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RESOURCES FOR CLINICAL INVESTIGATION

Report of a Study by a Committee of the

INSTITUTE OF MEDICINE

Division of Health Sciences Policy

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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MANDATE OF THE COMMITTEE[1]

The Committee for the Study of Resources for Clinical Investigation was constituted by the Institute of Medicine in response to a request by the National Institutes of Health for an assessment of the availability of appropriate resources for research related to patients. In the health sciences, there are many technical advances that offer considerable hope for the future if appropriate resources are available for clinical investigation.

Major concerns have been raised about the future of clinical investigation in the United States because of (a) fundamental changes in the organization of health care in the United States, (b) major efforts at cost containment in all areas of clinical medicine, (c) rapidly escalating expenses associated with drug development in this country, and (d) a reduction in the number of individuals pursuing a career in clinical investigation.

In its mandate, the Committee was asked to consider the following questions:

1. What changes in the health care system have had an impact on the environment for clinical investigation or the resources necessary for such research? How should funding for research and care be integrated?
2. How can the NIH increase interest in clinical investigation among medical students and residents? How can the training of young clinical investigators be improved to optimize their chances of success in the peer review process?
3. What might the NIH do to stimulate and facilitate the translation of basic research advances to clinical practice?
4. How might the NIH foster interaction between industry and clinical investigators involved in federally-funded research in order to exploit scientific opportunities while safeguarding federal stewardship of public monies?
5. How should research involving patient care be organized to provide optimal scientific return?
6. How can the NIH stimulate interest in outcome assessment of new and established treatment programs?

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[1]The National Institutes of Health directed the Committee to proceed expeditiously, relying on members to provide their collective judgment on the challenges facing clinical investigation. Committee members were asked to submit papers which were considered at the two meetings of the Committee (and reprinted herein as Appendixes) and, along with the data supplied by the National Institutes of Health, contributed to the findings and recommendations in this report.

PROCESS USED BY COMMITTEE

The goal of this study was to identify and analyze near and long term national needs for NIH-supported research involving patients. This assessment was to be done by considering recent advances in science, changes in the health care system and other factors that influence motivation, ability, and opportunity to carry out this type of research.

A committee of 15 members with expertise in medicine, surgery, pediatrics, psychiatry, health care financing, university and hospital administration, nursing research, health care services, molecular biology and industry research administration was appointed by the president of the Institute of Medicine with the concurrence of the president of the National Academy of Sciences. The majority of the members were active in clinical investigation. Guests were invited to meet with the committee so as to ensure the broadest range of perspectives.

Because of the complexity of the issues to be considered and the short time allotted for the completion of the task, two activities were undertaken prior to the first meeting. Each member of the committee was asked to define in writing a personal priority list of the leading issues in clinical investigation and the rationale for these choices. In addition, each was asked to suggest approaches to these priority issues as well as key references in the literature that could be distributed to the committee. From the responses, an outline of these issues was assembled by the committee chair. A request for more data and analyses was made of the staff and of the National Institutes of Health. In response to a question of the chair, NIH also provided a definition of clinical investigation and of clinical trials to be used by the committee in its deliberations. The written letters and papers from committee members, the data from the NIH and from the staff, and key publications were distributed to the committee prior to their first meeting.

Extensive discussions by the committee members at the first meeting led to the selection of four areas to be considered during the informal workshop held as the second meeting. The areas were (1) funding of clinical investigation in the United States; (2) training of the young clinical investigator in the United States; (3) organizational structure of clinical investigation; and (4) issues related to outcome assessment and cost-effectiveness analysis.

Prior to the second meeting the committee members prepared written papers to serve as the basis of the in-depth discussions of the four issues which had been selected. The written papers were distributed to the members and guests in advance of the meeting along with the publications which the members had requested and were discussed in depth by the group. The papers are included in the Appendix of this report. The Committee divided into small groups to prepare a summary of the deliberations and recommendations related to each of the four major issues as identified in this report. Based on the deliberations of these subgroups, a full Committee discussion of these issue-oriented summaries and recommendations took place.

INTRODUCTION

Advances in our understanding of both the normal and abnormal functioning of the human body from the cellular to the molecular level, combined with advances in biotechnology, have led us to the point where a number of major diseases not yet conquered are within our grasp to prevent or cure (1). The possibility of vaccines to prevent malaria or hepatitis-B viral infection, and of gene transfer therapy to cure inborn errors of metabolism are but a few examples of scientific advances that may dramatically affect the natural course of human disease.

At this time of unprecedented progress in our increase in knowledge in the biomedical sciences dealing with diseases of human beings, there is growing concern that progress in translating research observations into clinically useful products, devices and procedures will be slowed or even stopped entirely because of serious problems facing clinical investigation and clinical investigators in the United States (2-7, 12, 14, 17, 18, 21, 22, 24). These problems include: a) an inadequate supply and/or inadequately trained clinical investigators, b) lack of funding for clinical investigation, and c) failure to achieve methodological advances, particularly in clinical trials, that take into account both resource limitations and expanding opportunities for studies of new interventions.

This report summarizes the deliberations and recommendations of the Institute of Medicine Committee for the Study on Resources for Clinical Investigation. Four major areas of concern were identified. These areas were: (1) funding of clinical investigation in the United States; (2) training of the young clinical investigator in the United States; (3) resource considerations and necessary organization and structure of clinical investigation; and (4) outcome assessment research. Where the Committee felt it was appropriate, possible solutions to the problems were suggested. For other areas, it was clear to the Committee that easy answers are not currently identifiable. In some instances this was, in part, because of lack of appropriate and adequate data (see pp. 20-21). It was the unanimous opinion of the Committee that the problems outlined must be thoughtfully and vigorously addressed to prevent serious deterioration in clinical investigation in this country.

DEFINITIONS

For the purposes of the Committee's deliberations, the National Institutes of Health (NIH) provided the following definitions:

Clinical investigation is defined as that segment of clinical research for which an investigator directly interacts with patients in either an outpatient or inpatient setting. This definition excludes studies for which material of human origin is obtained through a third party and for which an investigator has had no direct interaction with the patient.

Clinical trial is defined as a scientific research study undertaken with human subjects to evaluate prospectively the diagnostic/prophylactic/therapeutic effects of a drug, device, regimen, or procedure used or intended for use in the practice of medicine or the prevention of disease. A clinical trial should be planned and conducted prospectively and include a concurrent control group or other appropriate comparison group. Excluded are studies of physiological or biochemical mechanisms in human beings (even though the studies may use drugs or devices as research tools), dose tolerance, dose ranging, or pharmacokinetics. Also excluded are early Phase II or pilot studies of drug, device, or procedure safety and efficacy, unless these studies are controlled and sufficiently large in scope to warrant their inclusion in the inventory. Clinical trials do not include registries, epidemiological surveys, or epidemiological studies conducted retrospectively.

It should be noted that this definition of clinical trial is the official NIH definition and is used for reporting to the United States Congress (8).

The Committee emphasizes that these are narrow definitions of clinical investigation and clinical trial and were employed as a practical consideration for the purpose of focusing attention in our deliberations.

Thus, although this study, in accord with the mandate, focuses its discussion and recommendations on this narrow aspect of clinical investigation, namely, that involving an investigator directly interacting with patients, the Committee would point out that there are other types of clinical investigation as described below.

The Committee felt that an appropriate definition of clinical investigation includes studies of individual subjects, groups of subjects, Phase I, II, III, and IV clinical trials, the use of human material for laboratory based research, epidemiological studies of human subjects and outcome assessment. The purpose of clinical investigation is to protect or improve the health of individual patients through translation into clinical practice of scientifically tested and evaluated innovations and improvements in preventive, diagnostic, therapeutic, and rehabilitative technologies.

The differences between the NIH's and the Committee's definition of clinical investigation are substantial and point up a major difficulty experienced by the Committee in its deliberations. For example, data available from the NIH and other sources do not specifically address funding available for clinical investigation as defined by the NIH. Rather, NIH data include support for these research activities plus funding for all research involving any human materials. This is an important point, because the Committee had a consensus impression that a large portion of what the NIH reports as funding for clinical investigation involves the use of human tissue and not direct

investigator-patient interaction as the NIH definition stipulates. The actual NIH funding level for the more narrowly defined programs of clinical investigation cannot be determined at the present time because of the manner in which the NIH collects and records its data. The Committee was convinced that if NIH wishes to maintain its definition of clinical investigation it must collect data accordingly. (See pages 20-21 for a list of the data this Committee recommended be kept for better definition of the problems related to clinical investigation).

In the opinion of the Committee, the above definition of clinical trials is also too narrow (8). A significant portion of clinical trials conducted in this country falls into the category of Phase I and early Phase II studies. The Committee felt it appropriate that these research efforts be included in a revised definition of "clinical trials". This is a particularly relevant issue at a time when the entire regulatory process for drug approval in this country, from Phase I to Phase III clinical trials, is under review at the national level (Food and Drug Administration, Office of Management and Budget, and Congress) (9-11).

Further, failure to consider clinical trials in this broader context could lead to inappropriate conclusions as to the requirements for trained investigators, the needed financial resources, the type of organization required to pursue clinical trials and the availability of patients.

A major recommendation of the Committee is that the NIH make a distinction in their data collection of funding between clinical investigation involving studies in which there is a focus on direct investigator-patient interactions and clinical investigation in which such interaction is not involved, e.g., studies using human tissue in a research project. Second, the full range of clinical trials, from Phase I through Phase III, should be incorporated into this definition. This would also include studies involving patients whose purpose is the elucidation of basic physiological processes or new procedures, such as gene therapy, which are conducted without drug administration. It follows that data with respect to resource utilization requirements for clinical investigations be collected and analyzed in a manner consonant with these definitions (see Issue 3, Recommendation 1).

Resource utilization and requirement information obtained through the use of these modified definitions will be far more valuable than that currently employed.

ISSUE 1: FUNDING OF CLINICAL INVESTIGATION IN THE UNITED STATES[2]

Perhaps the most serious concern raised by the Committee is that the changes in the environment for clinical investigation and in reimbursement for patient care may lead to increasingly inadequate funding of clinical research (2-7, 12, 13). Traditionally, funding of clinical investigation in the United States has been provided from several sources, including governmental and nonprofit foundation research grants, support from the pharmaceutical and medical device industry, and patient care charges. This last category includes the direct support of faculty and residents for postgraduate physician training, and the Medicare indirect education adjustment which was included in recognition of the higher costs of care provided in an environment where a great amount of teaching and clinical research are performed. Until recently, this category also included indirect subsidies provided by insurance companies and other third party payers through their tacit agreement to pay the costs incurred by patients participating in clinical research protocols and the higher costs in teaching hospitals.

There are several factors that will affect continued funding of the patient care costs associated with clinical investigation, including:

1) Changes in support of graduate medical education, both direct costs and the indirect education adjustment

2) Cost containment pressures from third parties to reduce hospital admissions and lengths of stay

3) Selective contracting and discounting by PPOs and HMOs

4) Differentials in inpatient and outpatient support of education and research costs.

Over many years health care costs in the United States have increased at a pace beyond that of general inflation. For example, Medicare hospital payments have more than doubled every five years since the program was initiated in 1966 (12). The reasons for these increases have been detailed, discussed, and debated in numerous studies and forums. Despite major efforts by governmental and non-governmental bodies during the past six to seven years there has been a continued upward surge in the cost of health care. Thus, it is expected that those who pay the medical bills for single individuals and large groups may move vigorously to cut costs by denying payments for all services where any investigational protocol is involved (2, 3, 5). Furthermore, the third party payers have been unresponsive to

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[2]See Appendix B:
Hanft, p. 31; Laubach, p. 36; and Rabkin, p. 48.

arguments that it is in their long term interests to fund clinical trials and related clinical investigation.

The Committee concluded that it is wholly inappropriate for third party payers to deny reimbursement for all appropriate and necessary patient care costs (not marginal costs owing to investigational intervention) that would have been incurred in any case simply because a patient is on an investigational protocol. Such denial would be tantamount to an abrogation of a contractual obligation. Medicare regulations already will not pay for care of Medicare beneficiaries for investigational therapies that may be the best available treatment (13). These policies interfere with the patient-doctor relationship and patient free choice. They also add a potential burden to the NIH in funding clinical investigation because of the absence of funding of necessary and appropriate patient care costs and by limiting patient access to investigational protocols (14). Finally, they limit the hospital's ability to continue to support early clinical investigation which is a significant portion of the costs of clinical investigation.

The marginal, incremental costs above standard patient care costs attributable to the investigational protocol should be borne by the sponsoring institution--pharmaceutical company, NIH, or a foundation. The Committee also believes that third party payers should seek to participate in funding of clinical trials above and beyond reimbursing for standard patient care costs because of the potential to increase the efficacy and cost effectiveness of diagnosis and treatment. While the short term fiscal benefit achieved by employers, health insurance policy subscribers, and the public through the denial of payment for services involved in clinical investigation is real, the long term negative impact from failure to support the conduct of clinical investigation may greatly exceed the short term gains. Excluding the potential direct economic consequences resulting from a reduction in human illness, it is possible that the delay of major advances in medical therapeutics may deny to the public the saving of lives, increases in societal productivity, and the improvement in the quality of life for thousands or even millions of individuals.

Recommendations

1. Payment of Standard Patient Care Costs

   Third party payers (government and non-government) should pay the necessary and appropriate patient care costs for beneficiaries enrolled in approved clinical investigation protocols. This requires a clarification in current Medicare regulations involving definitions of medically necessary care. State regulatory agencies should require conforming changes by all other third party payer policies.

2. Payment of Patient Care Costs in Specific Disease Settings

There are diseases for which appropriate and required care involves investigational protocols. Such diseases include certain types of cancer, genetic diseases, and possibly other severe, life threatening diseases. In these cases, third party payers (government and non-government) should pay the standard patient care costs while costs related to the investigational conclusions should be borne by the sponsoring agency.

