of participating in a clinical research protocol are similar to standard aspects of health care delivery, substantive differences exist. Participation in clinical research is voluntary. Participation in health care often is not. Current health care thinking places the patient at the center of the clinical care plan—a partner in the care process. The converse is often the case in the conduct of clinical research. The proscriptive nature of the research protocol often relegates participants to the role of passive recipients of interventions. From our perspective, we consider it self-evident that research participants must be located at the center of the clinical research process; they are, indeed, co-producers of the main product of the research process—translational science. For this reason research participants should be considered invaluable members of the research team. Considering participants as key members of the research team compels investigators to work diligently to understand participants' perceptions. Learning which factors positively influence participants' experiences provides the investigative team with the opportunity to design and implement research processes that incorporate those factors, thereby enhancing participants' perceptions of the quality of the research experience. These clinical research performance improvement activities are not only highly considerate of the study participants (and serve to incorporate them into the research team as intellectual contributors) but also are instrumental in assuring study quality and integrity. Addressing factors identified as problematic by study participants likely will enhance participant adherence to protocol requirements and minimize study drop-out, while concomitantly increasing the likelihood that participants will recommend study participation to others.

Only limited data have been published in the literature to date describing clinical research subjects' perceptions of their experiences as research participants. Verheggen and colleagues developed and fielded a survey designed both to assess participants' satisfaction with their clinical research experiences, as well as to analyze factors that were associated with participants' satisfaction with complex clinical

research processes. In this study the investigators interviewed the participants before the start of the study to assess their expectations of the study and then interviewed the participants during the conduct of the clinical trial.<sup>65</sup> Verheggen and colleagues reported that participants were generally satisfied with the medical/technical and interpersonal aspects of the study; however, participants reported substantially lower satisfaction with the amount of information they received about their health statuses during the course of the study (despite the fact that health status information was beyond the scope of the study). Additional factors identified as influencing a participant's satisfaction included the participant's attitude about clinical research (e.g., trust), the subject's interest in medical affairs, the participant's perception of her/his general health status, and his/her expectations of care during the trial (e.g., some participants anticipated being treated as "special" persons in the study and some anticipated feeling physically better as a result of participating in the study).<sup>65</sup> Morris and Balmer summarized research investigating the participant experience and the researcher—participant relationship into the following categories: (1) the bioethics approach—focusing on the moral imperatives that must guide the research relationship; (2) the trials management literature—focusing on the drivers and barriers to participation in clinical research; and (3) studies of patient-volunteers' understanding (i.e., participants' understanding of trial design and the informed consent process).<sup>63</sup> This study sought to describe how subjects and volunteers understand their participation in research, and, in particular, attempted to characterize the researcher—participant relationship. Morris concluded that the participant can assume a variety of disparate roles during the course of a research study (e.g., giver, client, collaborator, "guinea pig") and that these varying roles must be understood and appreciated by the investigator in order to establish a productive relationship with participants. In a more recent study, Morris interviewed small groups of female subjects from the United States and the United Kingdom to investigate the subjects' understanding of their research participation. Morris and her colleagues report that the subjects' primary concerns are related to the social issues that are associated with study participation rather than physical concerns. Additional "volunteer identities" were described (e.g., technoscience enthusiast, critics of health care), reinforcing the notion that participants assume various identities during the course of the research process. Nonetheless, despite these changes in identity, participants' perceptions about their research experiences can be used to inform the management of the research study and the relationships between participants and study team members.<sup>64</sup> Both Verheggen's and Morris' findings provide the foundation for a compelling argument for actively exploring and assessing

participants' perceptions of their clinical research experiences in more detail. Identifying the factors that influence participants' perceptions provides a template for the research community to develop processes and tools with which to measure participants' experiences objectively, ultimately identifying aspects of the clinical research experience that are ripe for performance improvement activities. Once these issues have been identified, interventions can be designed and implemented prospectively to address the problems identified, and investigators can track the successes or failures of their interventions. Based on the experiences with this approach in clinical care (described in detail below), we believe that this approach will improve participants' experiences substantially. More importantly, we believe that improving clinical research participants' experiences will, of necessity, improve the overall quality of clinical research, both clinically and scientifically.

