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ROUTINE PATIENT CARE IN CLINICAL TRIALS: WHOSE COST IS IT ANYWAY?

DINA BERLYN¹

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I would like to thank, of course, my parents for their support. I would also like to thank Dr. Timothy Vollmer who originally raised my awareness on this issue.

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I. INTRODUCTION

On June 07, 2000, President William J. Clinton issued an Administrative Declaration (hereinafter “the Declaration”) to then Health and Human Services Secretary Donna Shalala requiring Medicare to pay for the routine medical costs for Medicare recipients who were patients in clinical trials.² There were, at the time, pending in Congress, several bills which would have required Medicare to pay these expenses, but all except one only required coverage of these expenses in clinical trials for cancer. The “for cancer only” provision would create an irrational public policy that could in fact be harmful to progress against diseases other than cancer. The Declaration and its resulting regulations are not so limited; the President made the Declaration as a result of a report from the Institute of Medicine which argued that the President had the authority to make this change administratively.³

There were also several pending proposals, differing in scope, before Congress which would have mandated private third party payers to cover routine care costs for clinical trial patients. These proposals differed in that some were limited as to trial sponsor and some to trials for cancer therapy. The two that passed their house of origin in Congress will be discussed in some detail. The Bipartisan Patient Protection Act of 2001 (commonly referred to as McCain/Kennedy)⁴ was considered by the 107th Congress; it was nearly as broad in scope to private third party payers as the Clinton Declaration was regarding Medicare. Some state legislatures have recently addressed the issue as well, and this article discusses their differing approaches. Connecticut examined this issue, and the case study of this process supports the need for congressional action to create a uniform standard.

This article examines the issue of coverage for routine medical expenses for clinical trial patients by third party payers from both a medical and political policy perspective. It is critical for patients, investigators, and sponsors to know who is responsible for paying these costs. This issue affects the willingness of patients to enter clinical trials and has the potential to affect which diseases will be the subjects of clinical trials. This presentation first summarizes the basics of clinical trials and then explores the definition of routine care in clinical trials. Medicare

²Declaration, available at <http://www.whitehouse.gov> (last visited 1/17/01).

³Institute of Medicine, *Extending Medicare Reimbursement in Clinical Trials for Medicine* (Henry J. Aaron & Hellen Gelband eds., National Academy Press, 2000). The Institute of Medicine is a part of the National Academy of Science which is an independent organization.

⁴S. 283, 107th Cong. (2001).

reimbursement, an issue that has been the subject of recent decisive action, is the starting point. The article provides explanation and discussion of the possible models, federal and state, for mandated coverage by other third party payers of routine patient care in clinical trials. A policy discussion and analysis follow, which includes information on the potential effects of this change on third party payers as well as researchers and patients. The placement of the cost liability for these expenses is related to other issues of patient protection; there is a brief discussion of the dangers of research on human subjects past and present to place this issue within the larger context of patient protection. In general, this mandated coverage is sensible and would create good public policy. However, it is important that patient protection remain the top priority in what could be an increased number of trials. The wording of the mandate should be careful not to shift costs that are rightfully borne by the trial sponsor to others.

II. WHAT ARE CLINICAL TRIALS?

Clinical trials are part of the process that a new medical therapy (usually a drug or device) must undergo prior to approval by the Food and Drug Administration (FDA) and approved use by patients. This is the part of the approval process in which the therapy is tested on human subjects. The clinical trials generally have four phases. Phase I is concerned primarily with safety; it requires only a small number of patients (generally 20 – 80) and determines safe dosage and monitors side effects. If the drug or device is found to be acceptably safe, the study moves to a Phase II trial which uses a larger number of patients (usually 100 – 300) and studies efficacy as well as safety. Phase II does not compare the experimental therapy to any control group. If Phase II shows a promising effect and does not appear to uncover any previously undetected safety issues, the trial moves to Phase III.

Phase III is the mainstay of the clinical trial process. In Phase III the treatment is given to a large number of patients (generally 1,000 – 3,000) often at multiple locations, and the new therapy's effectiveness is compared either to a placebo or to the current standard treatment for the particular condition. This phase monitors safety, confirms effectiveness, and compares the new therapy to those currently available (or to a placebo) in terms of both safety and efficacy. This Phase is of extraordinary importance to the FDA when it decides whether to approve a new medical therapy. Phase IV is conducted after the therapy is approved, and this Phase simply monitors the patients on the new therapy for a specified period of time after approval.⁵

III. WHAT ARE ROUTINE PATIENT CARE COSTS IN CLINICAL TRIALS?

There are three basic types of costs associated with clinical trials: the cost of the investigational drug or device, the cost of data collection and analysis, and the cost of routine care for patient enrollees.⁶ The first two types of costs are traditionally borne by the clinical trial sponsor and this model is generally accepted with little disagreement. The question of who should assume the routine care costs for patients in clinical trials remains a contentious issue in both medicine and politics.

⁵<http://www.clinicaltrials.gov>; <http://www.womens-health.org>

⁶Society for Women's Health Research, *Clinical Research: Who Should Pay for Routine Patient Care Costs?*, June 19, 2000, at 4.

In order to implement President Clinton's order, The Health Care Financing Administration (HCFA) posted a National Coverage Decision (NCD) for Medicare coverage of clinical trials. After the posting the NCD and allowing comment, HCFA amended the Medicare Manual in September 2000 to include section 30-1. According to section 30-1:

Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries (*i.e.* there exists a benefit category, it is not statutorily excluded, and there is not a national noncoverage decision) that are provided in a clinical trial *except*:

*the investigational item or service, itself,

*items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (*e.g.*, monthly CT scans for a condition usually requiring only a single scan); and

*items and services customarily provided by the research sponsor free of charge for any enrollee in the trial.

Routine costs in clinical trials include:

*Items or services that are typically provided absent a clinical trial (*e.g.*, conventional care),

*Items or services required solely for the provision of the investigational item or service (*e.g.*, administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and

*Items or service needed for reasonable and necessary care arising from the provision of an investigational item or service — in particular, for the diagnosis or treatment of complications.⁷

HCFA's definition is at the broad end of the spectrum and includes significantly more coverage than some other suggested definitions of routine care. Not all of the proposed definitions are this clear. HCFA was influenced by the Institute of Medicine (IOM) which supports a broad meaning of the term and defines routine patient care as, "Care that would be received by a patient undergoing 'standard treatment.' This would include such items as room and board for patients who are hospitalized, diagnostic and laboratory tests and monitoring appropriate to the patient's condition, post surgical care when indicated, office visits, and so on."⁸ Section 30-1 simply expands on IOM's suggested definition and adds details which provide clarity.

