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Chapter 9

# Clinical Research

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# Clinical Research

## INTRODUCTION

Clinical research is research that is conducted on people in a medical setting and is distinguished from nonscientific medical experimentation by the presence of an established research hypothesis and design. It can range in complexity from an elaborate, multicenter randomized clinical trial<sup>1</sup> to a study by a single physician trying a variation of an old procedure in his or her own office; and its focus ranges from basic studies of human metabolism to evaluations of fully developed medical technologies. Clinical research on new medical technologies is an important part of the process of technological change described in the last chapter, bridging the gap between laboratory testing and the accepted use of a technology by physi-

cians. Such research can also be used to determine the value and best use of established medical technologies.

Some observers believe that Medicare's prospective payment system (PPS) for inpatient hospital services is inadvertently decreasing the level of funding for clinical research (241,404). In publicly asserting this, *such* observers implicitly recognize that Medicare, contrary to its own policy, has been paying for costs associated with experimental technologies. Such payments, to the extent that they have actually been made by Medicare, represent a hidden subsidy of clinical research. Any Medicare payments for experimental technologies have had a multiplier effect on the direct appropriations for clinical research.

In response to concerns that have been raised, the U.S. House of Representatives Committee on Appropriations directed the Health Care Financing Administration (HCFA) and the National Institutes of Health (NIH) to study the impact of PPS on clinical research. This chapter summarizes the evaluation questions applicable to such a study and discusses approaches to the problem.

<sup>1</sup>Clinical trials, a subset of clinical research, are the organized testing of new devices, drugs, therapies, or other changes on ill patients, often with control groups for comparison of results. The National Institutes of Health (NIH) *Inventory of Clinical Trials* (320) defines a clinical trial as:

... a scientific research activity undertaken to define prospectively the effect and value of prophylactic, diagnostic, therapeutic agents, devices, regimens, procedures, etc., applied to human subjects. It is essential that the study be prospective, and that the number of cases of patients will depend on the hypothesis being tested, but must be sufficient to permit a definite result to be anticipated. Phase I, feasibility, or pilot studies are excluded.

## POTENTIAL IMPACTS OF PPS ON CLINICAL RESEARCH

### Background: Medicare and Funding for Clinical Research

In 1983, the total budgeted national support for health research and development (R&D) was estimated at \$10.4 billion (362). The Federal Government contributed *over* half of this (\$5.4 billion), including \$3.8 billion from NIH; industry spent \$4.0 billion on health R&D; private nonprofit organizations spent \$0.4 billion, and State and local governments contributed \$0.6 billion. The level of health R&D had remained fairly constant, after inflation, in the 5 years prior to 1983 (362).

NIH spends a substantial amount on clinical research, although the precise amount devoted to clinical as opposed to laboratory research is unknown. Some of the research is done in NIH's own clinical center, while other research projects are carried out in general clinical research centers (GCRCs) located in hospitals and funded through NIH's Division of Research Resources. Still other efforts, primarily clinical trials, may take place in any clinical setting. These efforts are funded through grants and contracts sponsored by individual institutes. A 1979 survey of trials indicated that about 5 percent of the NIH health research



*Photo credit: National Institutes of Health*

A substantial amount of clinical research is supported by the National Institutes of Health. Some of this research is done in the Warren G. Magnuson Clinical Center, located on the NIH campus in Bethesda, MD.

budget supported clinical trials (306). Other organizations within the Public Health Service, such as the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), also spend a significant amount on clinical trials and other clinical research (56).

In addition to receiving budgeted support, clinical research has probably received a great deal of financial support, not explicitly budgeted or openly recognized, from third-party payers of health care costs. One of these payers is Medicare.

Since its inception, Medicare has been prohibited by law from paying for medical services and procedures that are not “reasonable and nec-

essary” (Public Law 89-97). This prohibition, combined with a legislative injunction against cross-subsidization, has been interpreted by HCFA as precluding Medicare payment for clinical research. In accordance with a Federal regulation issued in 1966 (42 CFR 405.422), Medicare policy does not allow reimbursement for research-related costs, including research-related patient care costs, that are over and above “usual” patient care for equivalent patients not on research protocols.

