The Clinical Research Enterprise encompasses a multifaceted array of physical, technical, and human interactions aimed at using new discoveries to help alleviate human disease and suffering. The process from scientific bench to patient bedside involves basic and clinical scientists, educational institutions, health care providers, health care financing organizations, voluntary health agencies, funding organizations, industry, research volunteers, and patients. Several speakers noted that the content and process of modern science are changing the ways in which knowledge is interpreted. For example, genomics has generated a fundamental and revolutionary change in how we view medicine. The vast amount of information that the Human Genome Project generates is stimulating new collaborations between biologists, chemists, computer scientists, and mathematicians. While bio and medical informatics provide new opportunities for streamlining clinical research, symposium participants warned that they also pose new threats to patient/research participant privacy and confidentiality.

At the other end of the health care delivery system, interest and expertise in measuring the effectiveness of medical interventions have increased. Symposium participants said that the growth of evidence-based medicine requires more valid and robust indicators of effectiveness. This need becomes even more pronounced in an environment focused on lowering health care costs. Clinical research underpins these issues and provides the basis for decisions regarding effectiveness and patient safety.
Today’s science allows clinicians to describe genetic variants that influence disease and drug metabolism, while tomorrow’s science will use genomics to diagnose, treat, and prevent disease.

The Impact of Genomics and Bioinformatics on Clinical Research

The announcement of the first draft of the human genome in June 2000 heralded a new era in biomedical research. To date, 85 to 90 percent of the human genome has been sequenced. The next step in this effort is to analyze the data and translate it into information that is useful in clinical practice. Vivian Cheung of the University of Pennsylvania described genetics as the study of heredity or variation and genomics as the study of the global approach to cells, organs, and organisms at the DNA, RNA, and protein levels. The distinction is important because it illustrates the ways in which genomics will change our approach to medicine. Today’s science allows clinicians to describe genetic variants that influence disease and drug metabolism, while tomorrow’s science will use genomics to diagnose, treat, and prevent disease.

David Altshuler of the Massachusetts Institute of Technology reiterated the current limitations of our genetic knowledge. “Genetics can help us understand the fundamental basis of disease, stratify patients based on their predisposed genetic risk for preclinical intervention, and tailor treatment to individual risk and response,” he said, adding, however, that “genetics is not a magic bullet.” Although modern genetics has been very successful in explaining diseases caused by a single gene, most common diseases are caused by a combination of multiple genes and the environment.

Eric D. Green of the National Human Genome Research Institute contends that “for the next two to three decades a major priority is going to be studying these DNA sequences and interpreting them to reveal the important features; for example, which regions actually encode for protein, which are vitally important in turning on and off genes, which regulatory networks are involved in transcription, and which sequences are important in determining how chromosomes function?”

Green emphasized that the Human Genome Project has demonstrated how the boundaries between the disciplines quickly become artificial and actually inhibitory and suggested that “you almost want to eliminate these boundaries…the most successful genome endeavors in the past decade have been those that have had valuable marriages between computer scientists, engineers, and biochemists and molecular biologists. There is absolutely no question that the same is going to be true from this point forward as well.”

Green noted that one tool that will help aid this collaboration is bioinformatics, which provides a common language for many disciplines. He added that computational tools also will be essential for sorting and organizing the vast amounts of information being produced and displaying the data in an integrated way that facilitates comprehension. While there will be numerous approaches to plotting the “proteome,” or protein map of the genome, none can be realized without the aid of supercomputers and bioinformatics. Thus, said Green, research in the postgenomic era will require a cadre of scientists trained to bridge the gap between information technology, engineering, and molecular biology. Public and private-sector training initiatives can help develop researchers who have a knowledge base in all three areas.

Judith Vaitukaitis of the National Institute of Health (NIH), National Center for Research Resources echoed Green’s assertion that clinical research in the 21st century will depend on access to complex, expensive research tools, a multidisciplinary and collaborative approach, and good information management systems. She sees a future in which clinical research centers and the private sector collaborate to provide a core set of neces-
sary resources (research participants, human resources, technical assistance, bioinformatics, and specialized laboratories and equipment) that can then be made available as national resources. The models for such centers already exist in the forms of research networks, tissue banks, and Internet-based databases.

To achieve some of these goals, academic health centers are turning to unique partnerships with industry to advance their clinical research agenda. For example, Massachusetts General Hospital has entered into a partnership with Millennium Pharmaceuticals and deCODE Genetics, said William Crowley of the Director of Massachusetts General Hospital. Affiliated with Harvard University, the hospital can take advantage of the companies’ innovative technology, use the proceeds to build research infrastructure, and gain access to the Icelandic DNA database, collected and maintained by deCODE Genetics. Millennium Pharmaceuticals has access to clinical researchers and a research population at Massachusetts General Hospital, and deCODE Genetics profits from its access to data on a comparison population as well as the opportunity to conduct joint research with Harvard faculty members.