3. Payment for Clinical Trials

The Committee believes that third party payers should seek to participate in funding of clinical trials above and beyond reimbursing for standard patient care costs. This approach provides the potential to increase the efficacy and cost effectiveness of diagnosis and treatment, thereby allowing for the possibility of significant financial gain in the long run.

4. Increase in NIH Funding Clinical Investigation

The data presented to the committee indicated that the amount being spent for clinical trials represents approximately six to seven percent of the total NIH budget (15). Although it was not possible to document the overall sum being spent on clinical investigation, it was the committee's judgment that increased support for clinical investigation would be valuable, preferably from new sources, but as a product of redistribution if necessary.

ISSUE 2: TRAINING OF THE YOUNG CLINICAL INVESTIGATOR IN THE UNITED STATES[3]

There is increasing evidence that the number of highly talented individuals finishing medical school and postgraduate residency training, and subsequently entering a career in clinical investigation is decreasing (1, 16-18). Simultaneously, there has been a relative decline in the proportion of the NIH budget devoted to training compared with that committed to research projects (19). As many as 20 percent of clinical traineeships and fellowships have been filled by individuals with the Ph.D. degree rather that the M.D. degree (17). This is occurring at a time when medical enrollments are higher than a decade ago, and when the excitement and challenge associated with clinical research has never been greater. There is legitimate concern that failure of young physicians to enter into careers in clinical investigation will seriously impair our ability to translate what has been discovered in the preclinical setting into medical advances that can benefit mankind.

There are a number of reasons why clinical research has lost a great deal of its appeal for physicians-in-training. These include the large debt borne by recent M.D. graduates, the discrepancy between the incomes of clinical investigators and their colleagues who have chosen to enter the practice of medicine, the increasing difficulty clinical investigators experience in getting funds for their research from NIH and other sources, and uncertainties about advancement in the academic community where accomplishments in laboratory research come sooner, and consequently, are often held in higher regard than these in clinical investigation (17, 18, 20, 21). In addition, one must add to this list the increasing length of time an individual must remain in training to become an effective clinical investigator (20, 21). This will also add to the financial burden felt by both the trainees and their families, and may very well cause an otherwise outstanding candidate for a successful career in clinical research to enter the full time practice of clinical medicine.

Finally, it should be recognized that training programs in clinical investigation must enroll more individuals than may ultimately continue in that career (22). Prior to entering a rigorous training program in clinical investigation, few individuals will truly know if they have the ability, interest, and temperament to succeed as a clinical investigator. Good programs will give them the opportunity to make an honest effort to succeed in the highly competitive and, at times, extremely frustrating world of the clinical investigator.

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[3]See Appendix B:
Merigan, p. 51; Nathan, p. 54; Peck, p. 57; Rose, p. 59;
Sherman, p. 61; Stolley, p. 63; Wells, p. 65; and Kelley, p. 70.

Recommendations

1. The Program

a) A national training program that annually produces approximately 1,000 new, well-trained, clinical investigators is estimated to be necessary to replace U.S. medical school faculty members who leave their investigative careers (21, 22).[4] Each M.D. trainee should receive up to five years of experience (which follows the standard clinical residency training), proceeding from closely supervised training experience and moving toward increasing independence (20). This five-year period should include at least one year of clinical subspecialty training since it is impossible to develop clinical investigators who lack knowledge of the particular discipline involved. The postgraduate training period for the M.D./Ph.D. fellow may require a shorter period than 5 years (e.g., perhaps 3), one of which should include clinical subspecialty training.

b) National training programs are essential for clinical investigators in other health professions such as nursing, clinical psychology or dentistry. These programs should prepare them to make scientific contributions to health care within their fields and should include those aspects of training described in recommendations 2-4 below.

2. Methods of Training

The training program should include, in addition to opportunities to master the fundamental biomedical science, design and responsible conduct of clinical trials, including a solid foundation in areas such as clinical trials methodology, biostatistics, clinical epidemiology and

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[4]This recommendation refers to clinical investigation broadly defined on page 2 of this report, because those are the only data available to this Committee.

The Institute of Medicine's study entitled Personnel Needs and Training for Biomedical and Behavioral Research (21) estimates that the expected number of positions to become available annually on clinical faculties of medical schools through 1990 under various conditions ranges from a low estimate of 1,380 to a high estimate of 4,860 (this number includes only new hires or those who rejoin faculties from temporary tours in government or industry and does not include interfaculty transfers.)

clinical pharmacology. In addition, efforts must be made to enhance an awareness of the ethical, social and economic factors related to clinical investigation.

3. Financing

a) NIH institutional clinical research training grants should continue and be expanded to become the major funding source for the first 3 years of this program.

b) In some instances, individual fellowships may be utilized to support the first 3 years.

c) In most cases, the final 2 years should be competitively funded by a mechanism similar to the NIH career developments awards.

d) Medicare should include, in its payment for hospital services, graduate medical education costs for the time that persons in formal clinical investigation training programs spend in direct standard patient care beyond the required residency years.

e) Pharmaceutical and medical devices companies should continue and expand funding for training of clinical investigators.

4. Career Path Stabilization

The clinical investigational trainee should be in a national system that provides career stabilization and secures ultimate entry into a track toward tenure. The academic institutions and the training program directors should encourage and follow the trainees. Furthermore, they must be held accountable for this process at the time of peer reviewed renewal of the Research Training Awards.

5. Data Collection

There should be a national program to collect appropriate data on clinical investigator training and outcomes such as:

a) number of clinical investigators in training as defined in this study;

b) historical funding activity;

c) productivity/publication track records;

d) demographics.

ISSUE 3: RESOURCE CONSIDERATIONS AND NECESSARY ORGANIZATION AND STRUCTURE OF CLINICAL INVESTIGATION[5]

The optimal organization and structure of that aspect of clinical investigation as defined by the Committee, i.e. patient related clinical research, requires a program which is creative, coordinated and supportive of the clinical investigator. Such a program must maximize the likelihood that important advances will be translated appropriately from the research laboratory to the level of effective patient care and disease prevention. In considering the organization of clinical investigation, the Committee considered concerns that have been voiced both within and outside the academic medical community with respect to issues of conflict of interest, such as those that might be perceived or, in fact, a consequence of personal economic relationships between clinical investigators and companies with whom they are collaborating in clinical research. For example, this relationship may include owning stock, receiving consulting fees, and serving on Boards of Directors.

Recommendations

1. Data Collection on Funding for Clinical Investigation

NIH grants supporting patient related clinical research should be specifically tracked. These should be separated from studies which, for example, use human tissue, but do not specifically involve subject-investigator contact. Currently, it is not possible to distinguish between these types of human investigations because all of the applications are categorized only as to whether or not human subjects are involved.

2. RO-1 Mechanism to Fund Clinical Investigation

Develop an RO-1 mechanism dedicated to patient related clinical studies. NIH research grants that represent studies ready for patient application should be reviewed by study sections set up for this purpose. The number of study sections, as well as the qualification of the members of these study sections, would be determined over time by the number and orientation of the grants submitted. Since the studies under review would be only those that are ready for patient application, the basic research leading up to the proposal would be supported primarily by other mechanisms. All such studies would continue to be funded by the relevant Institutes following current Advisory Council/Board procedures.

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[5]See Appendix B:
Kelley, p. 70; Larson, p. 75; and Lasagna, p. 78.

3. Funding of General Clinical Research Centers

Expand the funding and the mission of General Clinical Research Centers (GCRC). The general clinical research center has proven to be successful in the application of basic research advances to the bedside (23, 24). While the most appropriate mechanism for support continues to be the NIH, methods must be encouraged to allow support from other sources such as the pharmaceutical industry. The GCRC program should be expanded to involve non-hospital settings such as nursing homes, home care sites, and other non-traditional settings. In addition, the responsibilities of the Directors and other professional staff of the GCRCs should be expanded to include recruitment of the best qualified students, postdoctoral trainees, and faculty to a career in patient related clinical investigation. Finally, funding of GCRCs should be increased to support these expanded responsibilities (see Appendix B: Kelley, pp. 73-74).

4. Need for Conflict of Interest Guidelines

The NIH is strongly encouraged to adopt guidelines to prevent conflict of interest. Such guidelines should include rules for full disclosure (26).

5. Role of FDA in Determining Clinical Investigation Agenda

A large portion of United States clinical research resources, particularly from the pharmaceutical industry, relate to drug evaluation (27).

a) The NIH and FDA should examine why much larger numbers of large-scale clinical trials are or can be carried out in Europe than in the U.S.[6] It seems evident that additional studies carried out in the U.S. population could provide additional knowledge critical to the public health.

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[6]It has been possible in recent years to carry out large-scale intervention trials (of beta-blockers, adjuvant therapy in breast cancer, acute effects of thrombolysis) in Europe in great numbers. While there have been excellent trials in the U.S. of a similar kind (beta-blocker heart attack trial (BHAT), AMIS, persantine-aspirin re-infarction study (PARIS), trials of adjuvant therapy of breast cancer), there have been many fewer trials than in Europe.

b) We urge closer liaison between FDA and NIH to examine mechanisms to reduce delay and improve relevance of clinical trials associated with drug evaluation.

6. Exclusion of Patient Groups from Clinical Investigation

The Committee noted that for unclear and often inappropriate reasons, children are excluded from participation in clinical trials of innovative therapies with the exception of oncologic drugs and some anti-infectious agents. In addition, there is a perception that other specific groups such as women, minorities and the elderly may be inappropriately excluded from participation in clinical trials. The Committee recommends that the NIH examine this issue in detail.

7. Reasons for Limitation of Patient Accrual on Clinical Investigation Protocols

A study should be conducted of the extent to which patient accrual limits clinical investigation and the reasons for limited patient accrual such as possible exclusion by Medicare and Medicaid rules of reimbursement for necessary patient care (14), and reluctance of physicians to refer patients.

ISSUE 4: OUTCOME ASSESSMENT RESEARCH[7]

Clinical investigation, as defined for this study, does not include certain kinds of research that, in the opinion of the Committee, will become increasingly important in the years ahead. For example, in the area of drugs, where pre-marketing studies typically involve small numbers of patients, the actual use of medicines (and their impact on treatment outcome), are only partially predictable in advance of regulatory approval.

The ultimate utility of a drug in medical practice will be affected by the skill with which it is used, the presence of co-morbid states, and its relative performance compared not only with alternative drugs, but also with other alternative treatments (such as surgery or "watchful waiting"). Many other interventions in common use, including many major surgical operations and invasive diagnostic procedures, have not received the careful pre-marketing assessments directed at drugs (28-32). The result is the existence of large deficits in the information needed to provide a scientific basis for medical practice. Epidemiologic studies will be required to answer important questions that may arise at any time in the history of drugs and procedures available to treat common conditions.

"Outcome assessment" which includes the full spectrum of methods and approaches useful in evaluating the results of diagnosis or treatment is seriously underfunded, despite the fact that it is a crucial area for rational clinical decision-making, as well as health policy decisions (31). These considerations point up the need for a broader definition of "clinical investigation" than is contained in the definition proposed in the past.

There is strong support within the committee for greater emphasis on the evaluative clinical sciences and for a national program to assess the outcomes of alternative treatments. The outcome values to patients of many common interventions are not well understood, in large part because systematic investigations of efficacy, effectiveness and costs have not been conducted to compare treatment options available for a given condition or illness. Examples of underevaluated treatment options include major surgery, invasive and risky diagnostic procedures, drugs used for indications other than those evaluated in formal FDA-regulated efficacy studies, and the use of intensive care units. Other examples include costly differences in professional opinions on the relative advantages of treating patients in the hospital or the outpatient setting.

The conduct of this research should follow the pattern of biomedical and health services research with grants awarded to academic centers and

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[7]See Appendix B:
Wennberg, p. 82.

investigators based on peer review. Although the results of outcome assessments are of vital interest to many parties, the program must be free from regulatory or cost containment responsibility. The goal of this research is to improve the scientific basis for clinical and policy decision making.

Recommendations

1. Need for Increased Scientific Evaluation of Outcomes

The Committee recommends acceleration in the growth in the nation's commitment to an organized agenda for treatment outcomes research. The agenda should (1) establish research programs to assess major treatment options for priority conditions such as angina pectoris, cataracts, arthritis of the hip, and prostatism; (2) promote the development of assessment methodologies through a program of grants and contracts; (3) fund investigator-initiated proposals; (4) support training grants and fellowship programs in the clinical evaluative sciences; and (5) establish feedback and education programs to practicing physicians and policy makers.

2. Increase in Funding of Outcome Assessment

The Committee applauds the commitment of the Medicare Trust Fund to allocate funds for outcome research. We urge an increase in this level of funding over a period of years as methods are developed. Additional dollars should be provided from private health insurance funds and corporations that are self-insured to provide stability and desirable growth.

3. Examination of Role of NIH in Outcome Assessment

The NIH has considerable expertise in the area of outcome assessment. The Committee urges that the agency prepare studies on how it can be involved in the implementation of the above recommendstions.

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DATA NEEDED FOR BETTER PROBLEM DEFINITION IN THE FUTURE

Funding of Clinical Investigation

In addition to those areas requiring better data identified in the Summary of Deliberations and Recommendations, the following are areas in which the Committee felt that their deliberations were constrained owing to lack of data.

1. Documentation of the practices of third-party payers (Medicare, Medicaid, private insurers) in support of clinical investigation.

2. Documentation of the economic consequences for hospitals of their participation in clinical investigation (added costs associated with caring for patients on investigative protocols).

3. Additional documentation of the adequacy of funding for clinical investigation (as defined in this report) and that of clinical investigators' difficulty with obtaining adequate funding support.

4. Data as to the extent that clinical investigation is conducted in major teaching hospitals relative to other institutional settings and non-institutional settings.

5. Data to analyze if the change in the indirect Medicare subsidy for teaching hospitals has affected the conduct of clinical investigation.

6. Data to document whether the shortened hospital stay has impacted clinical investigation in hospitals.

7. Data to examine how the shift of care from the inpatient to the ambulatory settings has affected clinical investigation.

8. Data to examine how the change in hospital patient mix (e.g. sicker and fewer patients) has affected clinical investigation.