A cost-conscious environment recently resulted in a minor modification by Congress of this stringent restriction on the use of Medicare funds. The Social Security Amendments of 1983 (Public Law

98-21) and the Deficit Reduction Act of 1984 (Public Law 98-369) gave the Department of Health and Human Services (DHHS) (including HCFA) the power to assess “the safety, efficacy, and cost-effectiveness of new and existing medical procedures.” Medicare trust funds may be used to pay for patient care costs associated with these assessments if two requirements are met:

- the research is not of the sort that would be undertaken by industry or by NIH, and
- the procedure being investigated “has the potential to be more cost-effective in the treatment of a condition than procedures currently in use with respect to such condition” (Public Law 98-369, sec. 2313(c)(3)).

The same two laws also gave the Prospective Payment Assessment Commission (ProPAC), with the cooperation of the Secretary of Health and Human Services, the power to use Medicare trust funds to conduct clinical research investigating cost-effectiveness. As of August 1985, neither DHHS nor ProPAC had used this authority.

Despite the prohibition against Medicare payment for clinical research, under cost-based reimbursement, Medicare did sometimes pay for hospital costs related to clinical research. Some observers claim that the practice was widespread (160). The method of hospital reporting for Medicare Part A made it nearly impossible for fiscal intermediaries to determine whether an experimental technology was used for any particular patient. When presented with a hospital’s bill for services, the intermediary could not easily distinguish between charges that were related to an experimental procedure and those that were not. Intermediaries might sometimes learn from the Part B carrier that an experimental procedure was used in the hospital, but even then, it was difficult to identify the hospital costs or charges associated with the procedure. Moreover, when a patient underwent both established and experimental procedures during a hospital stay, it was difficult to determine what proportion of the cost of care was attributable to the experimental part of the patient’s stay.

Thus, under cost-based reimbursement, Medicare intermediaries might have been able to identify admissions that were purely for research rea-

sons or to disallow research costs such as those for data collection, but there was no reliable way to determine what proportions of ancillary tests and patient care costs were attributable to the use of an experimental technology during the hospital stay. A hospital billed Medicare for the services it provided to Medicare patients, and unless the intermediary determined through auditing that a service was associated with research, the hospital was paid.

Virtually all information regarding Medicare payment for experimental procedures under cost-based reimbursement is anecdotal. It is clear that, knowingly or unknowingly, hospitals were reimbursed by Medicare for costs associated with unproven technologies. It is not clear how extensive this reimbursement was because there have been no studies of the subject.

## Clinical Research Under PPS

Hospitals’ financial incentives regarding clinical research under Medicare’s PPS are different from the incentives under cost-based reimbursement. The fear that the incentives of the new payment system will affect hospitals’ willingness (or even ability) to maintain clinical research programs has made clinical research under PPS an issue in its own right.

Under PPS, hospitals lose money whenever they treat a Medicare patient with above-average per-case costs and make money whenever they treat one with below-average costs. When research patients are more expensive to care for than nonresearch patients, hospitals have an incentive not to participate in research. This incentive probably operates in the case of most research protocols that require more tests, more patient monitoring and care by staff, or longer hospital stays than the established mode of treatment. In cases in which an experimental technology is costlier than the alternatives, or data collection costs are not entirely covered by research funding, the hospital may have to absorb the extra costs. In any of these cases, PPS would tend to discourage clinical research.<sup>2</sup>

<sup>2</sup>The initial diagnosis-related group (DRG) prices were based on estimates of the average costs per DRG in 1981. Whatever research-related costs were reimbursed at that time are included in the DRG prices. This fact does not alter the financial consequences of treat-

(continued next page)