Many of the definitions of routine care in proposed federal legislation as well as enacted by state legislation are consistent with HCFA's definition, but less detailed. The varying versions of the Patients' Bill of Rights that were proposed in the 106th Congress offered little detail. The language from the House version of the Patients' Bill of Rights in the 106th Congress is identical to that in the Bi-Partisan Patient Protection Act of the 107th Congress regarding clinical trial coverage. That congressional language leaves significant discretion to the future rule making process: the plan or issuer "may not deny (or limit or impose additional conditions on) the coverage of routine patient costs for items and services furnished in

⁷Medicare manual § 30-1, adopted 9/2000.

⁸See Institute of Medicine, *supra* note 3, at 70.

connection with participation in the trial.”⁹ The legislation that was proposed also offered a definition of what is not part of routine care: “Routine patient costs do not include the cost of the tests or measurements conducted primarily for the purpose of the clinical trial involved.”¹⁰ The regulations that would have been required to implement this kind of federal legislation would have significantly affected the ultimate outcome of the policy.

Generally the state statutes have taken a middle ground — not as much detail as the Medicare Manual, but more guidance than the Congressional proposals. For example, New Hampshire’s statutes define routine care as, “The cost of any medically necessary health care service that is incurred as a result of the treatment being provided to a member of a health plan. Routine costs are those for which the health plan regularly reimburses its members, health care providers, or health care institutions subject to the terms and conditions of the member’s policy and the provider’s service agreement with the insurer.”¹¹ The New Hampshire statute also defines non-routine costs:

1. the cost of an investigational new drug or device that is not approved for market for any indication by the FDA
2. the cost of a non-health care service that a member may be required to receive as a result of the treatment being provided for the purposes of the clinical trial.
3. the costs that are clearly inconsistent with widely accepted and established regional or national standards of care for a particular diagnosis.
4. costs associated with managing the research associated with the clinical trial.
5. non-covered costs under the member’s policy plan or contract.¹²

It is not clear from New Hampshire’s statutory language whether, say, the administration of the investigational therapy would be mandated — that will have to be worked out with time, government action, and possibly litigation. Most of the states that have drafted these proposals have definitions similar to these.

Rhode Island which was the first state to take action on this issue, in contrast, did not include any definition of routine care in its statute. The Rhode Island law states that, “Coverage shall be extended to new cancer therapies still under investigation when the following circumstances are met.”¹³ The statute proceeds to list conditions including trial qualifications and sponsorship. It has no explicit statement eliminating the cost of the experimental drug and the trial-induced costs such as measurements. Rhode Island’s statute is brief, but disconcertingly vague.¹⁴

No definition can offer a clear answer for each and every claim submitted by a patient in a clinical trial, but the Medicare Manual provides a detailed definition, complete with examples which leaves less uncertainty than most of the available options.

⁹S. 283, 107th Cong. § 119; H.R. 2990, 106th Cong. § 1119. Engrossed in the House.

¹⁰*Id.*

¹¹2000 N.H. Laws 415:18-k(i).

¹²*Id.* at 18-k(h).

¹³*Id.*

¹⁴1997 R.I. Pub. Laws § 27-18-36.2.

IV. ARE THESE COSTS AFFORDABLE? HOW THE ROUTINE CARE COSTS FOR TRIAL PATIENTS COMPARE TO THOSE FOR PATIENTS RECEIVING STANDARD TREATMENT.

Data that compare the routine care costs for patients in clinical trials with those of patients receiving standard treatment are somewhat scarce although they are now under examination. The data that currently exist compare these costs for cancer patients only. This is in large part due to the high level of government funding of cancer research. There are four recent studies on this issue in oncology that show that the cost differences are not particularly significant.

In August, 2000, the Journal of Clinical Oncology published the results of a pilot study which found that the medical care costs for clinical trial patients were slightly lower than those for non trial patients (\$57,542 vs. \$63,721).¹⁵ This was the pilot study for the Association of American Cancer Institutes/Northwestern University Clinical Trial Costs and Charges Project. It compared data from 35 matched patient pairs in Phase II trials versus standard treatment.¹⁶ This is a work in progress and will yield significant additional data from a larger number of patients.

The Journal of the National Cancer Institute (JNCI) recently published the results of two studies comparing routine care costs for clinical trial cancer patients with routine care costs for cancer patients receiving standard therapy. One, published in January, 2000, examined the costs of medical care for 135 patients involved in 12 clinical trials at a health maintenance organization (HMO), Kaiser Permanente, in northern California with 135 matched control subjects who were not enrolled in clinical trials. This study measured the routine medical care costs for one year and showed that the overall cost for the clinical trial patients was 10% higher than for the non trial patients (\$17,003 for trial patients and \$15,516 for non trial patients). However, the study included a bone marrow transplant arm in which the medical care costs for the clinical trial patients were approximately double those for the non-trial patients. When the bone marrow transplant arm is left out of the analysis, the trial vs. non-trial costs are nearly identical (\$15,041 for trial patients and \$15,186 for non-trial patients).¹⁷

In May, 1999 the JNCI published a cumulative 5-year cost study done at the Mayo Clinic in Minnesota which showed that trial enrollees incurred 3.5% to 13% higher costs than control patients over follow-up periods varying from 1 to 5 years. After 1 year, trial enrollee cost was \$16,803 vs. control patient cost of \$14,896. The five-year costs was \$28,853 vs. \$27,870.¹⁸

Although Vik Khanna of State Health Policy Solutions suggested that the RAND Corp. was in the process of a study that compares the medical care costs for clinical trial enrollees and non-trial patients that extend beyond cancer, the RAND study that

¹⁵Bennet *et al.*, *Evaluating the Financial Impact of Clinical Trials in Oncology: Results from a Pilot Study From the Association of American Cancer Institutes/Northwestern University Clinical Trials Costs and Charges Project*, 18 J. OF CLINICAL ONCOLOGY 15, 2805-10 (2000).

¹⁶*Id.*

¹⁷Bruce H. Firemen, *et al.*, *Cost of Care for Patients in Cancer Clinical Trials*, 92 J. THE NAT'L CANCER INST. 7, (2000.).