The Role of Clinical Information Systems in Clinical Research

Not only are certain elements of the clinical research enterprise growing in volume, but they also are becoming more geographically dispersed. Through telemedicine and Internet connections, patient screening can be conducted from remote locations around the world. Virtual clinical research centers can be established by integrating modern technology with informatics. The real test of these centers will not be the technology but the data management, said John Gallin, Director of the National Institute of Health’s (NIH) Warren Grant Magnuson Clinical Center. Identifying and prioritizing informatics needs at national and institutional levels should be top priorities for funding agencies, said Gallin, who also commented that “data coordination with a standardized vocabulary, aimed at integrating patient care, research, and management, is a pressing need.”

At the NIH Clinical Center, efforts are already underway to develop an electronic data system, the Clinical Research Information System (CRIS). CRIS would assist clinical researchers with protocol writing and review; data capture for patient care and research; data management; adverse event detection and reporting; data presentation; and training and outreach. The quality of patient care will be improved through the creation of a single continuous record of care that will be maintained at the Clinical Center, said Gallin, and will provide all referring physicians with access to appropriate patient data, incorporate real-time alerts and reference material to support care decisions, provide comprehensive security for patient privacy, and minimize the opportunity for error.

The CRIS project at NIH is in many ways a pilot test of a system that could gain wider use. However, participants noted that barriers often arise when multiple institutions become involved over time; for example, inconsistencies in the way data are collected, the difficulty in drawing out discrete data from continuous data that have been captured, and the lack of decision rules that typically control a clinical trial. William Stead of Vanderbilt University envisions a time when “we should be able to get the advantages of data management that we need for clinical research as a simple by-product of managing the practice.” Stead said that better data management would provide abundant new opportunities to leverage informatics in clinical research through surveillance of populations and targeted trials and by relating distant health outcomes to health care processes. To
achieve these goals, Stead noted, standardized information technology and vocabulary are required.

The lack of consistent terminology and vocabulary has been a longstanding obstacle to clinical research, particularly longitudinal studies, agreed Christopher Chute of the Mayo Clinic. One of the most common coding systems, the International Classification of Diseases, Ninth Revision (ICD-9), was designed primarily for billing and was never designed to describe diseases, to capture clinical data, or to be used in health research.

SNOMED III is a comprehensive, multi-axial nomenclature classification system for indexing the entire medical vocabulary—including signs, symptoms, diagnoses, and procedures—that is due to be released in December 2001. Chute added that challenges include developing quality measures, adjusting for severity, training those who input the data, developing business and research data systems that work synergistically, and safeguarding patient confidentiality.

HMOs might provide fertile ground for conducting health services, epidemiological, and clinical research, said Richard Platt of the Harvard Pilgrim Health Care. Platt added that HMOs provide researchers with access to a defined population and provider group and the ability to intervene at the health care level. Despite these advantages, HMOs face similar data management and analysis problems, cautioned Platt. HMO databases were designed for business rather than research use, and they often lack common terminology. In addition, research needs often differ from clinical needs; thus, physicians may not include in the patient file information that would be relevant for research purposes.

Clinical information systems must put patient needs first and above all research goals, said Stan Huff of Intermountain HealthCare. Intermountain is using its clinical information system to supervise and assess quality assurance, follow patient outcomes and complication rates, and monitor disease outbreaks. According to Huff, a good clinical information system integrates decision support with the patient care process, has comprehensive content, captures real-time, point-of-care data, and facilitates clinical and administrative research.

Clinical Research and Evidence-Based Medicine

Several speakers noted that reliable clinical information, properly organized and managed for research purposes, could be used to construct rational, evidence-based medical care. The Agency for Healthcare Research and Quality (AHRQ), defines evidence-based medicine as “clinical decision making that integrates both individual clinical expertise and the best external evidence,” said Francis Chesley of AHRQ. The advantages of such an approach, said Chesley, are that it integrates medical education with clinical practice; it can be learned at any career stage; it reduces uncertainty; and it may allow for better use of limited resources.

On the other hand, it takes time to learn and practice; the evidence needed for decisions is often lacking; and the systematic evaluation of evidence requires interpretation. For these reasons, this approach has failed to have a major impact on practice variations, added John Wennberg of the Dartmouth Medical School. Wennberg said that physicians resist evidence-based practice and that there is a perception that outcomes research does not keep pace with dynamic changes in medical theory.
Larry Green of the American Academy of Family Physicians cautioned against relying too heavily on evidence-based medicine’s focus on health problems that are primarily found in large academic health centers. He argued that researchers also must study populations that receive health care from family physicians and community hospitals, as well as those that have no access to the health care system. Involving community health care providers in research is not the obstacle some claim it to be, said Green. “Community-based physicians are willing to participate in clinical research, particularly if they can see that the findings of the study will improve their clinical practice.”