In other cases, however, PPS may encourage clinical research. For example, the existence of a research program enhances a hospital's image in general and can act as a marketing tool to draw admissions. Also, some technologies may actually lower hospital costs during the research phase, because they are cheaper to purchase or because the research protocols themselves are less costly than alternative established treatments (i.e., they require fewer ancillary services or shorter hospital stays).<sup>3</sup> In such cases, hospitals have an incentive to participate in the research as soon as possible. Finally, many technologies may have the potential to lower costs once accepted for widespread use. Producers of these technologies have an incentive to enlist hospitals and physicians to participate in clinical research not only to show safety and effectiveness but also to gather cost information for later use in marketing.

PPS encourages the inclusion of cost-effectiveness studies as part of, or in addition to, the clinical trials of new drugs and devices. The manufacturer of a new technology has a strong selling point, much more so under PPS than under cost-based reimbursement, if it can show cost savings to hospitals from the technology. However, there are important tradeoffs in conducting cost-effectiveness studies simultaneously with clinical trials. The obvious benefit is that doing an economic analysis of a new technology at an early stage is time-saving, cost-saving, and a source of important information for users of the technology—hospitals and physicians. The primary drawbacks are, first, that the clinical trial environment may not present a realistic picture of how the technology will be used and its real cost tradeoffs; and second, that the costs of a technology in its early stages of development and use may be very different from its costs later in the diffusion stage (90).

The examples of possible PPS impacts on clinical cancer research at certain community hospitals (see box 9-A) and on NIH-sponsored GCRCs

ing above-average-cost patients, however; it simply makes the average rate of payment higher than it would otherwise have been (assuming that most research raises the cost of diagnosis or treatment). Incorporating past higher-than-average per-case costs into current prices effectively means that past implicit Medicare subsidies of research-related costs now subsidize the provision of patient care in general, although treating expensive research patients is still discouraged.

Surgical staplers, an alternative to manual sutures, are an example of one such technology (36).

(see box 9-B) suggest that the impacts on clinical research may be unevenly distributed. One strong potential difference is between teaching and nonteaching hospitals. Virtually all GCRCs, for instance, are in teaching hospitals. In cancer research, small nonteaching hospitals cannot meet

#### Box 9-A — PPS and Community Hospital Participation in Cancer Research

More concern has been expressed over the effect of Medicare's PPS on cancer research than on any other research area, and advocates of community hospital participation in cancer research have been particularly vocal (77). The National Cancer Institute's (NCI) Community Clinical Oncology Program is a program specifically for community, nonteaching hospitals that was established to increase the number of patients available to participate in clinical trials and to accelerate the transfer of new cancer treatment technologies to the community hospitals (364). NCI provides funding to cover administrative and data collection costs, without which community hospitals might not be willing to participate in trials. The trials themselves are coordinated by NCI-supported teaching and research hospitals.

With the introduction of PPS, some community hospitals believe that their ability to participate in clinical trials may be endangered if patients participating in research are more costly than those that are not. The Association of Community Cancer Centers has suggested that there be a separate diagnosis-related group (DRG) established for patients participating in research (404), and the National Cancer Advisory Board has suggested that, pending completion of relevant studies, "it may be prudent to continue to fund these patients [participating in NIH clinical trials] on a cost reimbursement basis" (363).

One problem with these approaches is that they require official recognition of Medicare reimbursement for research-related costs. Since DHHS has interpreted the Medicare law as prohibiting payment for most kinds of research, these options are not possible, in the view of DHHS, without regulatory or legislative changes (77). It has not yet been established that PPS is actually posing a barrier to the participation of cancer patients over age 65 in clinical trials, although there are several studies currently being planned or implemented to establish the relative costliness of these patients (see p. 137).