¹⁸Wagner, *et al.*, *Incremental Costs of Enrolling Cancer Patients in Clinical Trials: A Population Based Study*, 91 JNCI 10, 847-53 (1999).

was recently published compared only patient care costs in cancer clinical trials versus patient care costs for cancer patients not enrolled in clinical trials. This study showed that the routine patient care costs in cancer clinical trials are approximately 6.5% higher than costs for cancer patients not enrolled in clinical trials.¹⁹ This study is in line with the rest of the available data.²⁰

Clearly, more extensive data are needed before a conclusive answer is evident. However, from the data that are currently available, the loss to third party payers appears to be minimal or at least manageable if there is, in fact, any loss at all.

V. WHAT IS THE STATUS OF THIRD PARTY PAYER REIMBURSEMENT FOR ROUTINE CARE COSTS FOR CLINICAL TRIAL PATIENTS CURRENTLY?

A. Medicare

Prior to the Declaration, HCFA policy had been to deny reimbursement for routine care costs in clinical trials for Medicare beneficiaries.²¹ However, Medicare has unknowingly reimbursed for a significant percentage of these costs due in part to the fact that there is no way to indicate a patient's clinical trial involvement on the Medicare forms. The Institute of Medicine estimates that HCFA has actually reimbursed 50 percent of Medicare part B²² and 15 percent of Medicare part A.²³

HCFA has at times tried to enforce its non-reimbursement policy. For example, in 1993 HCFA, suspecting that it had been mistakenly reimbursing for these expenses in certain device trials, requested an investigation by the Office of the Inspector General (OIG, which is within the Department of Health and Human Services (HHS)) to discover whether HCFA had been improperly paying for investigational medical devices. The OIG's finding was that providers had improperly billed Medicare. What was determined to be improper was not merely the cost of the device but of the implantation as well.²⁴ This divergence between policy (not to reimburse) and reality (reimbursing on a significant number of the claims) leaves the patients in an insecure position which discourages them from participating in clinical trials because of the fear of being responsible for their own care expenses.²⁵ This uncertainty should now be resolved in light of the Declaration

¹⁹Goldman et. al, *Incremental Treatment Costs in National Cancer Institute-Sponsored Clinical Trials*, 289 J. OF THE AM. MED. ASSOC. 22, 2970-77 (June 11, 2003). Note that the date used in this study was compiled before Medicare began paying routine patient care costs in clinical trials.

²⁰Prior to its publication, RAND would neither confirm nor deny that this study extends beyond cancer. Vik Khanna of State Health Policy Solutions, LLP, stated that this study will extend beyond cancer at his presentation to the Connecticut Clinical Trials Task Force meeting on July, 2000.

²¹See Institute of Medicine, *supra* note 3, at 31; General Accounting Office, *Cancer Clinical Trials: Medicare Reimbursement Denials*, GAO/HEHS-98-15R, at 1 (1998).

²²Medicare part B is outpatient care, doctor's office visits, etc.

²³Medicare Part A is essentially hospital insurance.

²⁴Institute of Medicine, *supra* note 3, at 32-33.

²⁵*Id.*

and section 30-1 of the Medicare Manual; it is too early to know what the effects will be.

B. Other Third Party Payers

There is a great deal of variation between health plans regarding coverage of routine care costs for clinical trial patients.²⁶ The changes in our healthcare delivery system that have spawned for-profit Managed Care Organizations have changed the perspective of a significant percentage of third party payers toward the ancillary costs of clinical trials.²⁷ Additionally, the increasing use of clinical trials to investigate potential new therapies has vastly increased the magnitude of this dispute.²⁸ It is somewhat difficult to gain an accurate statistical picture of how these costs are paid because some of the routine patient care is submitted to the third party payers with no designation that it is related to a clinical trial.²⁹

In general, there appears to be a downward trend in reimbursement for routine care expenses for clinical trial patients by third party payers. Dr. Seth A. Rudnick at the October 1996 meeting of the President's Cancer Panel asserted that the downward trend is quite sharp. According to Dr. Rudnick, third party payers covered 80 percent of routine patient care costs in 1970, 70 percent in 1990, and only 50 to 65 percent in 1996.³⁰ The Blue Cross Blue Shield Association (BCBSA) conducted a study of HMOs in 1997 which showed a similar trend,³¹ but the BCBSA declined to release the report.

VI. WHAT ARE THE POSSIBLE MODELS FOR COVERAGE OF ROUTINE PATIENT CARE COSTS IN CLINICAL TRIALS?

The varying proposals for coverage of clinical trial patients' routine care costs represent not merely alternative solutions to a common problem but rather these proposals represent sharply conflicting philosophies on the appropriate role of federal and state government. The broadest end of the continuum would require all third party payers to cover these costs in both government sponsored and privately (generally drug or device manufacturing company) sponsored trials for all serious diseases. The proposals at the narrow end of the continuum would affect only self-insured Employee Retirement Income Security Act plans³² and cover only

²⁶President's Cancer Panel, FIGHTING THE WAR ON CANCER IN AN EVOLVING HEALTH CARE SYSTEM, National Cancer Inst. (1997). Telephone interview with Ingrid Saphire-Bernstein, Manager of the Office of Clinical Affairs at the Blue Cross Blue Shield Ass'n (August 2000).

²⁷National Cancer Institute, *supra* note 22, at C-32.

²⁸Telephone Interview with Dr. Timothy Vollmer, Former Director of the Yale M.S. Research Center (August, 2000). Dr. Vollmer is currently Chairman of Neurology at the Barrows Neurologic Institution in Phoenix, AZ.

²⁹Vik Khanna talk at July 19 meeting of the Connecticut Clinical Trials Task Force. *See also* Institute of Medicine, *supra* note 3. President's Cancer Panel, *supra* note 23.

³⁰National Cancer Institute, *supra* note 23, at C-32.

³¹*Cited in* Society for Women's Health Research, *Clinical Research: Who Should Pay for Routine Patient Care Costs?*, at 32 June 19, 2000.

³²The Employee Retirement Income Security Act of 1974 (ERISA) governs employer sponsored health plans and is discussed later in this article.

government sponsored cancer trials. The proposals are presented under three general categories: A. Medicare; B. Federal Mandates; and, C. State Mandates. The section on state mandates begins with an examination of recent happenings in Connecticut which has been working on the issue for the last two years; its story illuminates the need for a national uniform standard that can only be provided by Congress.