9. Analysis of whether or not particular patient populations have been systemically excluded from participation in clinical investigation, including Medicare patients, Medicaid patients, children, minorities, and women.

Training

1. Analysis of the number of clinical investigational trainees necessary in the United States to allow for approximately 1,000 new faculty each year.

2. Data to document the record of training programs in producing effective clinical investigators.

Organization of Clinical Investigation

1. Analysis of the role played by the GCRC in clinical investigation.

2. Analysis of the role of the GCRC in providing for training of young investigators.

Relationship of the Pharmaceutical Industry and the Food and Drug Administration

1. Analysis as to whether large scale clinical trials of acceptable scientific quality can be conducted outside the United States at less cost than that associated with such trials in the United States.

Outcome Assessment

1. Data giving the number of grants and contracts and the amount of money spent on those grants and contracts as well as intramural studies devoted to outcome assessment, by the NIH.

2. Data quantitated by the number and types of studies (e.g., randomized clinical trials, versus non-experimental design of various kinds) devoted to outcomes assessment in the various Institutes of NIH and in the intramural program, by the NIH.

APPENDIX A: Publications Consulted

PUBLICATIONS CONSULTED

ISSUE 1. THE FUNDING OF CLINICAL INVESTIGATIONS IN THE UNITED STATES

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Vaitukaitis, J. L. Changing Research Directions of Centers, p 1-6, 1987.

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4. THE NEED FOR CLINICAL INVESTIGATORS TO BE CONCERNED WITH THE ISSUES OF OUTCOME ASSESSMENT AND COST-EFFECTIVENESS ANALYSIS

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INTRODUCTORY STATEMENT TO POSITION PAPERS

The following sections contain position papers written by individual committee members. They served as one basis for the committee's deliberations and recommendations. In no instance, however, did the committee as a whole attempt to critique these papers and therefore they represent the individual committee members contributions to the issues. The committee's deliberations and recommendations are these summarized in the report. Only these deliberations and recommendations represent the committee's consensus.

APPENDIX B: Position Papers by Committee Members

ISSUE # 1:
THE FUNDING OF CLINICAL INVESTIGATION IN THE UNITED STATES

FUNDING OF PATIENT CARE COSTS ASSOCIATED WITH CLINICAL RESEARCH

Ruth S. Hanft

The majority of academic clinical investigation on human subjects takes place in teaching hospitals, particularly the principal teaching hospitals with large graduate medical education programs defined as academic medical centers. The changes in hospital reimbursement that have occurred since the early 1980's, changes in the organization and delivery of services, particularly the growth of HMO's and PPO's and increased cost containment activities of third-parties, have not yet but could have profound negative effects on the funding of patient care costs associated with clinical research. While the indirect education adjustment of medicare has softened the potential effects for some teaching hospitals and some teaching hospitals continue to show respectable surpluses, these surpluses are variable and may be of short-term duration.

Regrettably, there is a paucity of hard data on unfunded direct costs of research incurred by hospitals and more important, the indirect costs that reflect the increase in patient care cost that may result from joint research and patient care activities, not covered in private and public research grants. According to Lave and Anderson, "it is particularly difficult to estimate the incremental patient care costs associated with a research protocol."

The Commonwealth Fund Task Force on Academic Health Centers (AHC's) has identified clinical development aspects of research as costs folded into the costs of patient care. The task force's study attempted to identify the "extra cost" associated with clinical research in teaching hospitals. The study notes the difficulty in quantifying these costs on a consistent and accurate basis. Of particular concern is the implicit subsidy from AHC's over and beyond the explicit costs met by grants and contracts. Based on a sample of five AHC's and 121 research protocols, the findings are that the hospital operating budget subsidized about one third of the costs of clinical research of these protocols. The hospital contribution ranged from 11 percent to 39 percent.[1] The authors noted that it is not possible to generalize the findings, but concluded that there are substantial costs now being met by the hospitals.

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[1]The Commonwealth Fund: Report to the Task Force on Academic Health Centers "The Contribution of Academic Health Centers to Clinical Research." Unpublished - not for public distribution until published.

The factors that will affect the ability to continue to fund the patient care costs associated with clinical research are:

1. Changes in support of graduate medical education, both direct costs and the Medicare indirect education adjustment.

2. Cost containment pressures from third parties to reduce hospital admissions and lengths of stay.

3. Selective contracting and discounting by PPO's and HMO's.

4. Differentials in inpatient and outpatient support of education and research.

5. The growing trend of disallowing all patient care costs related to certain clinical investigations, whether or not patient care costs would have been incurred for other treatment modalities (discussed in another paper).

Changes in Support of Graduate Medical Education

Recent changes in graduate medical education support from Medicare have placed a limit on the increase in direct costs of education and limit the number of years of residency support, to first certification plus one year or five years. Residents as part of their activities participate in clinical activities with salary support provided by the hospital and reimbursed by Medicare. While these minor changes in direct cost support do not appear to have affected resident participation in clinical investigation, there is continued pressure to constrain and/or reduce Medicare support. Questions have been raised as to whether patient care funds should be the primary source of support for graduate medical education, based on discussions of who benefits and who should pay.

In addition, some teaching hospitals include the salaries of supervisory physicians (faculty) in the direct education costs. Support for these salaries by Medicare has also been questioned. Many faculty who supervise residents perform multiple functions, including clinical investigation.

Finally, two reductions have already been made in the Medicare indirect education adjustment and there is every indication that further reductions are imminent. The Inspector General of the Department of Health and Human Services released a study in July 1988 based on 1986 data, that showed that a sample of 310 teaching facilities earned net profits of 18.51 percent, with the indirect adjustment accounting for 37

percent of this surplus.[2] Recent anecdotal data suggests that these surpluses are declining. HCFA studies indicate that the indirect education factor should be set at 4-5 percent rather than the current 7.7 percent.

Until the early 1980's, Medicaid was required to follow the Medicare reimbursement methods. When the Medicare methods were changed, the states were permitted to select new methods of hospital reimbursement. Frequently, Medicaid pays below costs and recognition of direct education costs in variable. Few states provide the "indirect adjustment." Since many large medical education programs and clinical research programs take place in large public hospitals (state, county and municipal) and in not-for-profit teaching hospitals in inner cities, Medicaid policies are important for support of the patient care activities associated with clinical research.

There are currently no quantifiable data on the impact of changes on funding of patient care costs associated with clinical research.

Cost Containment Pressures from Third-Parties to Reduce Hospital Admissions and Lengths of Stay

Payment on the basis of diagnostic related groups and/or cost per case provided incentives to shorten hospital stays. These incentives frequently conflict with the time required for clinical research, setting up tensions between hospital administration financial requirements and research requirements.

Furthermore, the extensive use of preadmission certification and professional standards review, reduces admissions with the potential for reducing the number of patients available in hospitals for clinical research. Again, there is not quantifiable data on the effects of preadmission certification and professional standards review on the patient care associated with clinical research or the costs of clinical investigation.

Selective Contracting and Discounting by PPO's and HMO's

HMO's and PPO's restrict the choice of providers and seek out lower costs hospitals for most inpatient care services, except for very highly specialized services (Harvard Community Health Plan and a few others excepted). When they do contract with teaching hospitals, they seek discounts. Most of the hospitals with HMO and PPO contracts are non teaching or minor teaching hospitals that do not have extensive research

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[2]U.S. Department of Health and Human Services "Medicare Indirect Medical Education Payments to Teaching Hospitals," Office of the Inspector General, Office of Audit, July 28, 1988.

programs. The principal teaching hospitals, because of numerous factors, have higher costs than non teaching hospitals, estimated by a Commonwealth Study as 126% higher.[3] While the factors that contribute to these higher costs go well beyond research and direct education costs, selective contracting seeks lower cost providers for the majority of care. This can produce two effects: (1) A shrinking patient base for teaching hospitals and a narrower range of diagnostic mix, both factors having a potential impact on the scope of clinical investigation; and (2) support for the patient care costs related to clinical investigation.

Again, no quantifiable data are available.

Differential in Inpatient and Outpatient Support of Education and Research Costs

Numerous studies have commented on the lack of support for education that takes place in non hospital, outpatient settings. Medicaid Part B payments do not include these costs. Medicaid usually pays well below usual customary and prevailing fees and usually and customary fees of private insurers may not cover education or research costs. In addition, cost sharing by patients represents a higher proportion of outpatient than inpatient cost making in unlikely that additional costs attributable to research and education could be absorbed by individual patients.

The pressures to move diagnostic and treatment procedures outside of the hospital is changing the mix of patients available in teaching hospitals for clinical investigation. The movement of services outside the hospital can also affect the availability of a critical mass of human subjects for designing and implementing research protocols, particularly controlled clinical trails.

Again, there are not quantifiable data on the effects of these changes on clinical investigation.

Conclusions

While the potential impact of these changes can be conjectured and/or anticipated, the impact to date, primarily due to the Medicare indirect education adjustment, has not affected most of the teaching hospitals. In fact, some have experienced substantial surpluses. Exceptions may be teaching hospitals in states with all payor systems

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[3]The Commonwealth Fund: Report of the Task Force on Academic Health Centers "Prescription for Change," 1985.

like New York and Massachusetts with concentrations of hospitals that engage in large clinical investigation programs. As the recent Commonwealth study noted quantification of the hidden or "indirect" costs, the hospital contribution to clinical research will be necessary in order to develop viable and defensible options to support patient care costs associated with clinical research.

CLINICAL RESEARCH AND MANAGED CARE: WHO SHOULD FUND THE COST OF CARE IN CLINICAL INVESTIGATIONS?

Gerald D. Laubach

OVERVIEW

This paper discusses the relationship between third party insurance and clinical research, and briefly outlines the following: (1) the history of clinical research funding by third party payers and recent policy directions that challenge our research and development (R&D) enterprise; (2) potential moral, economic & legal consequences of reimbursement denials for clinical research; (3) long-term policy proposals that could preserve incentives for continued R&D, fulfill insurers' historical commitments to finance high quality patient care, and equitably share the costs of clinical research on promising new innovations.

The emerging problem of third party payers' abdication of their legitimate obligations poses serious moral, policy, and legal issues which must be addressed.

BACKGROUND

America's biomedical research productivity is threatened in a variety of ways. In recent years, cutbacks in NIH's budget request and Medicare's indirect teaching payments to U.S. hospitals have strained our system's ability to fund education and development of clinical researchers. Unnecessary Food and Drug Administration (FDA) regulatory hurdles (i.e. "clinical holds for non-safety related reasons") have made it increasingly costly and time consuming for manufacturers to bring new technologies to market. Indeed, the time to market for new pharmaceuticals has grown from seven to ten years, and for major new devices, to three years. The impact of these delays has, along with other factors, pushed medical product firms to conduct more clinical research overseas where it is easier and less expensive to recruit patients and researchers. Indeed, virtually every major new drug approved by the FDA in the last four years has relied, at least in part, on data from foreign sites [1].

Compounding these challenges is an emerging threat created by third-party payers who are abrogating their contractual and statutory obligations to cover costs of patient care for patients involved in clinical research. Faced with pressures to restrain medical spending, public and private payers are increasingly denying payment for patient care costs associated with new, yet promising medical technologies. Recently, health insurers have denied beneficiary access to investigational uses of new drugs such as Leucocyte Activated Killer

Cells (LAK), Human Growth Hormone, Alpha-Interferon, and Interleuken 2 *I1-2. A multitude of other therapies such as percutaneous disc surgery, implantable insulin pumps, and peripheral laser angioplasty have suffered a similar fate.

The policy trend threatens the delicate balance of U.S. biomedical research funding. More importantly, it raises the spectre that patients with the personal resources to pay out-of-pocket will receive new therapies before the less affluent, who can neither pay themselves nor convince their insurers to pay. These policies not only violate the spirit of our nation's commitment to equal access to health care, but also the payers' implicit contract to provide high quality medical care to their beneficiaries. Before public and private insurers embark on policy changes that exacerbate access problems, the long-term consequences for clinical research and societal equity must be thoroughly examined.

A. Clinical Research Funding by Third Parties

Historically, insurance companies have often reimbursed costs associated with the use of investigational procedures and products. While not quantifiable, most observers believe these payments account for tens of millions of dollars annually. Payers frequently reimbursed not only the patient care costs associated with the clinical investigations of new products, but also some of the incremental costs of research products and protocols.

Payment was made for at least two reasons. First, insurance clauses describing "covered medical expenses" were often ambiguously worded to provide coverage for expenses "necessarily incurred [2]" or "essential to the necessary care or treatment [3]," or "necessary for proper treatment [4]." Whenever courts had occasion to rule on the meaning of these words, usually as a result of an insurer's failure to pay, they invariably held that the insurer was required to pay for new therapies when these therapies (i) were prescribed by the attending physician and (ii) were of some perceived benefit to the patient. Courts, for example, have determined that laetrile treatments [5], experimental treatments for Mongolism [6], and a controversial treatment for obesity [7], are within the gambit of the "necessary and reasonable" insurance clause.

In each case, the court held that the insurer could have limited coverage by specifically excluding experimental or investigational therapies, or those therapies not approved by the FDA, but had failed to do so [8].

Private insurers have paid for clinical research also because even where there were contract prohibitions, the claims processing systems were not able to determine whether prescribed care was part of treatment

or an incremental cost of a clinical trial. Furthermore, third party payers were rarely aware that their subscriber has been enrolled in a clinical research protocol.

Court decisions and the insurers' de facto policies were consistent with equality of patients' access to therapies deemed appropriate by the attending physician. As one court stated, "[o]nly the treating physician should determine what the appropriate treatment should be for any given condition. Any other standard would involve intolerable second-guessing, with every case calling for a crotchety Doctor Gillespie to peer over the shoulder of a supposedly unseasoned Doctor Kildare [9]."