### Box 9-B —PPS and General Clinical Research Centers

NIH funds a General Clinical Research Centers (GCRCs) grant program that enables hospitals to designate certain hospital beds for use by patients participating in clinical research. Most GCRCs have facilities that are separate from the rest of the hospital, including their own kitchen, laboratory, and office facilities, as well as their own beds. A GCRC grant maybe used for some salaries, renovations, laboratory equipment, and operating costs, including the patient care costs for patients in the hospital solely for research purposes. There are approximately 75 funded GCRCs in teaching and research hospitals in the United States, with a combined total of about 600 hospital beds devoted to research (361). Examples of studies being conducted at GCRCs are studies of the effect of disease and age on drug disposition and action; studies of lecithin treatment for Alzheimer disease; and studies of calcium and phosphorus balance in kidney transplant patients.

Some of the patients using GCRC beds are in the hospital *only* to participate in research, and the costs of their care are paid for by the GCRC grant. Others, however, would be hospitalized whether or not they were participating in research. Some of these patients' care has been billed to Medicare in the past and has been reimbursed. Under PPS, however, the hospital must absorb any of these patients' costs that exceed the DRG payment. If these patients are more expensive than average to care for, and if the hospital has been reimbursed by Medicare for these costs in the past, part of the GCRC grant must be used to make up the difference unless the hospital is willing to absorb the cost. This in effect reduces the amount of research that the GCRC funds can support.

GCRCs may also be affected by any decreases in hospital occupancy rates that result from PPS incentives to decrease length of stay and emphasize outpatient services. Temporarily unneeded GCRC beds can be used as overflow beds by nonresearch patients, and reimbursement for those patients can help subsidize the costs of maintaining the center. If there are fewer overflow patients and the temporarily unneeded beds lie empty, the hospital's GCRC grant may not be able to support as many research beds, or, consequently, as many research patients (281).

No data on whether PPS is actually affecting GCRCs adversely were available as of August 1985. At centers where most of the patients are in the hospital solely to participate in the research protocol and Medicare has not been relied on extensively as a source of reimbursement, little impact is anticipated. It appears that a particular GCRC is more likely to suffer under PPS if: 1) patient care costs in the GCRC are greater than in the rest of the hospital, due to greater service intensity or longer lengths of stay; 2) research tends to be applied rather than basic research, with many patients in the hospital for necessary therapeutic reasons as well as for research; 3) the hospital has traditionally relied on Medicare and other payers for at least some reimbursement of patient care costs; and 4) overall hospital occupancy declines.

the requirements of the cancer centers' exemption to PPS,<sup>4</sup> nor are they eligible for Medicare indirect teaching allowances that might be used to subsidize research.

<sup>4</sup>Public Law 98-21 provides that hospitals fitting the National Cancer Institute's (NCI) definition of a "comprehensive or "clinical cancer center can apply for an exemption from PPS. The relevant regulations pursuant to this law specify that to qualify at least 50 percent of all patients discharged from these hospitals must have cancer as the principal diagnosis (49 FR 234). As of July 1985, five hospitals had met these provisions and been granted exemptions (337).

<sup>5</sup>Medicare payments for the indirect costs of medical education, based on the number of interns and residents per hospital bed, were instituted in 1980 when limits on reimbursement for medical care costs were tightened (175). With this extra allotment to teaching hospitals, Medicare may have been shifting some of its subsidy for clinical research from medical care reimbursement payments to indirect medical education payments. The purpose of the adjustment was

PPS may also affect research in different fields more or less strongly. Impacts may be stronger in research fields with a high proportion of diagnostic and therapeutic procedures in the experimental stage; with relatively costly new technologies; or with many Medicare-eligible patients affected. PPS may also have greater effects on diagnostic than on therapeutic procedures, because clinical research on diagnostic procedures often requires more duplicative testing or other services than research on therapeutic procedures.

to accommodate the generally higher costs of teaching hospitals that were not directly tied to teaching (e. g., residents' salaries) but were nonetheless assumed to be unavoidable consequences of having a teaching program. The factors contributing to these costs have not all been identified (175), but the existence of a clinical research program may be one component (160,241).