Perhaps the most perplexing trend among the coverage models is the inclusion of a “for/cancer/only” provision. Cancer is the subject of many clinical trials, but there is a greater chance that insurers already agree to cover the routine care for cancer trials because of agreements with NIH cooperative groups and because the American Association of Health Plans (AAHP) recommends that its members cover these costs for cancer.³³ NIH cooperative groups generally are a formal network of facilities that collaborate on research projects including clinical trials and that have an NIH approved peer review program. NIH is a partner but does not assume a dominant role.³⁴ Often these groups are able to work out an agreement with the relevant third party payers to cover routine care costs. In addition, cancer affects a large number of people which makes it attractive for pharmaceutical companies to sponsor cancer-related drug trials. Cancer receives an extraordinary amount of government support and is the subject of a large number of government-funded trials. Less attention has been paid to those who argue that this coverage is most needed for rare diseases for which there are limited prospects for new research if the cost is prohibitive to the sponsor. Dr. Timothy Vollmer warns that this policy allows insurers to discriminate against patients who have diseases without large politically active organizations, “they [the insurers] will continue to be able to reap profits from patients with rarer chronic illness simply because they are unlucky enough to have those diseases and that’s inappropriate.”³⁵

A. Medicare

President Clinton’s sweeping Declaration regarding Medicare superseded the more conservative legislation that was pending in Congress at the time of the Declaration. President Clinton accepted the advice of the Institute of Medicine³⁶ and did not limit the Declaration’s effect to a specific disease nor to publicly funded trials. Medicare is government funded and so the prospect of requiring these payments does not raise the issue of federalism (*i.e.*, whether the federal or state government has the power to require third party payer coverage).

In the realm of government-sponsored trials this debate takes on the feeling of an intragovernmental squabble. Since no one argues that the patients should pay, the debate is then whether the Health Care Financing Administration (HCFA), which administers Medicare, or the government agency sponsoring the research should pay these expenses. The significance of the Declaration’s assignment of these costs (even for government-sponsored trials) to Medicare is that this sets a precedent for third party payers to assume routine care costs for clinical trial patients.

³³See AAHP Board Statement on Clinical Trials (Dec. 11, 1988), at <http://www.aahp.org>.

³⁴See NIH Guide: DCT Clinical Trials Cooperatives Groups, (May 26, 1995), available at <http://grants.nih.gov/grants/guide/pa-files/PAR-95-063.html>

³⁵Vollmer Interview, *supra* note 24.

³⁶Institute of Medicine, *see supra* note 3, at 55.

Medicare is an extraordinarily influential force in healthcare in the United States; there are 39 million residents of the U.S. who receive Medicare benefits and that number is growing as our population ages.³⁷ Very often, other third party payers follow Medicare's lead.

At the time that President Clinton issued the Declaration, there was legislation pending in Congress that addressed the issue of Medicare coverage of routine care costs for clinical trial patients receiving Medicare: The Medicare Clinical Trials Mandate,³⁸ and the Medicare Cancer Clinical Trials Mandate.³⁹ Neither of these bills would have provided coverage as broad as the Declaration although each one contained fewer restrictions on the source of the sponsorship of the trial than the 106th Congress's proposed federal mandates which would affect other third party payers. The 107th Congress's proposal on the issue is broader than that of the 106th—perhaps following Medicare's lead. These will be discussed in the next section.

Both the House and Senate versions of the Medicare Cancer Clinical Trial Coverage Act of 1999 (S.784 and H.R. 1388) would have mandated coverage, as the title implies, only for cancer trials. The cancer-only provision created some concern among groups that work with other clinical trial populations that this would decrease the likelihood for reimbursement of routine care expenses for patients in non-cancer clinical trials.⁴⁰ The Medicare Clinical Trial Coverage Act of 1999 would, as the Declaration did, mandate coverage in clinical trials for all serious diseases.

All of these legislative proposals that were superseded by the Declaration provided coverage for a more limited number of trials than the Declaration and its resulting section in the Medicare Manual does. The pending legislation listed specific government sponsors that would qualify. All included any trial approved by NIH, FDA, the Department of Veterans Affairs (VA), the Department of Defense (DoD), and qualified non-governmental research entities identified by NIH guidelines. H.R. 61 also would have covered trials sponsored by the Department of Energy. By specifically listing which governmental agencies are covered, the legislation leaves out some other agencies, such as the Centers of Disease Control, that also sponsor clinical trials. The Declaration, because of its broad language does not limit trial sponsorship although to qualify the trial must be an approved one.

HHS posted its proposed guidelines to implement the Declaration on August 4, 2000,⁴¹ and the final NCD as well as the relevant section (30-1) of the Medicare

³⁷*Medicare Eligibility, Enrollment, and Premiums*, at <http://www.medicare.gov/basics/overview.asp>.

³⁸H.R. 61, 106th Cong. (1999).

³⁹S. 784, H.R. 1388, 106th Cong (1999).

⁴⁰Telephone interview with Jeanie Ireland, Senior Health Policy Advisor for U.S. Sen. Christopher Dodd (Aug., 2000).

⁴¹The final coverage decision in the Medicare Manual varies slightly from the proposed national coverage decision posted on August 4, 2000. The language from the proposed NCD defined routine care to include:

*Items or services that are typically provided absent a clinical trial (*e.g.*, conventional care),

*Items or services required solely for the provision of the investigational item or service (*e.g.*, administration of a noncovered chemotherapeutic agent), the clinically

Manual in September 2000. The Medicare coverage is broad and is consistent with the recommendations of the Institute of Medicine report. To Reiterate, the Medicare Manual defines routine costs to include:

Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries (*i.e.* there exists a benefit category, it is not statutorily excluded, and there is not a national noncoverage decision) that are provided in a clinical trial *except*:

*the investigational item or service, itself,

appropriate monitoring of the effects of the item or service, or the prevention of complications; and

*Items or service needed for reasonable and necessary care arising from the provision of an investigational item or service — in particular, for the diagnosis or treatment of complications.

all items and services that are otherwise generally available to Medicare beneficiaries (*e.g.*, hospital services, physician services, diagnostic tests) that are provided in a clinical trial except the investigational item or service, itself, items and services provided solely to satisfy data collection needs (protocol-induced costs), and items and services provided by the trial sponsor without charge.

...[Examples] include:

items or services that are typically covered in the absence of a trial (conventional care), Items or Services Required solely for the provision of the investigational item service (*e.g.*, administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service or the prevention of complications; and Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service—in particular, for the diagnosis or treatment of complications.

The guidelines propose “desirable characteristics of a trial” and request comments on the desirable characteristics. The HCFA proposal lists:

1. The principal purpose of the trial is to test whether the intervention potentially improves the participants’ health outcomes;
2. The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already commonly in clinical use;
3. The trial does not unjustifiably duplicate existing studies;
4. The trial design is appropriate to answer the research question being asked in the trial;
5. The trial is conducted according to appropriate standards of scientific inquiry.