The largest single public "insurer"--Medicare--statutorily stipulates that the program may not pay for any items or services that are "not reasonable and necessary for the diagnosis or treatment of illness or injury, or to improve the functioning of a malformed body member [10]." Within the Department of Health and Human Services, this concept historically has meant that investigational therapies are not reimbursed [11]. Despite this policy, a former Medicare administrator recently acknowledged that Medicare has not only paid for patient care associated with promising new therapies, but also these that are purely research expenses. Dr. Carolyn Davis explained that "payment of clinical research costs can occur when fiscal intermediaries or peer review organization are unable to separate all clinical research from clinical care [12]."

Thus, irrespective of contract language, both public and private payers had been unwilling to intervene between the patient and the physician. Moreover, pressures to control total medical costs were modest during the 1960s and 70s, where access, not cost was viewed as the problem and insurers did not seek to control research outlays. Insurers historically included the costs of clinical research in the premium package. Beneficiaries came to expect that they would be treated with the best available therapies and that this first class medical care would be covered by health insurance. It would certainly come as a shock to most patients if they were to be told that insurance contracts now pay only for second rate medical treatment.

B. Recent Third-Party Policy Changes Regarding Clinical Research

Medical inflation during the 1970s led to an extraordinary event in the 1980s, the adoption of the Medicare Prospective Payment System (PPS). PPS was a catalyst in galvanizing insurers to manage hospital expenditures better. Private insurers and Medicaid programs quickly took similar steps, adopting such programs as pre-admission authorization, inpatient length-of-stay review, and increased patient cost sharing. In addition, Health Maintenance Organizations (HMOs) and Preferred Provider Organizations (PPOs) were developed to tighten

medical utilization and medical prices. Once these macro programs were in place, third-party payers began turning their attention to forms of micro-management, such as managing outpatient care for high-cost chronic diseases, setting fee screens for specific medical and surgical procedures, and contracting with specific providers for high-cost/high-risk surgeries. As part of this micro focus, clinical research support has become a subject of attention. Many insurers are beginning to enforce contract exclusions for experimental therapies and others have adopted even more restrictive coverage limits along the lines suggested by the courts.

As detailed in Appendix A, Medicare adopted in 1987 a regulation incorporating its heretofore inarticulated policy regarding reimbursement for clinical research. The program now attempts explicitly to prohibit reimbursement for any service "related to" investigational drugs, products or procedures. In 1986, the national Blue Cross and Blue Shield Association also adopted more stringent guidelines as outlined in Appendix B. In general, the Blues do not recognize as eligible for insurance payment any investigative therapy that has not "received final approval by the appropriate regulatory body." Many commercial insurers and HMOs have also followed suit. The Harvard Community Health Plan and Group Health Cooperation of Puget Sound, for example, do not cover even approved drugs when used for non-FDA approved indications [13].

In focusing on clinical research expenditures, insurers have pursued short-term budgetary savings to the possible exclusion of other goals like enrollee satisfaction, quality of care, and long-term social equity. These impacts deserve closer examination.

C. Implications of Clinical Research Restrictions

Many third party insurers maintain that the benefits of clinical research accrue to the product manufacturers and future patients, not necessarily to the patient to whom the investigational therapy is provided. Factually, this view is simply inaccurate. Indeed, most medical innovations are clinically tested (and provided to insured patients), only when they already show promise. For example, bone marrow transplants are only used when they are expected to save lives. Further, new prosthetic implant designs are typically used as alternatives to older models, and next generation antibiotics are given to patients with serious hospital-induced infections that are not treatable with existing drugs. In these cases, the use of experimental treatments may mean the difference between life and death for the patient.

More fundamentally, these new restrictions may place doctors and hospitals in moral, ethical and legal dilemmas. Non-payment could severely limit a doctor's ability to prescribe for patients. Cost

issues would inappropriately have to be considered in a medical decision especially where a particularly expensive experimental procedure is contemplated. If the insurer declines payment because of the experimental nature of the procedure, and it is not utilized, the dilemma is obvious if the patient's condition suffers as a result.

The implications arising from the federal government's attempted adoption of these restrictions are even more disturbing. Congress, when it passed the Medicare bill, specifically prohibited "any Federal officer or employee to exercise any supervision or control over the practice of medicine or the manner in which medical services are provided...[14]. A mechanical definition of what is "investigational [15]" and, hence, not eligible for payment may inappropriately run afoul of the congressional mandate quoted above and may be inconsistent with the underlying Medicare legislation. A blanket prohibition against the use of any experimental or investigative drug or procedure, no matter how beneficial, certainly could be considered an unauthorized intrusion into the physician's medical practice.

Not only would this new "cost reduction strategy" greatly impact the practice of medicine, it could not be explained to patients and would lead to patient dissatisfaction with insurers and the health care system in general. A patient receiving treatment for an ailment expects the doctor to use all the available tools and the insurer to cover the costs of treatment. Pursuant to this cost reduction strategy, new and possibly lifesaving innovations are placed out of reach of many patients, contrary to their expectations and the long-standing practice. Treatment on the cutting edge of medical technology will fast become available only to those with the ability to pay. A two-tier medical delivery system will almost assuredly result with the vast majority of working men and women unable to receive the most up-to-date medical treatment.

Naturally, there will always be a need for exceptions. For example, who should pay for potentially costly lifesaving interventions for previously untreatable cancers? In this case, the insurer and researcher should engage in timely negotiations regarding the insurer's contribution (for example, payments could be predicated on a negotiated probability of a successful outcome).

D. CONCLUSION

Given the broad spectrum of what constitutes research, as well as the range of differences (positive and negative) between the expected costs of treating patients with experimental protocols vs. mainstream therapy, precise rules will require more detailed discussion. Nevertheless, the following principles should form the basis for an immediate policy debate:

- Public and private insurers obligation to reimburse for all appropriate patient care should be explicitly enforced, regardless of any concomitant involvement of the patient in a clinical trial. Historically, insurers have implicitly supported part of the cost of clinical research as a contribution both to the specific plan benefits as well as to society's investment in its future; this support should be maintained, and be made explicit.

- Sponsoring research organizations have a responsibility to cover the costs of basic research, the incremental cost of new research products or services, and the incremental protocol-driven costs (e.g., lab tests, data collection, etc.) necessitated by their research.

- The principle of "opportunity cost" (or the cost which they would have paid otherwise for patient care), should be the rule when patients are involved in clinical research. Insurers should expect to pay the opportunity costs for therapies which, although investigational, represent the most favorable treatment alternative considered by the patient's physician. In the case of an investigational orthopedic joint appliance, for example, insurers would pay all hospitalization, rehabilitation, and follow-up care the patient would have received for an alternative prosthesis. However, the incremental cost of the new prosthesis over the alternative may not be covered. For an enhanced investigational antibiotic for nosocomial infections, the insurer would likewise pay all standard treatment costs associated with providing an effective current generation product. The incremental costs, if any, of the new generation drug would be the responsibility of the researchers.

It is apparent that a major national debate on the issue of third-party funding for medical care is warranted. While the short-term risk to America's research infrastructure is limited by the relatively unsophisticated nature of claims processing, the uncertainty created for research is disturbing. This is particularly true since the ultimate financial benefit to payers would be small, if there are any at all. Short-sighted payer approaches abdicating patient care costs related to investigational new therapies make poor public policy and could seriously harm domestic innovation.

More importantly, patients may be at great risk of losing access to high quality care and be forced to obtain innovative treatments based on

ability to pay. This eventuality would not be in the interests of either society or the payer community, and also raises serious questions about statutory and contractual interpretation, as well as congressional intent.

Three courses of action are proposed:

1. State insurance regulators should intervene and stop the withdrawal of reimbursement for the essential costs of medical care, regardless of the involvement of a clinical investigator.

2. Legislators should reconfirm their commitment to access for appropriate medical care for all.

3. Legal action should be explored on an individual or class basis, if necessary, to prevent this erosion of responsibility.

ENDNOTES

1. Personal Communication, FDA Office of New Drug Evaluation.

2. Shumake v. Travelers Insurance Company, 383 N.W. 2d 259 (Mich. 1985).

3. McLaughlin v. Connecticut General Life Insurance Co., 565 F. Supp. 434, 450 (N.D. Cal. 1983).

4. Mount Sinai Hospital v. Zorek, 271 N.Y.S. 2d 1012 (Cir. Ct. 1966).

5. Shumake v. Travelers Insurance Company, supra.

6. Fassio v. Montana Physicians' Service, 555 p. 2d. 998 Mont. 1976.

7. Mount Sinai Hospital v. Zorek, supra.

8. At least one insurance company, Travelers Insurance Company, took the position that "a general exclusion from drugs and treatments not approved by the Food and Drug Administration would be undesirable since it would preclude coverage for rugs and treatments in the experimental stage which are known to be effective." Shumake, supra at FN2.

9. Mount Sinai Hospital v. Zorek, supra.

10. 42 U.S.C. - 1395y(a)(1)(A).

11. No court has directly addressed the interpretation of "reasonable and necessary" in this context. Hence, it remains to be seen whether the Department's interpretation is proper. For a discussion in the Medicaid content, see Penneke v. Preisser, 623 F.2d 546 (8th Cir. 1980); but see Rush v. Parham, 625 F. 2d 1150 (11th Cir. 1980).

12. Davis, C.K., The Impact of Prospective Payment on Clinical Research, JAMA, 1985. 253(5); P 686-7, February 1, 1985.

13. Personal Communication, Harvard Community Health Plan and Group Health Cooperation of Puget Sound.

14. 42 U.S.C. - 1395.

15. See Appendix.

APPENDIX

COVERAGE AND LIMITATIONS*

General Exclusions From Coverage

3300. General Exclusions

No payment can be made under either the hospital insurance or supplementary medical insurance programs for certain items and services.

A. Not reasonable and necessary (S2303);
B. No legal obligation to pay for or provide services (S2306);
C. Furnished or paid for by government instrumentalities (S2309);
D. Not provided within United States (S2312);
E. Resulting from war (S2315);
F. Personal comfort (S2318);
G. Routine services and appliances (S2320);
H. Supportive devices for feet (S2323);
I. Custodial care (S2326);
J. Cosmetic surgery (S2329);
K. Charges by immediate relatives or members of household (S2332);
L. Dental services (S2336);
M. Paid or expected to be paid under worker's compensation (S2370);
N. Nonphysician services provided to a hospital inpatient which were not provided directly or arranged for by the hospital (S2390).

3300.1 Services Related to and Required as a Result of Services Which Are not Covered Under Medicare

A. Medical and hospital services are sometimes required to treat a condition that arises as a result of services which are not covered because they are determined to be not reasonable and necessary or because they are excluded from coverage for other reasons. Services "related to" noncovered services (e.g. cosmetic surgery, noncovered organ transplants, noncovered artificial organ implants, etc.),

*Reprinted from the Medicare Carrier's Manual (Health Care Financing Administration), Part III, Claims Process, Volume 1, beginning page 2300.

including services related to followup care and complications of noncovered services which require treatment during a hospital stay in which the noncovered service was performed, are not covered services under Medicare. Services "not related to" noncovered services are covered under Medicare.

COVERAGE AND LIMITATIONS

B. Identify which services are related to noncovered services and which are not. Following are some examples of services "related to" and "not related to" noncovered services while the beneficiary is an inpatient:

1. A beneficiary was hospitalized for a noncovered service and broke a leg while in the hospital. Services related to care of the broken leg during this stay is a clear cut example of "not related to" services and are covered under Medicare.

2. A beneficiary was admitted to the hospital for covered services, but during the course of hospitalization became a candidate for a noncovered transplant or implant and actually received the transplant or implant during that hospital stay. When the original admission was entirely unrelated to the diagnosis that led to a recommendation for a noncovered transplant or implant, the services related to the admitting condition would be covered.

3. A beneficiary was admitted to the hospital for covered services related to a condition which ultimately led to identification of a need for transplant and receipt of a transplant during the same hospital stay. If, on the basis of the nature of the services and a comparison of the date they are received with the date on which the beneficiary is identified as a transplant candidate, the services could reasonably be attributed to preparation for the noncovered transplant, the services would be "related to" noncovered services and would also be noncovered.

C. After a beneficiary has been discharged from the hospital stay in which he received noncovered services, medical and hospital services required to treat a condition or complication that arises as a result of the prior noncovered services may be covered when they are reasonable and necessary in all other respects. Thus, coverage could be provided for subsequent inpatient stays or outpatient treatment ordinarily covered by Medicare, even if the need for treatment arose because of a previous noncovered procedure. Some examples of services that may be found to be covered under this policy are the reversal of intestinal bypass surgery for obesity, repair of complications from transsexual surgery or from cosmetic surgery, removal of a noncovered bladder stimulator, or treatment of any infection at the surgical site of a noncovered transplant that occurred following discharge from the hospital.

However, any subsequent services that are an integral part of a noncovered service; i.e., an extension of a periodic segment of a noncovered service or followup care associated with it, should be denied. Thus, where a patient undergoes cosmetic surgery and the treatment regimen calls for a series of postoperative visits to the surgeon for evaluating the patient's prognosis, these visits should be denied.

(See HCFA Pub. 13-3, S3637.15 and HCFA Pub. 10, S41518 for billing procedures.)

3303. SERVICES NOT REASONABLE AND NECESSARY

Items and services which are not reasonable and necessary for the diagnosis or treatment of illness or injury, or to improve the functioning of a malformed body member; e.g., payment cannot be made for the rental of a special hospital bed to be used by the patient in his home unless it was a reasonable and necessary part of the patient's treatment. See also S2328.

2303.1 Devices Not Approved by FDA Medical devices which have not been approved for marketing by the Food and Drug Administration (FDA) are considered investigational by Medicare and are not reasonable and necessary for the diagnosis or treatment of illness or injury, or to improve the functioning of a malformed body member. Program payment, therefore, may not be made for medical procedures or services performed using devices which have not been approved for marketing by the FDA.

2306 NO LEGAL OBLIGATION TO PAY FOR OR PROVIDE SERVICES

Program payment may not be made for items or services which neither the beneficiary nor any other person or organization has a legal obligation to pay for or provide. This exclusion applies when items and services are furnished gratuitously without regard to the beneficiary's ability to pay and without expectation of payment from any source, such as free x-rays or immunizations provided by health organizations. However, Medicare reimbursement is not precluded merely because a physician or supplier waives the charges in the case of a particular patient or a group or class of patients, as the waiver of charges for some patients does not impair the right to charge others, including Medicare patients. The determinative factor in applying this exclusion is the reason the particular individual is not charged.