What aspects of the clinical research processes do participants find objectionable? Virtually every clinical research professional can describe implementation issues that arise during the course of a research study that may complicate the conduct of the study or negatively may impact the study's outcome. The issues most commonly encountered by investigators include recruitment difficulties, poor participant adherence to protocol requirements, and problems relating to the retention of participants in the study. Understanding the underlying or root causes of these problems is a first step toward overcoming these impediments. Whereas some of these barriers to the successful conduct of a clinical research study can be attributed to administrative and process difficulties, many of them are linked directly to participant responses to study-related issues. If one considers the conduct of clinical research from the participant's perspective, one can begin to appreciate the system and process issues that can have negative (or positive) influences on participants' experiences, and, in turn, on participants' likelihood of adherence to study requirements, as well as on the individual participant's likelihood of completing the project.

The clinical research community can look to the health care industry for guidance in determining how to assess participants' experiences as research subjects. Although the processes of providing patient care in a hospital and the conduct of a clinical research study often markedly are different, at the center of each of these activities is a human being interacting with some aspect of the health care delivery system—whether the participant is an inpatient in a community hospital, a research subject in a Clinical Translational Science Award unit, or is being seen as a study participant in a researcher's office building. What happens to that human being and how that individual perceives the clinical research experience ultimately will inform both the clinical and scientific outcomes of those processes. One

needs to be mindful, as Morris and Balmer point out, that the participant—researcher relationship and the patient—doctor relationship are not wholly comparable.<sup>63</sup> That said, one can make the case that regardless of the type of relationship (or reason for the relationship), understanding how the patient and/or the participant perceives those relationships and interactions is important to both relationships' ultimate end points—in the case of the physician, positive health outcomes and to the researcher, a completed study with protocol adherence, no protocol drop-outs, no protocol violations and no missing data points.

A substantial amount of research and quality improvement work has focused on evaluating the patient's experience in the traditional health care environment,<sup>66,67,68,69,70,71</sup> and, we believe, these data and this approach provide an ideal mechanism for learning about clinical research subjects' perceptions of their clinical research experiences.

Eliciting feedback from patients who have been hospitalized regarding their impressions of interactions with specific aspects of the health care experience has become a standard component of almost all health care organizations' operations. Data from these surveys are used for myriad purposes. One clear goal is to use these data to improve the quality of the care and services provided to patients. Continuous process improvement activities in hospitals are driven by the information provided by patients about their perceptions of the care and services they received.<sup>72</sup>

The literature is replete with examples of improvements in clinical care driven by feedback provided by patients. Some of the most notable examples include: enhancing communication among the health care team to improve patient outcomes and processes,<sup>73,74,75,76</sup> improving pain management,<sup>66,77</sup> and providing useful and timely discharge instructions.<sup>78,79,80</sup> Patient survey data also are used to inform state and federal health care policy and as a measure of the quality of care delivered for hospital reimbursement purposes. The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS), a survey tool administered by most hospitals in the United States, is used to guide Medicare reimbursement, as well as for public reporting of the quality of individual hospitals.<sup>81</sup> Accrediting organizations such as the Joint Commission, the College of American Pathologists, and the American Association of Blood Banks require that some aspect of the patient experience be evaluated as part of their accreditation programs. Recent advances in the science of patient-focused survey techniques, coupled with the maturation of hospital-based quality improvement strategies, have led to improvements in clinical outcomes as a result of patient survey activities.<sup>68,82</sup>

Historically, patients' interactions with the health care system were assessed using tools that asked a patient to rate his/her satisfaction with the care and services provided. Surveys that elicit a person's satisfaction are designed to

measure the difference between a person's expectations and/or needs and her or his experiences.<sup>73</sup> Crow and colleagues describe satisfaction as a relative concept—where satisfaction is wholly dependent on the individual's construct and perspective.<sup>83</sup> The fact that these perceptions may be highly disparate can be illustrated by the following example. Two patients arrive at the emergency room, both with severe upper respiratory symptoms. Each patient waits 3 hours to be seen. The care provided to each patient is comparable and the clinical outcomes of the visits are identical. However, despite the similarities of their clinical experiences and outcomes, each patient's relative satisfaction with the encounter may differ substantially. One patient, who has prior experience with the system and perhaps has private insurance and ready access to the health care delivery system, reports a very low satisfaction with the encounter because, in his view, he had to wait too long to be seen by a physician. The other patient, uninsured, inexperienced with the system, and who has had infrequent access to medical care, rated the interaction as highly satisfactory because he expected that he would be denied care and, even if not denied care, that his wait would be lengthy. In this example both patients received the same care, both had effectively identical clinical outcomes, but their perceived experiences were vastly divergent, due entirely to individual expectations.