The guidelines also offer examples and request comments on questions which can be answered on a yes/no basis and would be of assistance in determining the desirability of a specific trial. The examples offered in the guidelines are,

Is the trial approved by an Investigational Review Board (IRB)?

Does the trial have a written protocol?

Has the trial been approved by a Federal agency?

Has the trial received any external non-Federal funding?

Has the trial been reviewed by any external, non-Federal group?

Does a data safety and monitoring board provide independent oversight of the trial?

Clearly the purposes of sections on desirable characteristics of a trial and on the criteria questions sections of the NCD are to ensure that the clinical trials eligible for reimbursement are reputable, with a good chance of success, and do not put the beneficiaries at undue risk. These sections are to ensure good quality control.

*items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (*e.g.*, monthly CT scans for a condition usually requiring only a single scan); and

*items and services customarily provided by the research sponsor free of charge for any enrollee in the trial.

Routine costs in clinical trials include:

*Items or services that are typically provided absent a clinical trial (*e.g.*, conventional care),

*Items or services required solely for the provision of the investigational item or service (*e.g.*, administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and

*Items or service needed for reasonable and necessary care arising from the provision of an investigational item or service — in particular, for the diagnosis or treatment of complications.⁴²

The Medicare Manual offers a reasonable option for defining both routine care and a desirable trial. If the final guidelines are as thoughtful and helpful, HCFA has the opportunity to lead both the federal and state governments in finding a sensible path on this issue.

An Administrative Declaration can be easily reversed if, for example, President Bush objects to this policy interpretation. For this reason some legislators may work to support the Declaration with decisive legislative action.

B. Proposed Federal Mandates

1. The 106th Congress Missed a Window of Opportunity

The struggle over the various proposals for a Patients Bill of Rights in the United States Congress was a highly publicized debate in the 106th Congress. In the end, of course, none of these proposals passed. All versions of this legislation included some language pertaining to third party payer coverage of routine medical care costs for clinical trial patients.⁴³ The differences among the proposals for coverage of routine patient care costs represented, in part, fundamentally different views of the appropriate role of the federal government.

One of the significant differences among the proposals was which third party payers would be affected. This difference affected all sections of the relevant versions of the Patients Bill of Rights. The scope depended on which sections of The Employee Retirement Income Security Act of 1974 (ERISA) were targeted by the legislation.

ERISA governs, among other things, group health plans which are established or maintained by employers or employee organizations and provide medical benefits to employees. ERISA does not affect government employees, churches or church related facilities. There are two types of ERISA group health plans: self-insured and fully-insured. In a fully-insured ERISA plan, benefits are purchased from a health

⁴²See Medicare manual § 30-1, (adopted Sept. 2000).

⁴³The more limited version was S. 1344 106th Cong. § 730 (1999) which is the same language as H.R. 2990, 106th Cong. § 730 (1999) that was engrossed in the Senate. The broader version was H.R. 2990, 106th Cong. § 1119 engrossed in the House.

insurance issuer and the issuer is subject to all relevant state laws; therefore the state has some indirect control even though a state cannot regulate the plans directly due to ERISA's strong preemption clause.⁴⁴

In Self-insured ERISA plans, claims are paid directly by the employer either from company assets or from a tax-exempt trust funded by some combination of employer/employee contribution. Self-insured ERISA plans are completely shielded from any state regulation and are subject only to the regulations in ERISA.⁴⁵ The more liberal version of the Patients Bill of Rights which passed the House of Representatives, and is referred to as the House Bill or Norwood/Dingell, would have affected both kinds of plans, thus creating one mandate for all third party payers.⁴⁶ The more conservative legislation which passed the Senate and is referred to as the Senate Bill, would have only affected self-insured ERISA plans and left the regulation of fully insured ERISA plans to the states.⁴⁷ The problem created by this states-rights approach would be the lack of a uniform national standard. In fact, by leaving fully insured ERISA coverage at state option, there would be no guarantee that those covered by fully insured ERISA plans would receive this coverage at all.

Both the House and Senate Bills limited the mandate to clinical trials sponsored by NIH, DoD, and the VA. One effect of this limitation would be to prevent fraudulent trials from sprouting up to gain profit from this policy change. These government sponsored trials must follow strict, but not foolproof, regulations concerning the treatment of human subjects.⁴⁸ These ethical issues are the subject of discussion in a later section of this article. The limitation by sponsor may also have been an attempt to reduce the possible effect on the third party payers in the event that the policy is not revenue neutral as expected.

The Senate Bill from the 106th Congress also limited the coverage mandate to one disease: cancer. The restriction to cancer trials reflects a conservative approach that claims to start with one disease in order to observe the effect of this type of mandated coverage and then use this information as part of a step by step approach. The choice of cancer as the target reflects the political influence of the advocacy organizations for that disease. However, often it can be difficult to change such a policy once it is the norm,⁴⁹ and the routine care expenses for patients in clinical trials for new cancer treatments are often covered now due to efforts such as NIH Cooperative groups. The Senate proposal would have given aid where it was needed least.

⁴⁴Phyllis Borzi & Sara Rosenbaum, Prepared for the Kaiser Family Foundation, *Pending Patient Protection Legislation: A Comparative Analysis of Key Provisions of the House and Senate Versions of H.R. 2990*, (March 2000) at 32-33.

⁴⁵*Id.*

⁴⁶H.R. 2990, 106th Cong. § 1119 (1999).

⁴⁷S. 1344 106th Cong. § 730 (1999).

⁴⁸45 C.F.R. 46 (2002) governs these trials. The trials must gain approval of an IRB, undergo peer review, and follow detailed ethical standards.

⁴⁹Telephone Interview with Jeanie Ireland, Senior Health Policy Advisor to Senator Christopher Dodd. (Aug. 2000). Many members of Congress recognized this and fought for legislation that would include all serious diseases and all third party payers.

The House Bill would have required third party payers to cover routine patient medical care in clinical trials for serious or life threatening diseases for trials funded by NIH, DoD, and the VA. This legislation was not limited to cancer, and it was not limited in effect to self-insured ERISA plans. Norwood/Dingell reflected support for federal authority and a desire for a uniform national standard.