Evidence-based medicine depends on valid and reliable data; however, in some areas of research, it is not possible to conduct large trials, which raises uncertainty about the usefulness of evidence gained from smaller studies, said Joseph C. Cappelleri of Pfizer, Inc. Cappelleri described his findings from an investigation of the differences between mega trials and meta-analysis of smaller trials. Cappelleri and his colleagues found that, in general, the conclusions drawn from mega trials and meta-analysis agree, but when they don’t, possible explanations include publication bias (for example, small studies demonstrating no affect are unlikely to be published), dissimilar patient populations, and protocol differences. As a summary measure of patient or study differences, the control rate in a study (the proportion of events in the control group) may also help to explain discrepancies between large trials and meta-analysis of smaller trials. Cappelleri stressed that these research methods are complementary, each with benefits and drawbacks, and that meta-analysis should also be applied to examine study and population differences.

Health Care Purchasers’ Reliance on Clinical Research

Although clinical research can contribute to improving health care by focusing on the prevention, diagnosis, and treatment of disease, this is not enough, said Jeffrey Kang of the Health Care Financing Administration (HCFA), adding, that research also has a major role to play in assessing and determining how to improve quality of care. Kang reminded participants that the Medicare program (administered by HCFA) only covers health care services that are “reasonable and necessary,” and making that determination means that HCFA must review clinical evidence. Moreover, said Kang, factors that affect coverage decisions include product or service effectiveness and efficacy compared to other interventions, as well as the appropriateness of use in defined populations. Ideally, said Kang, HCFA would like to base all of its coverage decisions on clinical evidence; however, this evidence is limited.

Robert Galvin of General Electric Company emphasized that better quality care need not be more expensive and that well-designed research can help eliminate overuse and misuse of health care services. He predicts that a market-based, competitive approach will only work for health care if consumers become informed about health care decisions. Increasing consumer awareness means that consumers will expect to be informed about research opportunities. He argued that clinical research can contribute to improving health care by focusing on prevention, diagnosis, and treatment of disease, but this is not enough. Research also has a major role to play in assessing and determining how to improve quality of care. He does not believe that better quality care is necessarily more expensive, particularly if research is used to eliminate overuse and misuse of health care services. He predicts that a market-based, competitive approach will only work for health care if consumers become savvier about health care decisions. When asked about the purchaser’s role in financing clinical research, Dr. Galvin stated that corporations finance...
clinical research through taxes, donations to foundations, and directly when it is in their direct interest to do so.

Anthony Kotin of Internet Healthcare Group said that insurers are feeling pressure to finance clinical research because they are facing demands from patient groups to pay for unproven therapies. He mentioned that one option is for insurers to develop a separate fund so employees can purchase additional coverage that covers the cost of clinical research. Southwest Bell tried this and found that it was very profitable because employees purchased "but rarely used" the additional coverage. He also believes there will be new opportunities for clinical research investigators to conduct research on large-scale datasets collected by payers in the near future.

About the Clinical Research Roundtable

The IOM’s Clinical Research Roundtable (CRR) was established in response to the expressed needs of a spectrum of clinical research interests, as described in the 1998 Graylyn Consensus Development Conference report. The purpose of the CRR is to provide a forum for discussing pressing issues facing clinical research in the 21st century. The CRR membership includes individuals from the academic health community, federal agencies sponsoring and regulating clinical research, private sector sponsors of clinical research, foundations, public and private sector insurance programs, health plans and insurance companies, corporate purchasers of health care, and representatives of patient interests. The CRR meets quarterly to discuss the challenges facing clinical research and to explore and develop strategies for enhancing the awareness and understanding of clinical research in order to sustain a more supportive environment for high-quality clinical research.


For More Information...

Please visit the project web site at www.iom.edu/crr.

This study was funded by the American Medical Association, Association of American Medical Colleges, Agency for Healthcare and Quality, Veterans Administration, Centers for Disease Control and Prevention, U.S. Food and Drug Administration, National Institutes of Health, Robert Wood Johnson Foundation, Blue Cross and Blue Shield Association, Johnson & Johnson, Burroughs Wellcome Fund, Merck and Company, Pfizer Inc., and the Doris Duke Charitable Foundation. The views presented in this report are those of the Institute of Medicine Clinical Research Roundtable and are not necessarily those of the funding agencies.
Clinical Research Roundtable

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