## APPROACHES TO EVALUATING THE IMPACTS OF PPS ON CLINICAL RESEARCH

### Critical Evaluation Questions

The introduction of PPS has raised concerns about federally financed clinical research that are somewhat different from the issues discussed in previous chapters. In particular, it has stimulated discussion about whether HCFA has a role in supporting such research. Under Medicare's cost-based reimbursement system, it is likely that HCFA frequently reimbursed hospitals for the patient care costs of patients participating in research protocols, although the extent of such subsidies is unknown. Under PPS, however, there is no extra payment for research-related patient care costs.

The impact and evaluation issues raised in this chapter need to be separated from the policy issues. Quantitative and qualitative studies can assist in answering the question: How is PPS affecting the level and type of clinical research performed, relative to the situation under cost reimbursement? Such studies cannot assist in answering the ultimate policy questions: Should support for any negatively affected areas of clinical research be reinstated, and who (if anyone) should bear the costs of that support?

The potential impact of PPS on clinical research is an evaluation area in which the most fundamental baseline data are lacking. There are no data, even inadequate data, on the size of the past and present Medicare subsidy for such research; on whether research patients cost more to treat than nonresearch patients; on how much more they cost; on what the components of any extra costs are; on whether some kinds of research protocols result in higher marginal costs than others; or on the distribution of these factors across research areas.

The size of the Medicare subsidy for clinical research under cost-based reimbursement has important implications. If the subsidy has been large, then PPS will probably result in a reallocation of resources away from clinical research, resulting in less total research or less research in specific areas or settings, such as community hospital par-

ticipation in cancer trials. If the subsidy has been low, PPS will have little net overall effect on clinical research, though again it may have more effect in some areas than others.

### Impact Measures

Operational measures of the size and distribution of implicit Medicare subsidies for clinical research are difficult to define. The lack of good conceptual measures means that determining the real size and extent of PPS impacts on clinical research will be virtually impossible. Given this, the question becomes one of what proxy measures, however far removed from the desired conceptual measures, are available.

One possible strategy for evaluating PPS impacts on clinical research is to measure changes in the purchasing power of research dollars. NIH, the primary explicit funding source for clinical research, could assimilate data on the number of patients enrolled in clinical trials, manhours funded, and other measures of clinical research activity. If Medicare subsidies are reduced (or increased) by PPS, each NIH dollar spent on research will appear to buy less (or more) research than it did before PPS, even after adjustments for inflation. This change in purchasing power would be independent of the NIH budget (although if the purchasing power of research dollars decreased the total amount of research would also decline unless the NIH budget increased to compensate). An analysis of changes in purchasing power could be conducted across the various research fields to determine which areas are the most affected.

A second possible strategy for evaluating PPS impacts on clinical research is to target areas where effects might be expected. As discussed above, two examples of areas that appear particularly troublesome are cancer research in community hospitals and research in NIH-sponsored GCRCs. On a focused level, it is possible to examine, for instance, the size of community hospital participation in clinical cancer trials; the total research-related costs per patient in those trials;



and the amount of those costs that exceed revenues from NIH, industry, or other research funding sources. While the difficulty in measuring research-related costs and other variables still makes this research design far from ideal, it nevertheless may be adequate for policy decisions.

On a focused level, it may also be possible to examine shifts in the setting of care. PPS may encourage more research in outpatient and home settings, and it has been suggested that the Food and Drug Administration should accept research in nonhospital settings as meeting its requirements where such research is appropriate (39). Conversely, PPS may have particularly adverse effects in research areas such as mental health for which the trend is toward inpatient research (231).

#### Data Sources

No single database contains information on amounts of clinical research performed in the United States. Information on the level of clinical research funding is available from separate sources—e. g., NIH or ADAMHA—and changes in the amount of research performed largely reflect changes in the research budgets of these organizations. HCFA has been directed by Congress to study jointly with NIH the impact of PPS on clinical research (301) and to report to Congress by the beginning of 1985, but there are currently no data to directly support a comprehensive analysis; as of August 1985, the analysis had not been completed (see ch. 10).