Although the two bills discussed above were the only ones that passed their house of origin in 106th Congress, other policy options exist. One alternative that was proposed would have covered clinical trials for serious or life threatening diseases, private insurers and group health plans BUT only NIH and cooperative groups of NIH.⁵⁰ This would have limited the impact on third party payers (which is desirable to some legislators) but would still have offered this moderate assistance to patients with diseases other than cancer.

Another proposal would have contained a cancer-only provision but would have included FDA approved [privately sponsored] trials as well as government funded trials under mandated coverage. This would greatly expand the liability of third party payers in scope, but limit it by disease — and again to the disease that needs this assistance least.

Alternatively, a mandate could include FDA approved [privately sponsored] trials as well as government funded trials and cover all qualified clinical trials. This would be as broad in scope and effect to other third party payers as the Declaration is for HCFA. The 106th Congress seemed a bit leery to make a leap of this magnitude. On balance, the House proposal contained in the Norwood/Dingell Patients Bill of Rights might have been a logical starting point. If this plan had been implemented and proven successful, Congress could have expanded the mandate to privately funded trials.

2. The 107th Congress Begins With a Broader Proposal, Perhaps Affected by the Strength of the Clinton Declaration, but Still Fails to Act in the End

The 107th Congress began consideration of the Patient Protection Act of 2001 shortly after the defection of Senator James Jeffords from the Republican Party which gave control of the Senate to the Democrats. The future of this legislation appeared immediate and promising until the September 11, 2001 tragedy which put patients rights on the back burner for the moment. This legislation addressed the issue of mandated coverage of routine patient care in clinical trials with Section 119 of Senate Bill 283, The Bipartisan Patient Protection Act of 2001 (McCain/Kennedy). This section is nearly identical to Sec. 1119 of the Norwood/Dingell version of the Patients' Bill of Rights from the 106th Congress.⁵¹ The one clearly significant difference is that the McCain/Kennedy bill included all clinical trials for serious or life threatening conditions approved and funded by the FDA.⁵² Norwood/Dingell⁵³ would have and McCain/Kennedy⁵⁴ would also have mandated coverage for clinical trials for serious or life threatening conditions

⁵⁰S. 6, 106th Cong. (1999) and H.R. 358, 106th Cong. (1999).

⁵¹H.R. 2990, 106th Cong.

⁵²S. 283, 107th Cong. § 119(d)(1)(C) (2001).

⁵³H.R. 2990, § 1119(d)(1)(A) - (C).

⁵⁴S. 283, 107th Cong. § 119 (d)(1)(A) - (D).

approved and sponsored by NIH, Cooperative Groups of NIH, Veterans Affairs and Defense.

The inclusion of the FDA would expand the mandate under this patient protection legislation to include privately funded trials—this provision would significantly increase the reach of the mandate. It may well be that this expansion was fueled by the broad quality of the mandate in the Medicare Manual; Medicare is often influential in that way.

Between the aftershocks of September 11, 2001 and the war with Iraq, this issue seems off the radar of the 108th Congress. Now that the war is over, the Patients Bill of Rights may return to the agenda. There is a bill in the 108th Congress, H.R. 597, the Patient Protection Act which addresses the clinical trial issue. Section 119 of this bill is essentially identical to Sec. 119 of SB 283 of the 107th Congress.

C. Status In The States

A number of states have addressed the issue of third party payer reimbursement for routine medical care costs of clinical trial patients. One precursor to state requirements on clinical trial coverage was that prior to 1997 a few states (about 10) moved to require third party payer reimbursement for autologous bone marrow transplants for breast cancer patients.⁵⁵ This treatment for breast cancer was often considered experimental and as such denied by insurance carriers. From this mandated coverage, it was not a tremendous leap for legislatures to investigate mandated coverage of routine medical care costs for clinical trial patients. Of course none of the state mandates affect self-insured ERISA plans in any manner whatsoever.

The majority of states that have adopted requirements for clinical trial coverage have addressed it through legislation and a majority of these mandate coverage limit the mandate to cancer. Once again this appears to be due to the political force of cancer and the fact that many third party payers already cover these expenses for cancer so that such a mandate does not create much additional cost to insurers. The states that require third party payer reimbursement for routine medical care costs are: Arizona, California, Delaware, Georgia, Illinois, Louisiana, Maine, Maryland, Massachusetts, Missouri, New Mexico, New Hampshire, North Carolina, Ohio, Rhode Island, Vermont, and Virginia.⁵⁶ New Jersey and Michigan have formed voluntary agreements with their third party payers and Connecticut passed legislation regarding the third party payers under its jurisdiction because attempts to work out a voluntary agreement were unsuccessful.

⁵⁵Of the states that have these laws: Florida, Massachusetts, Minnesota and New Hampshire require that any basic health insurance package reimburse for this treatment; Georgia, Missouri, New Jersey, Tennessee and Virginia require this as a coverage option but allow the insurer to charge more for premiums that cover this treatment; Kentucky requires that any policy that covers high dose chemotherapy for breast cancer also covers bone marrow transplants when the standard chemotherapy has not been effective. See Carla Piazza, *Mandated Benefits: Coverage of Experimental Treatment/Clinical Trials*, National Conference of State Legislatures Health Policy Tracking Service (July 3, 2000).

⁵⁶Carla Piazza, *Mandated Benefits: Coverage of Experimental Treatment/Clinical Trials*, National Conference of State Legislatures Health Policy Tracking Service (July 3, 2000).

1. Connecticut: A Long and Winding Road

Connecticut began to examine the issue of mandated coverage for routine patient care in clinical trials in its 2000 session of the Connecticut General Assembly and passed legislation mandating coverage for cancer only in 2001, and the story reveals some of the disadvantages of this state by state approach. In the 2000 session of the Connecticut General Assembly, the Joint Committee on Insurance and Real Estate raised bill 580, An Act Concerning Clinical Trials for Cancer Patients, at the request of State Senator Edith Prague.⁵⁷ After the bill was raised as a result of this request it was evident that the bill was significantly flawed.⁵⁸

Senator Prague testified at the public hearing on the bill and noted that the language was in dire need of amendment.⁵⁹ When she left the hearing after her testimony, Senator Prague was approached by Mr. Donald Roll of Anthem BCBS of Connecticut who asked if she might consider voluntary action by health insurers an acceptable solution to this problem, at least temporarily, rather than an immediate legislative mandate.⁶⁰ Mr. Keith Stover of the Connecticut Association of Health Maintenance Organizations also expressed support for the voluntary approach. Senator Prague was willing, especially in light of the short session and the flawed nature of the pending legislation, to explore the option of a voluntary agreement.⁶¹

Shortly after the 2000 session of the General Assembly ended, Senator Prague began the Clinical Trials Task Force which held its first meeting on June 7, 2000 – the same day that President Clinton issued the Declaration regarding Medicare. At the June 7 meeting it was not clear that the agreement would cover cancer only,⁶² but by

⁵⁷In the even year “short session” individual legislators can only propose bills that relate to the budget and taxes. Committees, however, can raise bills on any subject germane to them and often bills are raised by committees due to an individual legislator’s request to a committee chair.