The following sections illustrate the applicability of this exclusion to various situations involving services other than those paid for directly or indirectly by a governmental entity. (For a discussion of the latter, see S2308).

A. Indigency. This exclusion does not apply when items and services are furnished an indigent individual without charge because of his inability to pay, if the physician or supplier bills other patients to the extent that they are able to pay.

B. Physician or Supplier Bills Only Insured Patients Some physicians and suppliers waive their charges for individuals of limited means, but they also expect to be paid if the patient has insurance which covers the items or services they furnish. In such a situation, because it is clear that a patient would be charged if insured, a legal obligation to pay exists and benefits are payable for services rendered to patients with medical insurance if the physician or supplier customarily bills all insured patients--not just Medicare patients--even though noninsured patients are not charged.

Individuals with conditions which are the subject of a research project may receive treatment financed by a private research foundation. The foundation may establish its own clinic to study certain diseases or it may make grants to various other organizations. In most cases, the patient is not expected to pay for his treatment out-of-pocket, but if he has insurance, the parties expect that the insurer will pay for the services. In this situation, a legal obligation is considered to exist in the case of a Medicare patient even though other patients may not have insurance and are not charged.

C. Medicare Patient Has Other Health Insurance Except as provided in SS3335ff., S335if., and 3340ff., payment is not precluded under Medicare even though the patient is covered by another health insurance plan or program which is obligated to provide or pay for the same services. This plan may be the type which pays money toward the cost of the services, such as a health insurance policy, or it may be the type which organizes and maintains its own facilities and professional staff. Examples of this latter type are employer and union sponsored plans which furnish services to special groups of employees or retirees or to union members and group practice prepayment plans.

The exceptions to this rule are services covered by automobile medical or no-fault insurance (S3338ff.), services rendered during a specified period of up to 12 months to individuals entitled solely on the basis of end stage renal disease who are insured under an employer group health plan (S335ff.), services rendered employed individuals age 65 or older.

THE FUNDING OF CLINICAL INVESTIGATION IN THE UNITED STATES

Mitchell T. Rabkin

Under virtually any definition of clinical investigation fall a variety of patient care encounters ranging from an intervention superimposed on the activities of an otherwise clinically necessary ambulatory visit or inpatient admission—the nature of which is essentially unchanged by the experimental process—to ambulatory or inpatient encounters essentially solely or primarily for the purpose of carrying out the experiment. Hesitancy of third-party payers to pay the costs of these encounters is understandable—they must have concerns over whether they are paying out excess dollars for encounters entirely for the purpose of the experiment or, even where some diagnostic or therapeutic effort useful to the patient is carried out, whether they are paying for such "mixed" episodes taking place with greater frequency than might otherwise be useful or at greater cost than appropriate for the needed clinical encounter alone.

In the case of the federal government and Medicare, patients may be hospitalized for reasons acceptable to Medicare, but because the hospital payment is predicated on admissions averaging a standard length of stay, experimental efforts which might be instituted during such admission (and might not have been anticipated prior to admission) may lead to dire economic consequences for the hospital should they require additional length of stay, since payment for the added days will not follow. Because other payers are moving toward similar modes of payment, this concern goes beyond that of the Medicare patient.

One approach which might be made to Medicare would be to call for a new DRG which represented admissions or added days, etc., for clinical investigation. Obviously, this could not be an unlimited opportunity for the hospital. Restrictions could be placed not only on how that DRG was assigned—the limits could be placed on the nature of the hospital that could use that DRG, the nature of the approval process both inside and beyond the institution that would sanction such an admission, etc., the permissible extent of any such application and the overall total of such days and other resources allowed, for example, in relation to the total inpatient days of the institution or to other characteristics.

A mechanism of this sort would allow Medicare to recognize the importance of clinical investigation, to support that aspect of it not typically supported by specific research grants nor by Medicare today, yet the mechanism could limit overall both the average cost to the payer per experimental admission and the total of such costs for clinical investigation the payer would provide any one hospital. Such an arrangement could then allow flexibility to the individual hospital, through internal allocation and monitoring by its own research committee and administration, so that longer hospital stays for clinical

investigation could be tolerated, were they appropriate, for example, albeit at the expense perhaps, of allowing fewer admissions that year for purposes of clinical research.

A similar and perhaps more ideal arrangement could be made by NIH itself with selected hospitals. After all, the Biomedical Research Support Grant recognizes the need for flexible institutionally-allocated funds in amounts related to the institutions volume of NIH-supported research. Could not a similar program be developed specifically for clinical costs not otherwise covered, again in relation to some functional measure of clinical research activity and giving the individual institution the opportunity for decision making, documentation and control with respect to the specific allocation of these funds within their general prescribed use?

Similar arguments could be made for private insurers, since the costs of R&D to improve a product are standard in virtually all other business transactions. However, because insurers are working to diminish their payout at present, it is unlikely that Blue Cross, commercial insurers or HMO's would be responsive. Hence the creation on an NIH-based program would be more useful and, in the last analysis, more appropriate since the determination of which institutions might warrant this support for clinical investigation support could best be done by NIH rather than the usual third-party payers, including Medicare.

ISSUE # 2:
TRAINING AND SUPPORT OF THE YOUNG CLINICAL INVESTIGATOR IN THE UNITED STATES

ENCOURAGEMENT AND SUPPORT FOR CLINICAL INVESTIGATORS, PARTICULARLY YOUNG INVESTIGATORS

Thomas C. Merigan

A major problem today is the need to encourage young clinicians to become clinical investigators. In the current era of very rapid advances in fundamental research in biological sciences, including medicine, it is particularly important that the United States have creative investigators to transfer biologic insights from the laboratory to the bedside or in the clinic. They should be able to devise ways to get critical answers to the questions of the utility of new diagnostic procedures or interventive strategies.

In recent years, led especially by the oncology and cardiology field, large scale Phase III clinical investigative efforts have appropriately begun to involve the statisticians in the earliest possible phase of protocol design. In addition, Phase I and Phase II studies quite appropriately deeply involve pharmacologists in the former, and statisticians in the latter, to determine the best dosing strategy for minimum toxicity and maximum efficacy. By working with these other individuals and having the responsibility for developing the best overall developmental scheme for drugs, clinical investigators have developed a professionalism in the therapeutics area. The general clinical research center can be an ideal setting for Phase I and Phase II therapy studies. Phase III studies should be conducted in other clinics and wards aimed toward the general staff managing the observations, in order to predict field applicability of the approach.

The way to learn clinical investigation is for young investigators to be directly involved in both development and execution of specific protocols. This can be done in our first rate academic institutions where there is an available team of trainers for a given disease area whose competence spans all the involved disciplines. The trainees and teachers can work together to develop a protocol which answers the most contemporary questions in any given clinical area. They can also work together on executing existing protocols and planning subsequent steps with industry and governmental sponsors. The training of fellows in this program should be for at least two years to allow them to obtain a full insight into a complete cycle of protocol conception, formulation, execution and analysis. Such training programs can be financed by either industry or government, or most likely, a combination of the two. In order to give maximum future flexibility and scientific rigor, it could occur after a period of bench research training and be accompanied with relevant university course work (statistics, experimental clinical trial design, etc.), as well as active series of seminars and journal clubs covering all activities in the disease area.

New on the scene are consortium groups that represent multi-institutional centralized efforts. Some of these are the various cancer control programs. For example, the Eastern Solid Tumor Group, the Leukemia Task Force B, and recently, the AIDS Clinical Trial Group has been formed by the NIAID. Specifically, in the AIDS Clinical Trial Group, a continuing effort is mounted at a nationwide level and involves many institutions, drugs and individual protocols. Young investigators can play critical roles in these efforts and learn skills that they can take to future academic or industrial positions.

To make this career track attractive on a long term basis, institutions must recognize this discipline with tenure commitments to the best individuals, which provide stability for those who make long term commitments to the area. This, in turn, requires stable governmental and/or industrial support. We must recognize that encouraging development of specialized centers of excellence requires giving investigators the tools they need to get the answers to the problems they pursue. Industry also must be willing to fund certain costs for the clinical trials, above and beyond the cost of producing material for study, and the specialized observations of efficacy or toxicity that are required in the care of the patients with the disease under study. Funds to assist in training, support for attending meetings, well publicized prizes for investigator excellence, and endowed professorships, will all help to maintain the durability of the career pathway. The NIH must recognize that they must also support certain large scale trials or RO1's in the clinical investigative area if we are going to provide our citizens with the best medical care. One can see when there is a national threat such as AIDS, the balance swings toward cooperative group networks. One can then rapidly get comparisons between drugs, standardized schemes of drug development, and increase speed of data acquisition, whether a new agent comes originally from the smallest academic laboratory or the largest multinational drug company in the world.

For some areas, the issue may be the need for more technology transfer from the area of basic science within the traditional disease area. Because a given area is out of favor, industrial support may be lagging, and yet the science is compelling as it has been recently in the vaccine area. Strategies such as the RO1 mechanism can then be used for single or even multi-center (consortium) studies. Considering such applications would be difficult for the usual NIH study sections which are perhaps sometimes oriented toward study of biologic or disease mechanisms rather than clinical trials. We could set up new initial review groups to critique applications involving study sections with the proper balance of medicine, biologic, statistical and pharmacologic expertise to really prioritize such studies among other applications. It is especially important for the NIH to recognize good young individuals who are committed to and productive in the area of clinical trials through RCDA support. This would allow them to concentrate their efforts in the area and obtain their final training. It will also be important both to devise specialized training programs for the best

centers in this area, as well as having individual fellowship support mechanisms available nationally to support this effort. In order to support the highest quality of medical investigation, grant mechanisms rather than the complicated contract mechanisms are the appropriate conduit for funding this work. Either cooperative groups or R01 grants can be used when there are adequate review mechanisms.

Finally, if we are going to continue to have fundamental research, which is critical in offering new options for this kind of technology transfer, then we must view this clinical research as complementing and not competitive with basic work. The clinical research field has been developing its own complexity which should be understood by the public, Congress, and the basic scientist. Clinical investigators must become understandable and develop an appropriate dialogue with all of the supporting groups. The public may think that only the original fundamental finding or the final definitive clinical trial is crucial. Instead, the whole chain of work that leads to an effective clinical approach must be credited by these who are describing advances if the public is to obtain an idea of the total effort. Then they will understand that all aspects are necessary if we are to maintain our preeminence in the field of medical research. Then technology transfer can be supported with the additional funding it requires in this era of diminishing available resources.

TRAINING IN CLINICAL INVESTIGATION

David G. Nathan

Problem

Biomedical research is divided into patient related research that can be carried out only by physicians or, to a limited extent, by the nurses and basic research that can be performed by these holding either the M.D. or Ph.D. It is clearly apparent that a career in biomedical research has become a decreasing option for medical school graduates. During the past twenty years there has been a decline in first time RO-1 applicants by M.D.'s, and a marked rise in applications submitted by Ph.D.'s. The M.D./Ph.D. applicant pool is so tiny as to be negligible. The training grant mechanism, which widens the opportunity for M.D.'s to become grant applicants, is less successful in inducing such trainees to apply for grants than is the fellowship program. This is probably an artifact created by the fact that it is necessary to make a more specific choice about career in order to obtain a fellowship. But the two years of training supported by the training grant mechanism are insufficient. Unpublished data by NIH clearly demonstrates that at least four to five years of training are necessary to produce an investigator who can successfully gain an NIH grant in today's competition.

Burdened by debt and concern about future funding, young physicians are turning away from the careers that seemed so promising for graduates of the 50's and 60's. Recently, the NIH has developed five year physician-scientist, clinical investigator and academic investigator awards to complement the traditional research career medical awards for medical school graduates, but the funding for these awards is limited. In 1985, 769 physicians were being supported for further training by these mechanisms. Even when fully developed, these programs will support only about 250 physicians each year, far fewer than the necessary 1,000 physicians trained well enough to compete in the research arena and prepare to fill the vacancies that are created in medical school faculties by retirement and attrition.

In addition to insufficient length of training, several other factors inhibit the successful development of a group capable of maintaining U.S. strength in patient related (clinical) investigation.

1. Rules and regulations involving investigation of new drugs are complex and ponderous, and the interaction of conservative drug companies with FDA regulators can be stultifying. Indeed, investigations of new therapies in children are nearly impossible to carry out in the present climate. This discourages pediatricians from careers in clinical investigation.

2. Clinical research center budgets are shrinking to the point at which this important mechanism of support is becoming nearly impossible to utilize. It would be far better to close some CRC's and distribute their budgets to others than to starve all of them.

3. Hospital budgets are in such serious disarrays, particularly in certain states, that it is becoming impossible for the hospitals to support clinical research. Indeed, they are fighting for their lives.

4. Boards in internal medicine and pediatrics can become unwittingly inflexible and erode the time necessary to train clinical investigators by reducing the options of chairmen of clinical departments.

5. The National Institutes of Health is no longer a breeding ground for clinical investigators. Medical school graduates are not being urged to go to the NIH for clinical associate training. Such a migration provides two to three years of training at government expense. Graduates can then return to the university for the remainder of their training. Such a mechanism provides the time necessary to train a physician to become an investigator. Indeed this pathway is the major basis of the explosion in clinical research that occurred in the 50's and 60's.

Proposal

The purpose of encouraging clinical investigation is to provide new knowledge that will improve patient care and sustain and renew the clinical faculties of U.S. medical schools.

Though manpower estimates are unreliable, it can be calculated that approximately 1,000 new well trained clinical investigators must be produced each year by an effective national training program to replace U.S. medical school faculty who leave their careers. Therefore, a national training program that produces approximately 1,000 trained clinical investigators per year should be developed, and each trainee should receive five years of experience in investigation during the training period. This five year period should include at least one year of clinical specialty training since it is impossible to develop clinical investigators absent knowledge of the clinical specialty involved.