In the early to mid-1990s, survey developers shifted the focus from measuring individuals' satisfaction with care and services to assessing what patients actually experienced during specific episodes of care.<sup>67,84</sup> Survey methodology changed from asking patients to rate their satisfaction with care experiences to asking patients to report whether some aspect of care occurred or not, and, if it did occur, with what frequency. Questions from the HCAHPS survey such as: "During this hospital stay, how often did doctors explain things in a way you could understand?" and "Before giving you any new medicine, how often did hospital staff describe possible side effects in a way you could understand?" elicit objective data that are actionable.

Coincident with this shift in survey philosophy was a movement toward patient-centered care and services. Patient-centered care is defined as providing care that is respectful of, and responsive to, individual patient preferences, needs, and values, as well as care that ensures that patient values guide all clinical decisions.<sup>85,86</sup> The concept of patient centeredness, or in the case of the clinical research environment, participant centeredness, creates a tension and runs headlong into the core of the clinical research process (i.e., both the proscribed nature of study design as well as the power of aggregated data). However, moving to a more participant-focused model of research implementation does not suggest that the clinical research community abdicates control of the scientific process to

research subjects. Rather, this new model compels the investigator to consider the participant's perspective actively when designing or implementing a study.

Measuring quality through the research participant's eyes will better prepare researchers to consider the participant's perspectives when designing and conducting clinical research. In the health care setting, although providers often believe that they understand what is important to patients, they may be, and often are, incorrect.<sup>73,87,88,89</sup> In a study that was designed to examine the differences between nurses' and patients' views of what is important in nursing care, Lynn and McMillen found that nurses underestimated the degree to which patients' value quality nursing care. For example, patients ranked "nurse gives patients medications on time" as the fourth most important item on a list of factors influencing quality; nurses ranked this item as the forty-second most important on the list.<sup>89</sup> In a second study designed to compare patient, nurse and physician assessments of quality of care with patient satisfaction in critical care units, Shannon and coworkers found that nurses' and physicians' perspectives were associated with their personal views of their work environments, more than organizational factors, patient characteristics or other patient outcomes. For example, clinicians who believed that working relationships between doctors and nurses were positive overestimated both the patients' views of quality as well as the levels of patients' satisfaction with the care provided.<sup>90</sup> In a third study that was designed to assess patients' and physicians' ratings of the importance of different elements of quality of care, both patients and physicians agreed about the importance of clinical skills; however, patients ranked the provision of information as significantly more important than did physicians.<sup>88</sup>

In an effort to understand in more detail what patients find important, the Harvard University-based Picker Institute conducted focus groups and interviews with patients, family members, friends, and health care professionals to find out what aspects of care are most important to patients and their families. Seven dimensions of patient-centered care emerged from the analysis of the extensive qualitative data and a review of the pertinent literature.<sup>69,86</sup> The dimensions of patient-centered care are: (1) coordination and integration of care and services; (2) respect for patients' preferences, values, and expressed needs; (3) emotional support; (4) involvement of family and close others; (5) physical comfort; (6) information, education, and communication; (7) continuity and transition from hospital to home; and (8) access to care and services. These dimensions of patient centered care served as the framework for development of the Picker survey instruments.<sup>69,88,91</sup>

Guided by this initial work, the Picker Institute developed a core survey instrument based on careful quantitative

and qualitative scientific investigation. Ongoing development efforts reinforced that the dimensions of patient-centered care remain the critical areas on which to focus from the patient's perspective. Focus groups conducted by the National Research Corporation—Picker in 2001 reinforced that the issues identified in the 1980s were still relevant for patients. In addition, new content issues have emerged since development of the original instruments. For example, patient safety has become a highly relevant issue. Subsequently, in 2002, a group of patient safety items was developed using the original Picker Institute model. These items now are included on the core Picker survey instruments. The HCAHPS survey, the first national, standardized, publicly reported survey of patients' perspectives of hospital care, uses specific, actionable, and meaningful questions similar to those on the core Picker survey instruments.<sup>89,90,92,93</sup>

The NIH Clinical Center has been surveying patient/participants using a Picker-derived survey instrument since the mid-1990s. The NIH Clinical Center is motivated to understand how patient/participants perceive the care they receive during their participation in studies conducted at the NIH Clinical Center as one method to assure that the needs and expectations of this special group of individuals who volunteer to contribute to scientific discovery are met. In 1995 the Clinical Center partnered with the Picker Institute to develop a method of eliciting patient/participant feedback about critical aspects of their experiences in clinical research at the NIH Clinical Center. The Picker Institute's philosophy of eliciting information from patients about their experiences was used to develop the NIH Clinical Center's survey. The survey was tailored to the unique clinical research environment of the Clinical Center and was designed to include several questions addressing the experience of participating in clinical research.