⁵⁸13.2(C) 27580, 2000 Gen. Assem., Short Sess. (Conn. 2000). Sec. 1 addresses individual health insurance policies; section 2 addresses group health insurance policies. Problems with the bill included a statement that insurance plans cannot deny coverage for any “procedure, treatment, or use of any drug as experimental” if it is in phase I, II, or III or a clinical trial for cancer treatment. This does not describe routine medical care costs for clinical trial patients and could be interpreted to require third party payers to cover even costs directly related to the clinical trial such as the cost of the experimental drug itself. Clearly, that was not the intent of Senator Prague or anyone else advocating for this type of legislation. The bill then states that, “If a drug is the subject of a clinical trial that a pharmaceutical company or other drug sponsor is required to complete to obtain approval for the drug by the federal Food and Drug Administration, such coverage shall not be required and the pharmaceutical company or sponsor shall pay for the drug and related care”. This language is somewhat unclear regarding the meaning of “related care.” It is possible to interpret this language to include routine medical care costs for clinical trial patients definitively within the responsibility of the trial sponsor. This also was not the intention of Senator Prague.

⁵⁹Interview with Edith Prague Senator, Conn. General Assembly, Hartford Ct., (July, 2000).

⁶⁰*Id.*

⁶¹*Id.*

⁶²*See* meeting minutes available from Connecticut State Senate Democrats

the second meeting it was settled, with no explanation, that the voluntary agreement would only address cancer trials, despite some objections. The consultant hired to assist in the drafting of the agreement was funded by the American Cancer Society. In the second meeting on July 19, a steering committee was selected to draft the agreement to be presented to the entire task force at a later date.⁶³ This meeting was originally scheduled for September 20, 2000, but was postponed due to disagreements over the language. The working group, heavily weighted towards the third party payers, did agree to wording for the agreement on December 4, 2000, but the language was totally unacceptable to many members of the Task Force. The language that the working group proposed would have provided a better tool for denying coverage than for expanding it. The defects included limiting coverage to phase III of prevention trials, and specifically denying coverage of single institution trials conducted solely under the approval of the Institutional Review Board (IRB) of that institution.⁶⁴ Although other disease organizations asked to be included in the process, these requests were denied.⁶⁵ The working group went back to work but was unable to draft an agreement before the legislature was back in session. In the meanwhile, Connecticut's largest HMO, Physicians Health Services (PHS), announced that it was changing its policy and would now cover routine patient care for cancer clinical trials.⁶⁶ Perhaps with the knowledge that this will soon be required, PHS presented a statement that allows it to control, for the moment, the language of its own coverage of these expenses. PHS now covers routine care for patients enrolled in cancer trials approved by the NIH, the FDA, the VA and the DoD. It is limited to cancer.

Senate Bill 325, An Act Concerning Health Insurance Coverage During Clinical Trials, was raised by the Public Health Committee early in the 2001 session. It included many of the same flaws as the working group's draft of the voluntary agreement. The bill required third party payers to cover routine care in clinical trials for cancer only. The bill required coverage for phases I, II, and III of treatment trials but only phase III of prevention trials. There is a limitation that the mandate does not cover single-site trials. The mandate is broad by sponsor; it requires coverage for trials approved by NIH, the FDA, the VA, DoD, and National Cancer Institute cooperative groups.

At the March 1, 2001, public hearing on this bill representatives for the Connecticut State Medical Society and the Connecticut chapter of the National Multiple Sclerosis Society testified on the need to extend this mandate beyond

⁶³The author was in attendance at the July 19, 2000 meeting. This information is also available in the meeting minutes.

⁶⁴This draft is not published, but is available from the author.

⁶⁵Specifically, Betty Gallo who is the lobbyist for the MS Society as well as several other disease organizations approached the task force.

⁶⁶See <http://www.phshealthplans.com/news/nycancer.html>

cancer.⁶⁷ Some members of the Public Health Committee did express concerns with the cancer-only limitation.⁶⁸

After the hearing, Senator Prague agreed to hold a meeting with lobbyists from the HMOs and representatives of the Multiple Sclerosis Society.⁶⁹ The HMO lobbyists stated their strong opposition to expanding the bill and stated their intent to oppose the bill if it was expanded. After a lengthy and at times heated discussion, the HMO lobbyists made several small concessions: They agreed to make clear that the paperwork requirements in the bill would pertain only to cancer trials as that was the only coverage mandated by the bill and they also agreed that there could be a statement on the floor, written by HMO lobbyists and the MS Society, for the purposes of legislative intent that there was no intent to have a harmful effect on clinical trials not covered by the bill. In addition, they agreed to meet in good faith after this session to discuss expansion of the mandate. The MS Society representatives were clear that they wanted the coverage expanded to clinical trials for all serious diseases, not just for MS. They had planned to invite representatives from other disease organizations both because this is a more rational policy and because there is strength in numbers. SB 325 did pass, but unfortunately, the MS society got nervous because some of their funding comes from HMOs and they cancelled the plans to work for expansion of the mandate. If a bill similar to the McCain/Kennedy Bipartisan Patient Protection Act passes Congress, these discussions will be moot.

The power of the HMO lobbyists in controlling legislative action in Connecticut on this issue is disconcerting; this description of the recent happenings in Connecticut offers support for the usefulness and efficiency of a national standard. The likelihood that there will be 50 such struggles with successful results is slim. One plan in Congress could affect all third party payers, would require only one fight, and would result in far more security for patients interested in clinical trial participation.

2. State Coverage Beyond Cancer

Maryland, Maine, New Hampshire and North Carolina all mandate coverage for routine care costs in clinical trials for cancer or “other life threatening diseases.” The mandates from these four states present small variations, but what is left unanswered by the text of all four state statutes is what “life-threatening” includes. The interpretation of this term will determine how effective the legislation will be in encouraging the development of new effective therapies for rare diseases which are

⁶⁷See the Public Health Committee transcripts from March 1, at <http://www.cga.state.ct.us>; Dr. Michael Saffir testified for the Connecticut State Medical Society and Dr. Timothy Vollmer as well as the author testified for the Multiple Sclerosis Society.