Funds for such a program can be found in part in the NIH training budget, and in part in the HCFA budget which supports training through the Medicare program. A fraction of the funds used to train residents should be diverted from HCFA to the NIH to spend in a well designed five year clinical investigation training program in peer review selected institutions.

This will probably lead to a reduction in the number of training programs, but an increase in their quality. They should be well funded so that fellows can be reasonably supported with wages sufficient to reduce the ravages of debt and encourage the commitment of necessary time.

Such a program will be criticized because the grants will tend to be awarded to institutions with already large and successful biomedical and clinical research programs. Therefore, geographic distribution will be less important than quality distribution, but it will be necessary to face such an action if we are to preserve excellence at a time when purchasing power will be maintained only with heroic effort.

The business community, particularly the pharmaceutical industry, can make a major contribution to such a program by adding to fellowship stipends in the designed training centers that are producing the necessary personnel, including investigative nurses and data managers so necessary on modern clinical investigation teams.

Conflict of Interest

Clinical investigation demands complete objectivity on the part of investigators, but successful drug development can be highly lucrative. This can lead to a serious conflict of interest, particularly if the clinical investigator has a financial stake in the outcome of his or her investigation. Therefore, it should be understood that an investigator of any drug or device must not hold a significant equity interest in the company manufacturing such a device. Patients must be considered solely as patients and not as objects that advance the equity position of physicians.

Fee for service is a time honored and respected approach to reimbursement for medical care, but there is a major difference between the concept of fee for service and the holding of an equity position. Patients are not part of a physicians' capital and must never become so.

TRAINING OF CLINICAL INVESTIGATORS

Carl C. Peck

Selection of Candidates for Training in Clinical Investigation

Strategies should be developed to identify candidates for training in clinical investigation who have a high probability of success (e.g., finishing training and initiating/sustaining clinical investigation careers). Experience in research traineeships in clinical pharmacology suggests that pre-training research experience, medical specialty board certification, advanced science degrees, and quantitative science backgrounds are characteristics frequently observed among clinical pharmacologists who are engaged in clinical investigation.

Faculty

The training program director should be an established clinical investigator with demonstrated skills in both research and teaching. The associated academic faculty should comprise scientists representing acknowledged skills in the areas encompassed by the program content described below. The faculty should be committed to comprehensive education of trainees, not simply to the availability of "cheap lab help."

Program Content and Duration of Training

While training should always be individualized, the trainee should expect exposure to certain generic skills in clinical investigation as well as specialized research skills inherent in his/her research area. Generic skills in clinical investigation include:

experimental design/biostatistics/data analysis
ethics of human experimentation and research ethics
scientific writing and presentation
general laboratory skills, including computing
critical evaluation of scientific information

The minimum duration of training in clinical investigation is two years; success as a clinical investigator in computing for scarce research funds appears to increase for those who have undertaken more than two years of training.

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PROBLEMS IN SUPPORT OF STUDIES OF MAJOR MENTAL ILLNESS

Robert M. Rose

- Approximately one in five to one in six of the population suffer from moderate to severe mental disorders, based on recent data from the epidemiological catchment area (ECA) based on probability sample of 20,000 individuals in five U.S. cities.

- Major progress has been made in the last five to ten years in clinical neuroscience research. New strategies such as MRI, PET scanning and molecular probes have made enormous advances and promise major breakthroughs in understanding major mental illness in the next decade. Very significant problems exist in longitudinal clinical investigation of patients with severe mental illnesses, such as schizophrenia. Nature of the disorder requires long-term care and the efficacy of therapeutic agents takes many weeks to be ascertained. Diagnostic related groups in psychiatry have very significant impact on inhibiting clinical research on psychiatric patients (Pincus et al., Archives of General Psychiatry 42: 627, June 1985).

- There exists little support for studies of inpatients with major psychiatric illness and a great threat exists for essentially eliminating long-term support with the developing cost containment mechanisms.

- NIH has CRC funded bed costs to the total of over 600 beds in the country. There is no equivalent in ADAMHA for funding of bed costs for longitudinal research with patients with severe mental illness. Those places where some support is available, such as the V.A. and state hospitals, there are major problems in that there is a relative absence of researchers in those environments and the population is not typical of many patients diagnosed with major mental illness.

- Despite the major advances in neuroscience and clinical neuroscience, ADAMHA funding did not keep up with NIH from 1970-82. During this time there was approximately 75 percent increase in funded RO1s at NIH and a 25 percent drop in funding at ADAMHA. In the last few years the ADAMHA budget has kept pace with the NIH budget, although it has not recaptured the loss of this past decade. These figures have been documented in AAMC Health Policy Project Report.

- In summary, patients with major mental illness require special longitudinal support for clinical research. Such clinical research is increasingly relevant given the advances in neuroscience, but there is a dearth of mechanisms currently and studies are increasingly threatened by cost containment mechanisms.

- There is a major problem in the development of junior investigators in psychiatry. Only in the last 10-15 years has there been a significant emphasis in developing biological research and its relevance.

- The average age of investigators supported by NIMH are in their mid-40s. Psychiatrists are principal investigators on only approximately one-third of all RO1-sponsored research at NIMH, with this fraction much lower among those less than 35 years of age.

- The Research Career Development Award mechanism of NIMH has yielded a very major contribution to the pool of investigators studying major mental illness as documented in a recent RAND Corporation study done for the NIMH.

- Nevertheless, there remains a great shortage of adequately supported psychiatric investigators available to continue the clinical neuroscience research for major mental illness.

- Serious thought must be given to developing some long-term mechanisms of support, similar to the strategies used in supporting investigators for long periods of time in studying disorders of the heart and in cancer research.

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THE FUTURE OF CLINICAL INVESTIGATION

Barry Sherman
(submitted with the concurrence of David W. Martin, Jr.)

Concerns for the future of the clinician investigator are not new. Recent discussions have focused on the need to encourage and sustain the development of physicians who are also highly sophisticated laboratory scientists. Those discussions have identified several problems:

1. The need for in-depth post residency/fellowship training and the lack of sufficient funds for such training.

2. The ambivalence of many, who at the end of their complete clinical training, foresee the need to embark on the necessary additional years of training in laboratory science.

3. The uncertainty engendered by the prospect of a career of self-sustained research funding via grant applications in an increasingly competitive environment.

4. The need to balance the demands of time for serious research against demands for patient care and teaching in an academic setting.

Consideration of those issues has resulted in new NIH funding programs such as the Physician Scientist Program, but no one has addressed the fundamental questions; perhaps because there are no ready answers.

Much less attention has been given to the fate of the physician scientist involved in patient-oriented investigation. Here the problems are even more serious because they involve not only issues of training and its funding, but perceptions of the relative "value" of scientific endeavor within an academic community.

Since only a physician can conduct human investigation, it is paradoxical that the path to such a career is even more clouded than it is for the individual committed to purely laboratory science. Today there are few, if any, training programs designed for the individual who wishes to carry out human investigation, and not unexpectedly, there is little or no funding for such undertakings. It is essential to understand that in 1988 it is effectively impossible for an individual investigator to obtain NIH funding for human investigations. Thus, it is impossible for an individual with such interests to foresee a career of self-sustained funding through the grant mechanism. Lack of available funding makes these physicians less valued in the academic marketplace so that the individual interested in a career in human investigation cannot look forward to a position in academic medicine in the traditional sense.

Today's situation is very illogical. It may be time to recognize that for most people a medical education, residency, and fellowship training is not the most logical path to a career in fundamental science. It is equally illogical that we have succeeded in eliminating the clinical research physician in the United States at a time when his/her role may never be more important in bringing the advances of the "new biology" into the arena of medical care.

This is not the situation in Europe or Japan where the physician engaged in the study of human physiology, the pathogenesis of disease, and the role of new therapeutics is productive and highly regarded. It is important in this regard to recognize that the role of the physician engaged in human studies is much broader than conducting randomized clinical trials.

For the physicians who graduated following World War II, it was possible to move from a medical education to a career in academic medicine that included a strong participation in laboratory science, as well as bedside investigation. This was made possible through clinical fellowship training programs that included both specialized clinical training, as well as laboratory research. With time it was recognized that many trainees eventually chose a career in clinical practice and that it was no longer necessary to train large numbers of highly skilled sub-specialists, that the research of such individuals was often derivative and that their scientific training was inadequate to sustain a long career in productive laboratory investigation.

While the clinical fellowship of the past had many deficiencies, it did produce numbers of highly motivated young physicians trained in laboratory methods and issues of the time. These individuals participated in productive research for a varying number of years, perhaps moving from laboratory-based to bedside-based research or assuming other roles within the academic medical center.

We now need to recognize that in dealing with the inadequacies of clinical fellowship training programs, we have narrowed the entry path to those few physicians willing to study for a second career and accept the risks of the granting mechanism. The current situation demands re-examination of the need for physicians in the clinical research process. If the judgment is that there is a vital role for the clinician scientist, then new programs must be developed to adequately train them and fund their work throughout an academic career.

THE TRAINING OF CLINICAL INVESTIGATORS

Paul D. Stolley

One of the reasons postulated to account for the declining success of M.D. investigators in obtaining NIH-funded grants is their lack of training in research methods as contrasted to Ph.D. investigators (who do not spend so much time learning clinical medicine). While there is not enough evidence at present to determine whether or not a deficiency of research methods training truly is an important factor in the decline of the success in clinical investigators obtaining grants, there is information as to the reasons why grants are not awarded by NIH. The main reasons for the turndown of grants include the lack of specificity and originality of the question(s) being posed, inappropriate measures, inadequate statistical analysis and other reasons relating to insufficient training and competence in research methods.

The training of clinical investigators must include a transmittal of knowledge about research methods and a mastery of certain epidemiological and statistical techniques and skills. For example, whether or not to emplcy a randomized controlled trial or a non-experimental design; attention to adequate sample size and sampling methods; the need for a control group and other fundamental concepts must be taught clinical investigators if they are to compete successfully in obtaining grants. Sophisticated statistical methods are not the issue here, but rather the ability to reason statistically and to understand the basic uses of the various research strategies is more to the point.

Statistics and epidemiology are usually allotted a brief time in the medical school curriculum and taught early in the 4-year course, when it is less appreciated. The beginning investigator or Fellow in training about to start his or her research is better motivated to learn statistics than is the first year medical student who is not quite sure how relevant the subject will be to their future work.

Courses in research methods and experience in protocol design should be considered an essential component of the post-graduate fellowship training of persons training for a career as an investigator, whether the type of investigation pursued is "basic," "applied," or "clinical;" whether they involve human subjects or experimental animals; and whether the object is survey research or an experimental study.

The history of medicine and therapeutics is replete with premature advocacy and acceptance of therapies and theory due to inadequate understanding of research methods, the "rules of evidence" and epidemiological analysis. Example include the use of DES in pregnancy, gastric freezing for bleeding ulcers and lobotomy for schizophrenia. Thus, improved teaching of epidemiological and statistical methods may improve the practice of medicine as well as the quality of research.

Finally, any attempt to loosen the "rules of evidence" in the name of "innovation" or "productivity" should be looked on with some caution and suspicion as the alleged economic justification may be hard to sustain after careful scrutiny.

THE SURGEON AS A CLINICAL SCIENTIST

Samuel A. Wells, Jr.

It has been repeatedly emphasized that the role of the clinician in biomedical research has been diminishing over the last two decades. There are many reasons for this, ranging from the disproportionately decreased support from the federal government for health related research and development, as compared to that for defense and space, to the fact that the external pressures and career goals of today's graduating medical students and clinical residents have substantially changed from what they were even a few years ago.

There are substantial data to show not only that the constant dollars appropriated by Congress to the National Institutes of Health (NIH) actually decreased from the mid 1970s to the mid 1980s, but also that clinical investigators competed for those dollars less well than did their colleagues in the basic sciences.

Most clinical scientists have had their primary training in either internal medicine, pathology or pediatrics, and it is assumed by many that the current plight of the clinician investigator only applies to individuals in these specialties. This of course is not the case, but it is clear that investigators in surgical disciplines have become minor players in this arena and there are several ways in which this can be documented.

In 1987, the NIH awarded 21.5% of its total extramural budget for research grants to departments of internal medicine of medical schools. Departments of surgery, excluding ophthalmology and otolaryngology, received 10.5% (1). By 1982 the proportion awarded to departments of internal medicine had increased to almost 27%, while that awarded to departments of surgery decreased to 5.1%.

A rather simple indicator of this reduced research effort is the number of articles in scientific periodicals that cite sources of financial support for the reported investigation. Citations in surgical journals peaked at 40% in 1970 and decreased to approximately 25% by 1980 (2).

In a recent review of research in surgical oncology, Avis and associates (3) analyzed data concerning grant applications submitted to and funded by the National Cancer Institute (NCI) during the time period from 1980 to 1985. Of the total number (6407) of grant applications submitted, 44% were from departments of internal medicine, while only 16% were from departments of surgery and 4% were from departments of obstetrics and gynecology. The success of grant applications (awarded/submitted) from departments of internal medicine, pediatrics

and radiology ranged from 34% to 36%, while the successes of grant applications submitted by departments of surgery and obstetrics and gynecology were 25% and 26% respectively. In evaluating trends during the six year period, it was evident that by 1985 the number of grants submitted by departments of internal medicine increased 55% (363 to 566), while grants submitted from departments of surgery had actually declined 17% (203 to 168). In reviewing the success rate of grant funding by department, it was apparent, with the exception of radiology, where the percentage of successful applications increased (34% to 37%), that success rates of all other departments decreased, with a disproportionate decrease in surgery, obstetrics and gynecology: internal medicine (37% to 34%), pediatrics (42% to 34%), surgery (31% to 19%), and obstetrics and gynecology (39% to 15%). In considering all grants submitted to the NIH during the same period, similar patterns of grant submission and success rates were seen indicating that the problem was not specific to the NCI.