Some information on support for clinical trials has been prepared by NIH in response to a separate congressional request, but this information does not include detailed data on ongoing trials or even data on patients' age (178). Such clinical trial data have not been compiled systematically by NIH since 1979, though some individual institutes have continued clinical trial inventories for their own purposes (306). Observed changes in the total number of trials, number of patients participating in trials, and dollars spent on trials are likely to be due to NIH budget allotment decisions. But it might be possible to extract from this information changes in relative purchasing power for clinical trials. If data were available on the age distribution of patients enrolled in trials,

the exposure of specific research areas to PPS could be assessed. Any analysis would still be limited by the difficulty of attributing changes to PPS and the fact that the underlying data would include only clinical trials, but it could serve as a useful indicator of specific areas for further study.

The only research area receiving widespread scrutiny relating to PPS is cancer research. There are currently three efforts to establish the relative costliness of research patients and the impact of DRGs on cancer research:

- The National Center for Health Services Research and Health Care Technology Assessment (NCHSR&HCTA) is conducting a study that compares the hospital costs of patients enrolled in National Cancer Institute (NCI) clinical trials with the costs of non-protocol cancer patients (351). Data sources for the study are NCI data on patients enrolled in clinical trials and a sample of discharge abstracts and hospital bills drawn from a list of hospitals participating in NCI trials. The study is scheduled for completion in 1986.
- The Eastern Cooperative Oncology Group (ECOG), an affiliation of Eastern U.S. hospitals participating in cooperative cancer research and related activities, is currently analyzing data from a preliminary study on the extent of hospitalization for patients on cancer protocols. If the results suggest that patients over age 65 (about 23 percent of ECOG patients enrolled in clinical trials) undergo significant hospitalization, ECOG plans a further study to address more directly the potential impact of PPS on hospital care for these patients (199).
- The Association of Community Cancer Centers is attempting to estimate the relative costliness of patients participating in research at its member hospitals (206). Preliminary studies of costs in three hospitals (in New Jersey, Oklahoma, and California) supported the hypothesis that research patients have higher costs (404).

These efforts may help shed light on cancer research, but the results cannot be generalized to other medical fields.

## CONCLUSIONS

The impact of Medicare's PPS on clinical research raises issues unlike those in other areas of the health care system. In the past, under cost-based reimbursement, third-party payers, including Medicare, implicitly subsidized clinical research. Despite the fact that support for all clinical research (except that involving cost-effectiveness) is and always has been contrary to Medicare policy, in practice, the imposition of per-case payment may significantly affect the amount and type of clinical research performed,

NIH data on an important subset of clinical research, clinical trials might be used to measure changes in research dollar purchasing power as a way of identifying potential areas for further examination. Data on the age of patients enrolled in NIH-funded trials could also be used as a very simple indicator of areas where PPS impacts are likely to be strong. (Of course, these measures would say nothing about what effects prospective payment might have if it were extended to non-Medicare payers, or whether PPS might stifle any efforts to increase enrollment of elderly patients in clinical research. ) At present, these data are not collected by the Federal Government on a continuing basis; nor are they supplemented by

equivalent data from other funding sources, public or private.

Detailed studies of specific areas of clinical research could also be useful. The selection of areas for study should depend on a careful assessment of the real potential for discouragement of clinical research, such as areas of research in which it is important to enroll elderly inpatients,

The ultimate question regarding PPS and clinical research is one of policy: Should Medicare pay for health care costs associated with experimental technologies? Congress has recently given DHHS limited authority in this direction, by directing that the agency may pay some research-associated costs if the research is intended to determine the cost-effectiveness of a technology (Public Law 98-369). This move represents a break from the previous philosophy that all medical research should be financially and organizationally divorced from payment for medical care. The very fact that the issue of PPS effects on clinical research has arisen argues for a reconsideration of the relationship between funding for clinical research and payment for medical care.