For the past 15 years the NIH Clinical Center has used these data to identify opportunities to improve our patient/participants' experiences. Issues such as communication with clinical staff, attention to emotional support, and the participant's understanding about the point at which he or she can cease participation in a study have been identified as areas that required focused review and attention. These issues and others have been addressed using the NIH Clinical Center's organizational performance improvement structure. Interventions have been implemented and improvements have been measured. Many of these issues would not have been identified as problematic had the NIH Clinical Center leadership not actively queried their research participants about their perceptions of these processes.

In 2003 the leadership of the Rockefeller University Hospital Center for Clinical and Translational Science expressed interest in the NIH Clinical Center's survey and, subsequently, began using a similar survey to measure the

experiences of their research population. The vision of this collaboration between the Rockefeller University and the NIH Clinical Center was to use data from each institution to understand patients' perceptions of these individual clinical research environments and to benchmark performance. Although this survey provides both institutions with an effective tool for flagging individual organizational issues related to clinical care and clinical research, a shortcoming of the survey is that it was not initially tested for reliability or validity in the broader clinical research environment. In 2005 the Rockefeller University, the NIH Clinical Center, and National Research Corporation—Picker partnered to develop a valid and reliable survey instrument specifically to measure participants' perceptions of their clinical research experiences. A two-phased investigation was designed to: (1) identify factors which are considered by participants to be important to the research experience; and (2) develop and implement a survey tool using the data gleaned from Phase One of the project.

Eight academic medical centers participated in Phase One of the study. Twelve focus groups from the medical centers were convened, comprising research participants from one of the following categories: (1) individuals affected by a disease or disorder under study, in an interventional study (defined as "Affected"); (2) participants enrolled in long-term, disease pathogenesis and natural history studies (defined as "Natural History"); or (3) healthy volunteers in studies including an intervention (defined as "Healthy Volunteers"). Using a standardized script, an experienced moderator guided the participants through a series of questions and scenarios designed to elicit feedback about aspects of the clinical research process that they deemed influential to their perception of that experience. Topics discussed in the focus groups included:

1. Reasons for joining the research project
2. Informed consent
3. Likes and dislikes about the clinical research experience
4. Reasons to remain as a participant in the research study
5. Reasons to discontinue participation in the research study
6. Family involvement and reaction to participation in the research study
7. Expectations versus actual experiences in clinical research participation
8. Enrollment recommendations
9. Suggestions for making research participation easier
10. Experiences relating to recruitment for the clinical research study
11. The role of incentives
12. Misconceptions about research.

Analysis indicates that the factors that most positively influence participants' perceptions of their research experiences include: their relationship with the research staff; the quality and attentiveness of the medical care provided to the patient in the context of the study; and the opportunity to learn more about their disease processes. Factors that were most frequently associated with negative perceptions of the clinical research process were: pain and discomfort; logistical inconveniences; and unprofessional or dismissive behavior by members of the research staff.<sup>94</sup>

Analysis of these focus group data will lead to the development of a survey to be used by clinical research professionals to measure participants' perceptions of the clinical research experience. The ultimate goal of the project is to use data from these surveys to inform efforts to improve the participant experience as well as to improve the overall quality of the clinical research process.

## CONCLUSION

Patient safety, clinical quality, and efficient and effective processes of care delivery are of equal import to clinical care and clinical research. Irrespective of the approach taken, we believe that clinical researchers and institutions involved in clinical research must collect data from a variety of sources, including the solicitation of perceptions from participants and staff input about their research experiences, to improve the processes involved continually.

Developing clinical research programs include: structured approaches to obtain reliable information about the factors contributing to process failures and adverse events (including careful root cause analyses); mechanisms for assessing trends in process and outcome failures, structured approaches to identifying risk points prior to study implementation (e.g., failure mode and effects analysis); and obtaining participant insights about their perceptions of the clinical research experience will provide the necessary data to allow institutions and investigators to improve the clinical research experience. We believe this will increase substantially the likelihood of successful completion of clinical studies.

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