It is alarming that clinical investigators in all fields of medicine are having trouble gaining research support from the federal government, however, the problem in the surgical specialties is critical and becoming worse. It is tempting to blame the scientific community generally and the NIH and other funding agencies specifically for this dilemma, but these groups are not what is wrong with surgical research and we should examine the reasons why academic surgeons have submitted fewer grants and have failed to get them funded. We can then consider what corrective action should be taken.

It takes five years to complete a general surgical residency and an additional year if one pursues a fellowship in vascular surgery, transplantation surgery or critical care. If one wishes to be trained in cardiovascular surgery, plastic surgery or pediatric surgery, the fellowship programs are two years in length and there is a trend for many of these specialties to increase their training programs to three years. It is easy to see why a surgical resident might not wish to spend one or two years in the research laboratory, especially if the clinical training program is to be seven or eight years in length. Many program directors who require that residents spend time in the laboratory have problems deciding the best time for this experience. Most programs are structured so that the surgical resident takes time out for research after two or three years of residency, and although many are productive during this time, they lose contact with the laboratory when they return to the residency for several more years of clinical training.

Most surgeons, including those in academic medical centers, are active clinically and because the performance of operative procedures and the care of patients thereafter are time consuming, and also because surgeons have other administrative and teaching duties, they have less time to spend in the laboratory than do their colleagues in most other clinical disciplines. A seemingly simple solution would be for surgeons

to change their life style and not operate so that they might have time for laboratory research. Indeed, some surgeons have abandoned clinical surgery altogether. While this might have its rewards, these individuals usually find themselves estranged from their associates and their specialty. Successful surgical investigators are able to balance the laboratory and the clinic, but almost uniformly these are surgeons who have spent substantial time in basic laboratory research, usually during the residency years, so that they are well prepared to compete for peer reviewed research funds when they join a medical school faculty.

Medical school is very expensive and most students incur substantial debt before graduating. In 1986, the average indebtedness of the graduating senior at the Washington University School of Medicine was $38,000, and by 1988 it had increased to $45,000. Even if students choose surgery, or a surgical specialty for a career, many will not wish to spend time in the laboratory because they do not want to delay their training. Most graduating surgical residents (even many who have spent time in the research laboratory), find the life style and financial rewards of private practice too enticing. This is not difficult to understand considering the societal pressures that exist today.

What can the academic surgical community do to attract highly talented persons into surgical research? There are three key considerations:

1. The American Board of Surgery and the surgical specialty boards must reconsider the structure of their residency programs. Rather than continue to lengthen the number of years required for training, it should be possible to decrease them. The American Board of Surgery requires five years of residency training (four of which must be spent in clinical surgery). Residents wishing to pursue training in cardiothoracic, pediatric or plastic surgery should need only four years, or in some cases three years, of general surgery clinical training before entering these specialty residencies. This will be a very controversial matter for the boards to deal with, but it is an obvious way for programs to provide residents an experience in laboratory research without adding years to the training program. The fact that the federal government will almost certainly decrease funding for residency programs makes this proposed alternative more likely.

2. Departments of surgery must provide the necessary atmosphere where residents can do research. This often means establishing meaningful collaborations with colleagues in the basic science departments or other clinical departments where residents can spend two or more years in the research laboratory acquiring the necessary educational and methodological skills.

3. Resources must be provided for laboratory training. While the NIH provides support for laboratory training through individual and institutional national research service awards, few departments of surgery have been successful in obtaining them. The federal government should be encouraged to provide increased funding for training surgical investigators since without the proper environment and program structure, residents will not acquire the necessary skills and knowledge base to compete successfully for research support. Also, academic departments of surgery must divert clinical resources for research training primarily through "seed money" for supporting the young surgeon after he or she has completed the training and is preparing to apply for funding from the federal government or like sources.

Surgical research has made and will make vital contributions to clinical medicine. We must remember that without surgeons there would be no organ transplantation, coronary bypass surgery or joint replacement. The surgical community must develop a sense of purpose about training the next generation of clinical scientists and the decreasing availability of resources make the task a formidable one.

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ISSUE # 3:
ORGANIZATIONAL STRUCTURE OF CLINICAL INVESTIGATION IN THE FUTURE

RESOURCE CONSIDERATIONS AND SUPPORT OF CLINICAL INVESTIGATION
Optimal and Necessary Organization and Structure of Clinical Research

William N. Kelley

The optimal organization and structure of that aspect of clinical investigation as defined by the Committee, i.e. patient related clinical research, requires a program which is creative, coordinated, and supportive of the clinical investigator. Such a program must also maximize the likelihood that important advances will be translated with all due speed from the research laboratory to the alleviation of pain and suffering for the individual patient.

1. Develop an RO-1 mechanism dedicated to patient related clinical studies. Research grants which represent studies ready for patient application should be reviewed by study sections set up entirely for this purpose. The number of study sections, as well as the qualification of the members of these study sections would be determined over time by the number and orientation of the grants submitted, but in any case, shall not be less than one study section committed to this purpose for the entire NIH. Since the studies under review would be only those which are ready for patient application, the basic bench research leading up to the proposal would have to be supported by other mechanisms and, if such research was incomplete, the studies would have to be completed by other mechanisms. For consideration by this (these) study section(s), the studies would also not be appropriate protocols for the CRC or for clinical trials. Such studies also would be appropriate only for those institutions with an established IRB and a funded CRC, and all such proposals would be subjected to review by the IRB and the CRC prior to submission for support to the NIH. All such studies would be funded by the appropriate institute using the standard cutting score mechanism.

2. Expand the funding and the mission of clinical research centers. The general clinical research center has proven to be highly successful, if not critical, in the application of basic research advances to the bedside. While the most appropriate mechanism for support continues to be the NIH, methods must also be encouraged to allow support from other sources, such as the pharmaceutical industry. The CRC program also should be expanded to non-hospital settings, such as nursing homes, home care sites, and other non-traditional settings. In addition, the responsibilities of the

Directors and other professional staff of the CRCs should be expanded to include recruitment of the best qualified students, postdoctoral trainees, and faculty to a career in patient related clinical investigation. Finally, funding of CRCs should be increased to support these expanded responsibilities. Specific recommendations are summarized in Appendix 1. Success or failure of the competitive renewal of these CRCs should be determined, in part, by how well these goals described in Appendix 1 are met.

3. Clinical Trials. Clinical trials continue to be an extremely important aspect of patient-related clinical research. While clinical trials are critical to this structure and organization, they will be described in detail by others.

4. Provide a funding mechanism to insure rapid implementation of clinical advances that are beneficial to human kind, but are not cost effective for implementation by the pharmaceutical industry. There have been many advances over the past century which have proven to be extremely important but do not justify an investment for profit. Perhaps vaccines and orphan drugs represent good examples of this phenomenon in the past. It is quite clear that this not only will continue, but could be greatly expanded in the future. For example, if human gene therapy proves to be as successful as many believe it will, it may well be possible to develop an approach to cure a disease with only a one time application of the appropriate therapeutic modality at the time of birth. While this example could be an exaggeration (at least in the early years), it is difficult to envision how such an advance would be able to generate a return on investment to even recover development costs. On the other hand, it is quite easy to recognize how such an advance might be preventative or curative for literally millions of patients, thus reducing dramatically the disability and death from a specific disease, and perhaps saving countless billions of dollars, in addition to untold human despair. Provision of funding for this purpose would need to be incremental to current NIH programs; it would be highly inappropriate for programs to reduce or displace the funding for basic research which is necessary to achieve these advances. We would, accordingly, recommend that one percent of the health care expenditures of the United States be budgeted for this purpose to be provided (on a voluntary basis) by

all entities which reimburse for health care, including HCFA, Blue/Cross-Blue/Shield, the commercial insurers, etc. It might also be reasonable to ask that financial support be provided from the life insurance industry.

In summary, it is quite clear that the most rapid and appropriate application of advances in basic biomedical investigation will be realized when support is combined from the NIH, the pharmaceutical industry, the insurers of health care and of life. We would summarize our concept as follows:

Mechanism:	Basic advance	Clinical	RO-1	CRC	Clin.Trials	Implementation
Source:	NIH	NIH	NIH	Industry NIH Health Care Payors		Industry Health Care Payors

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While the NIH would continue to provide the major support in most of these steps, critical support from other sources as appropriate would insure final success at a maximum rate.

There are several major issues which deserve consideration by this committee relating to the above organization and structure. First, a mechanism to assure that fraud is basically non-existent must be in place, strictly adhered to, but not onerous. Secondly, we must insure that there is no conflict of interest among the investigators participating in this program at any stage. This could best be handled by defining very clearly anything which might conceivably represent a conflict of interest and asking the investigator to insure that such is not the case. An important principle related to this would be full disclosure of any consulting relationships, equity participation by the investigator or by any family members, such as parents, siblings, spouse, children, or a trust of any sort. The importance of such a full disclosure and review by appropriate parties cannot be over emphasized.

APPENDIX 1

Recommendations for NIH Supported CRCs

Medical Students

- Increase personal involvement of CRC physicians in medical school research programs at each medical school.
- Increase funds available for support of medical student research in the CRC from $4,000 to $15,000 a year and allow specific prospective budgeting for such a program.
- Consider the success of the CRC in supporting medical student research as an important factor in competitive renewals (eg. number of students supported, number of protocols involving students, number of abstracts and publications involving students, and, in the long run, number of students pursuing a research career.

Resident

- Require and fund rotation of one medical or pediatric resident for each eight funded CRC beds.
- Encourage participation of residents in developing and carrying out protocols on the CRC.
- Encourage extended rotations (eg. 3-6 months) for residents with specific interests who would qualify.
- Consider the success of the CRC in supporting resident involvement in clinical research as an important factor in competitive renewals.

Fellows

- Develop a program which would stimulate, support and/or even fund involvement of physician scientist awardees during the final 2-3 years of his or her PSA (i.e. the clinical phase), in collaboration with the appropriate institute.
- Provide funding for an additional year thru NRSA-funded trainees who have made a commitment to utilize the CRC for their research.

Junior Faculty

- o Increase the number of clinical associate physicians to a total of 150 FTEs from approximately 40 FTEs. Do not limit to 3 per center.
- o Increase the duration of support from a maximum of 3 to a maximum of 5 years.
- o Expand the support beyond salary from $5,00 to $20,000 per year.

ORGANIZATION AND STRUCTURE OF CLINICAL RESEARCH

Elaine L. Larson

The success of the NIH extramural programs as a catalyst for the development of biomedical science has been phenomenal. Continued success, however, requires ongoing scrutiny of organizational structure with appropriate and timely modifications made to assure continued optimal conduct of clinical investigation. Four organizational recommendations are made below which might expand the potential for economic use of research facilities and the incorporation of basic science into practice.

1. Develop mechanisms to facilitate more multicenter trials. Although expertise and interests of individual researchers are essential to the creative process of science, some clinical problems are better addressed on a larger scale. Major clinical trials designed to characterize basic biologic phenomena or to test innovative technologies, drugs or devices, could be centered in fewer federally funded clinical research centers. Such centers could focus scarce resources such as cadres of highly trained researchers and measurement and analytic equipment within scientific settings best suited and equipped to successfully carry out rigorous clinical investigation. Protocols could be standardized across such centers so that the requisite sample sizes could be attained. Selected centers could assume responsibility for certain aspects of the study (e.g., tests which require costly equipment or highly trained staff could be conducted in a few sites or complex statistical analytic strategies could be supervised from one or two sites for an entire project). There are ongoing multicenter clinical trials as well as the General Clinical Research Centers funded through NIH that would serve as models and conduits for this plan.

2. Develop mechanisms to facilitate "research without walls" and expand sites available for clinical investigation. Currently, the bulk of federally funded research is conducted in large tertiary medical institutions where researchers and facilities are centered. Research conducted at such institutions is extremely costly. In addition, certain types of research are not appropriate within those settings where funding has been traditionally allocated. Examples include evaluation of alternative therapeutic modalities or systems of care delivery, assessment of programs for disease prevention and health promotion (e.g., AIDS education for high risk populations, smoking cessation programs, prenatal care designed to reduce low birth weight), and cost analyses of clinical therapies and programs. These types of applied research link basic science to improvements in technology and practice and may be conducted in a less costly, most efficient, and more appropriate manner in alternative sites like private and state-operated extended and chronic care facilities, community agencies or schools.

Use of such alternative sites for clinical investigation has several advantages. The selection biases inherent in the use of large medical centers are reduced, access to study populations more representative of target populations but inaccessible in traditional research settings is enhanced, and some of the costs associated with conducting clinical research may be reduced. Most importantly, use of these sites focuses clinical investigation more directly on some of the major health care needs of the nation.

Currently, the funding structure within the NIH is not well designed to facilitate research in sites other than academic health centers. Mechanisms not only to allow but to actively encourage research without walls should be designed. To assure that such clinical research is in no way compromised in terms of research design or scientific rigor, there must be guidelines and protocols addressing issues which need to be resolved such as how to develop research agreements among various non-traditional research sites, how to deal with ethical and human subjects considerations, and how to assure adequate scientific supervision of decentralized projects.

3. Facilitate linkages for clinical investigators between government, academia, and industry. On the research spectrum NIH funding has placed emphasis on basic science whereas the focus of industrial research and development is on technology and product development. There are currently no adequate mechanisms in place to assure smooth flow of scientific research to technologic innovation, nor to facilitate joint sponsorship of clinical investigation by industry and government. The need for increasing collaboration from all three sectors has been consistently identified within the scientific community (references below) but investigators will look to NIH for direction regarding how and when to seek out such new relationships, since there are many real misgivings about the issue. Important tasks include the development of guidelines to protect the interests and reduce conflicts of all parties and the definition of roles of these parties within research continuum from basic to applied research.

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OPTIMAL AND NECESSARY ORGANIZATION AND STRUCTURE OF CLINICAL RESEARCH

Louis Lasagna

The NIH is in a position to lead an effort that might correct some glaring deficiencies and meet critically important national needs in the general areas of clinical investigation. The problems that need to be addressed are the following:

1. The decline of academic clinical pharmacology in the U.S.

2. The absence of specific training programs for individuals working in the field of drug development, be they in industry, academia, or the government, and needing the background to conceptualize the process of bringing a new drug to the public, from its very beginning through to it usage in practice.

3. The paucity of attention to new techniques for assessing drug benefits and costs (both somatic and monetary) to complement the well-worked out techniques for controlled clinical trials which suffice to gain regulatory approval but are inadequate to address the issue that appear after registration is achieved.

Several decades ago, largely due to the leadership of Dr. Robert Grant of the National Heart Institute, the U.S. led the world in federally supported training of clinical pharmacologists. In time, industrial support (Burroughs Wellcome, PMA, e.g.) augmented NIH support. Today the number of such training programs of high quality and critical mass is pitifully small, and the annual output of graduates trained in the discipline is minuscule. The U.K. and Sweden have outstripped the U.S. in their support for academic units of this type.

The reasons for this parlous state are multiple: The failure of clinical pharmacology to achieve a clear image in academia of its potential value and the absence of academic support for such individuals once past their training, the "taint" of "applied" research in academia, and the recent worship of molecular biology as if somehow all scientific progress could be achieved by focusing on molecular level research.

Industry and the FDA, unlike academic, appreciate the crucial importance of clinical pharmacology to their daily activities, but suffer from a lack of individuals well-trained for the process of drug research and drug evaluation. There is very little in the formal training of physicians or Ph.D.'s, e.g. that prepares them for such a role. Pharm.D's and pharmacists are only slightly better off in some regards.

The background needed includes training in medicinal chemistry, clinical medicine, pathology, toxicology, pharmacology (both pharmacokinetics and pharmacodynamics), epidemiology, biostatistics, experimental design, economics, ethics, food and drug law, risk perception, risk communication, and risk/benefit analysis.

The evaluation of a drug prior to FDA approval is not adequate to define its proper use after marketing has begun. The pre-approval process focuses on "group" performance, in controlled trials, conducted often by expert physicians, in patients whose heterogeneity and exposure to other variables of importance are necessarily limited. Once a drug is approved, the situation changes drastically: physicians of all levels of training and expertise are free to prescribe the drug for patients with other co-morbid states, or multiple drugs, variably compliant with prescribing directions, and in outpatient settings where control and supervision are reduced. Comparative performance (both with regard to quality and cost) becomes more important. Cost containment pressures have an increasingly strong impact.

What could NIH do?

1. Either alone, or in concert with academia, AMA, industry, FDA, etc., NIH could assess what is needed in the way of training and post-training support, to restore U.S. clinical pharmacology to a position of strength.

2. A similar role could be played by NIH in evolving a "curriculum" for training individuals for drug discovery, research, and evaluation. Since such a curriculum needs to be both realistic and imaginative, the best brains in the several fields mentioned earlier need to work out a syllabus which could not only build on accepted lore and custom, but would revise current inadequacies in concept or application. (Statistical thinking, e.g., is desperately in need of reworking as it is currently invoked.) Teaching materials could be prepared (written, audio-visual, computer-linked learning, etc.) and periodically updated, so as to maximize the utility of those new curricula.

3. At the level of post-marketing research, much needs to be done. The benefits of many drugs are now inadequately measured, while their costs (somatic and monetary) are often paid a lot of attention. Large scale, lengthy, expensive controlled trials cannot possibly be done for every new drug marketed in such areas as lipid-lowering, blood pressure reduction, or thrombolysis. Can we assess the putative long term benefits by epidemiologic data: (It seems paradoxical that those who answer "no" to this question are willing to concede that the pressure to develop blood pressure lowering drugs or cholesterol-lowering drugs comes predominantly from epidemiologic evidence.)

A new drug is like a new surgical procedure; with time, the choice of target population and the skill with which therapy is applied change, as they should. "Fine-tuning" of treatment for individuals, based on data suggesting baseline variables that predict response, is the goal, not treatment of the "average person." There is probably as much good to be gained from the wiser use of drugs we already have as from new drugs still to be developed.

The challenges are real, the potential benefits are enormous. Will NIH lead the way?

ISSUE # 4:
THE NEED FOR CLINICAL INVESTIGATORS TO BE CONCERNED WITH ISSUES OF OUTCOME ASSESSMENT AND COST-EFFECTIVENESS ANALYSIS

THE NEED FOR CLINICAL INVESTIGATION TO CONSIDER THE ISSUES OF OUTCOME ASSESSMENT

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The extraordinary progress in the advancement of basic biologic research is a proud accomplishment, perhaps the most distinguished of our era. The expansion of understanding of the nature of human biology and the mechanism of disease, and the associated growth of a spectacular technologic capacity to intervene in biologic processes, has fostered the rapid proliferation of treatment theories on how to improve patient well-being. But, in contrast to the well established policies and mechanisms for promoting biomedical science, support for the evaluative clinical sciences--the measurement sciences used to test the validity of clinical theories concerning the prevention, diagnosis, and treatment of disease--has been inconsistent and unsystematic. With the exception of the evaluation of new drugs, there is no mechanism in place to assure that major clinical theories are systematically evaluated.

The nature of innovation in the pharmaceutical industry (where research proceeds in a reasonably orderly fashion from the bench to human experimentation), lends itself to regulatory approaches to establishing proof of efficacy. The regulatory legislation of the 1960's was followed by a massive investment by the drug industry in the evaluation of new drugs, an investment that is recovered from patient dollars through the price of drugs. By contrast, the investigation of efficacy for other treatments where regulatory requirements have not been imposed is unsystematic, and that which is undertaken is largely on the basis of investigator-initiated grants with funds coming from general revenue tax dollars. The amount of money devoted to randomized clinical trials for drugs--estimated at about $1.5 billion in 1987--contrasts sharply to the amount allocated to all other types of treatment theories, and exemplify the current imbalance in investment in outcomes research. For example, the outcome research program of the National Center for Health Services Research and Health Care Technology Assessment discussed below, received an appropriation of only $6 million dollars in FY 1989.

The immediate consequence is an increasingly inadequate scientific basis for clinical decision-making. The basic probabilities for the outcomes of specific treatments are often unknown or in controversy and patients and physicians face unnecessary uncertainty in choosing among alternative treatments.

> The last few years have seen the rapid proliferation of medical theories concerning the best way to treat chest pain caused by impeded blood flow in the artery that feeds the muscle of the heart. Some physicians recommend surgery--the well-known coronary bypass operation. Others recommend coronary artery

angioplasty--the insertion of a balloon catheter into the heart's artery, which is then expanded to reduce the obstruction. Still others recommend drug treatment. Debates about the relative value of these different treatments rage in clinical medicine, but because the outcomes are not systematically compared, the debates cannot be settled.

There are new ways to treat arthritis of the hip and knee. One approach involves the surgical replacement of the hip or knee joint, and for physicians and patients who choose this method there are a number of alternative ways of accomplishing the replacement. There are many choices, but no consensus on which approach is best for the patient. There is also considerable disagreement about when, in the natural history of the disease, the operation should be planned, if at all. These differences in opinion translate into costly differences in the rates at which various services are performed in different parts of the country.

The evaluation of the outcomes of clinically different approaches to treating common medical conditions such as back pain, pneumonia and gastrointestinal disease, is perhaps the most neglected area of all. In many communities in this country, physicians favor the outpatient setting for treating these patients, while in other communities, the standards of practice favor the use of hospitals. Similar uncertainties and controversies about correct practice exist concerning the value of intensive care units.

The secondary consequences are large variations in costs and utilization among apparently similar populations treated by different (but equally qualified) physicians. For example, per capita expenditures under the Medicare program for residents of Boston were about 80 percent higher than for residents of New Haven. Higher rates of hospitalizations for chronic medical conditions accounted for much of the differences in expenditure. As variations such as these become more widely known outside of the profession, they are a source of growing embarrassment to physicians and an invitation for cost containment agencies to intervene directly in the practice of medicine.

The need is for a broad extension of the mandate to evaluate medical interventions to include the full spectrum of relevant treatment, clinical theory and outcomes. The mandate must be expanded to include diagnostic and therapeutic procedures and established drugs used in novel ways, as well as the use of hospitals and intensive care units compared to their

alternatives. In addition to traditional measures of mortality, morbidity and physiologic or biochemical parameters of outcome, good outcomes research requires good measures of symptoms and how treatment affects them. It also depends on functional status and quality of life measures. These measures are becoming increasingly important as, more and more, the stated objectives of many medical interventions is the reduction of symptoms and improvement in well-being.

A well conceived outcomes research program will also take advantage of newer methods for evaluating symptoms and functional status; use large claims databases for establishing the probabilities for outcomes; use decision analysis to test medical theory as part of the assessments undertaken to establish the scientific and ethical feasibility of conducting clinical trials. It will also invest in the development of new methods for evaluating outcomes, particularly for use in non-experimental situations, such as the comparison of death rates among hospitals or treatments. For these comparisons, well tested methods for adjusting severity are needed. For epidemiologists and clinicians to have confidence in this research, it must be formally peer reviewed and be part of public sector science. It will also invest in research into ways for improving drug evaluation strategies, particularly methods for comparing drugs to treatments, such as surgery where the classic double blinded randomized clinical trial are difficult and sometimes unethical to conduct.

Extending the mandate to evaluate efficacy and effectiveness presents a challenge to research scientists, funding agencies, and policy makers. In contrast to the situation for new drugs, other treatment innovations often arise within the context of everyday practice as part of the problem solving process. The uses now made of hospitals and ICUs, as well as many surgical operations are good examples. It would not be easy to subject such practice conventions to formal regulation, simply because there is no clear distinction between "regular" practice and innovation. Moreover, because the innovators often are individuals or members of small groups, and their products are not generally patentable, they have little capital and little incentive to invest their own resources in outcomes evaluation. The result of a serious effort to regulate innovation would almost certainly be the stifling of innovation.

The failure of the current investigator-initiated grant mechanism to meet the challenge of outcome assessment suggests, however, that a new approach is needed. The National Center for Health Services Research is initiating a program which provides one model of how a research program might be built. The program uses the extramural grant mechanism to fund assessment teams that accept responsibility for evaluating alternative treatment theories for specific common disease conditions (for example, prostatism or stable angina). The interdisciplinary teams, composed of clinical investigators, epidemiologists, practicing physicians, and others with relevant skills in the evaluative clinical sciences, are

required by the terms of their grant award to keep track of treatment innovations in their area of responsibility and undertake for all treatments the equivalent of phase I and phase II assessments now required for drugs. Based on their assessments, the teams are to identify priority clinical trials (phase III studies) that are needed, making their recommendations on a periodic basis. They are also responsible for conducting phase IV studies. Funding for the program is from patient dollars--from the Medicare trust fund. Priorities are according to common conditions for which at least one current treatment arm possess particularly high costs and/or risks for Medicare enrollees. About 15 teams will be needed to cover the majority of surgery and medical hospitalizations. Table 1 gives an example of the priority areas under consideration for this program.

The program provides a non-regulatory model for assuring that systematic evidence of efficacy and effectiveness is developed. How the information on efficacy and effectiveness is used will depend on other mechanisms, agencies or incentives. The goal of outcomes research is better clinical science--to establish the facts and test theory--not to make specific regulatory determinations.

Many sources of funding and various research programs contribute to outcomes research. In FY 1987, the National Institutes of Health spent about $420 million on clinical trials. The Food and Drug Administration and the drug industry contribute at least $1.5 billion to assessments. But the lack of regulatory mandate means that many important priorities--such as those listed in Table 1, are left unattended. The peculiar need for a public program responsible for the systematic rationalization of the scientific basis of clinical theory suggest the need to designate a single agency with responsibility for setting the baseline outcomes research agenda--for assuring that systematic attention is given to the important unanswered scientific questions, particularly for "big ticket diseases." Evaluations under this agency must be done in a timely and ongoing way. The National Center for Health Services Research and Health Care Technology Assessment is a good candidate. It is situated within the orbit of government-sponsored, peer-reviewed science, and historically this agency has been responsible for much of the methodologic research that now makes a concerted effort to evaluate outcomes possible. Its study section members represent the various disciplines that constitute the evaluative clinical sciences.

One outstanding problem is that the level of expectation and acknowledgment of mission needed from policy makers for NCHSR to accomplish this mandate is insufficient. The current level of funding--$6 million in FY 1989--is inadequate. The budget for an acceptable program is $200 million. Achieving consensus that NCHSR can accomplish this mission requires assurances that it can grow rapidly as a credible scientific institution. The National Institutes of Health has the resources and the experience to assure the rapid and orderly growth of an agency with this mission. At the same time, the agency

must remain responsive to the needs of patients and policy makers for assurance that assessment priorities are met and that the core group of scientists whose careers are situated in the evaluative clinical sciences are mobilized. It is time to consider carefully the option of moving the National Center into the NIH.

Suggested Priority Conditions or Illnesses for Phase I and II Assessments Under the National Center for Health Services Research and Health Care Technology Assessment's Patient Outcome Research Program (S. 2181)

Condition	Treatment Controversies
Stable Angina	Bypass Surgery vs Angioplasty vs Drugs
Unstable Angina	Bypass Surgery vs Angioplasty vs Drugs
Arteriosclerosis Causing Stroke	Endarterectomy vs Drugs
Peripheral Vascular Disease	Bypass Surgery vs Angioplasty vs Medical Management
Lens Extraction	Surgery (by type) vs Watchful Waiting
Gallstones	Surgery vs Stone Crushing vs Medical Management vs Watchful Waiting
Arthritis of the Hip and Knee	Surgery (by type) vs Medical Management
Non-Cancerous Conditions of the Uterus	Surgery (by type) vs Hormone Treatment vs Watchful Waiting
Prostatism	Surgery (by type) vs Angioplasty vs Drugs vs Watchful Waiting
Ear, Nose & Throat Conditions	Surgery (by type) vs Various Drugs
Herniated Disc	Surgery vs Various Medical Treatments

Acute and Chronic Medical Conditions:

Back Pain/Strain	Hospitalization vs Ambulatory-based Care;
Gastroenteritis	ICU vs Usual Ward Care
Respiratory Disease	
Heart Disease	