⁶⁸Representative Winkler expressed concerns during the hearing and Sen. Harp shared her concerns with the author after the hearing. In fact at the hearing after Dr. Saffir testified on behalf of the Medical Society, Rep. Winkler expressed her understanding that the bill had been meant to affect all clinical trials and suggested that it might be possible to remove the word cancer. She was not correct and this was not done.

⁶⁹The attendees were Sen. Prague, Mr. Keith Stover, Mr. Don Roll (HMO lobbyists), Dr. Timothy Vollmer, Attorney Shelley Marcus, Ms. Sharon Finn, Ms. Susan Raimondo, Ms. Betty Gallo (representing the MS Society), and the author.

not now, due to the small numbers of patients, attractive diseases for study. The breadth of the mandates will rest with the definition of this term whether through regulation or case law.

The broadest and most comprehensive state legislation is the Maryland Clinical Trials Act (MCTA). The Maryland mandate covers all phases of clinical trials, and a broad range of public and private sponsors.⁷⁰ Maryland is the home of the NIH, and generally friendly to research.

In 2000 Maine enacted a law which mandates coverage of routine patient care in clinical trials for cancer and other life threatening diseases.⁷¹ The Maine statute, like the MCTA, has no restrictions regarding the phase of the trial. However, the mandate by the Maine law narrows the potential impact of the legislation because it severely restricts the required coverage by trial sponsor. Maine's form of caution should provide a more sensible outcome than most of the states that have adopted this mandated coverage but limit the impact on third party payers by limiting coverage to the already protected cancer trials instead of limiting by trial sponsor.

Additionally, New Hampshire requires coverage of routine patient care costs for clinical trial patients in clinical trials for cancer or other life threatening diseases. While the scope of the New Hampshire law is broad in terms of sponsor, an ambiguous provision may limit the mandate by phase.⁷² Another interesting note is that this New Hampshire legislation also contains a provision to study coverage of bone marrow transplantation.

⁷⁰See MD INS. CODE ANN., [Insurance] § 15-827 (2002). The Maryland law requires all insurers and managed care organizations to cover routine care costs incurred in all phases of qualified clinical trials for cancer or other life threatening conditions. The legislation affects all trials approved by the NIH, an NIH cooperative group, the FDA in the form of an investigational new drug application, the VA, or an institutional review board of an institution in the state which has a multiple project assurance contract approved by the Office of Protection from Research Risks of NIH. In order to be deemed a 'qualified' clinical trial, the investigators must possess sufficient expertise and experience, there must be no clearly superior standard treatment, and there must be a reasonable expectation from clinical or preclinical data that the treatment will be at least as effective as standard therapy. An entity seeking coverage under the provision mandating coverage for investigations approved by a state IRB must also keep an updated list that is posted electronically citing the phase of the trial, the approving entity, the disease which is the subject of the trial, and the number of participants in the trial.

The MCTA uses the term "patient care" for routine care and defines these costs as the "cost of a medically necessary health care service that is incurred as a result of the treatment being provided to the member for purposes of the clinical trial." The MCTA specifically excludes the cost of the investigational drug or device and costs associated with managing the research associated with the clinical trial. The MCTA definition is broad and similar in scope to the IOM proposal.

⁷¹See 2000 Me. Legis. Serv. 24A § 4310 (West). The Maine law mandates coverage of patient care expenses in approved clinical trials for a life threatening illness for which no standard treatment is effective. The Maine statute has no restrictions regarding the phase of the trial, but for mandated coverage to apply to the trial, it must be approved and funded by the NIH (or a cooperative group or center) or the Department of Health and Human Services. The Maine statute includes far less detail than the MCTA.

⁷²2000 N.H. Laws § 415:18-k This legislation has an internal conflict. The New Hampshire law states that it requires coverage for Phases I, II, III and IV and then states that a case by case review should be done to determine coverage for Phases I and II.

North Carolina enacted a law in its 2001-02 session which required coverage for treatment of life threatening medical conditions. The North Carolina law requires coverage for phases II, III, and IV of trials. Its sponsorship requirements are broad; it requires coverage of trials sponsored by NIH, NIH cooperative group of center, the Food and Drug Administration, The Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, The Department of Defense, and the Department of Veterans Affairs.⁷³

Although the statutes in the four states that mandate coverage of routine patient care costs in clinical trials vary from each other only slightly, all the legislation is so new that the effects are not yet known. Studying the differences in impacts on third party payers in each of these three states should provide useful data to other states considering this kind of legislation and to congress if, as is likely, the patients rights issue rises again in the 108th congress.

3. States That Mandate Coverage For Cancer Trials Only

Five states mandate coverage for routine patient care in clinical trials for all types of cancer through legislation: Rhode Island,⁷⁴ Arizona,⁷⁵ Louisiana,⁷⁶ California,⁷⁷ and Virginia.⁷⁸ New Jersey and Michigan⁷⁹ have voluntary agreements with their insurers to cover routine patient care in cancer trials. As with the states that mandate coverage beyond cancer, there is some variation in the coverage required.

Rhode Island, the first state to enact mandated third party payer coverage for routine patient care in clinical trials, requires coverage for Phases II, III and IV of NCI authorized trials where there is no clearly superior approved therapy.

The Virginia law requires slightly broader coverage than that required in Rhode Island. It requires third party payer coverage for routine patient care in Phase II, III, and IV of cancer trials with no differentiation regarding Phase II. Virginia's statute additionally provides for a case-by-case review for Phase I trials.

Louisiana, like Rhode Island, required coverage of routine patient care in Phase II, III, and IV for cancer clinical trials. There is no provision in Louisiana's law regarding Phase I and the trial must meet additional criteria.⁸⁰

⁷³See North Carolina Session Law 2001-446. Part III, Subpart A.

⁷⁴1997 R.I. Pub. Laws § 27-18-36.2 (The Rhode Island statute does not mandate Phase I coverage and contains no explicit definition of routine care. It also states that in Phase II trial costs customarily borne by the sponsor will remain with the sponsor).

⁷⁵2000 Ariz. Legis. Serv. 371 (West).

⁷⁶L.A. REV. STAT. ANN. § 22:230.4 (West 2000).

⁷⁷See CA Senate Bill 37, signed August 9, 2001. See also <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>. Medicaid is also mandated to cover these costs in CA.

⁷⁸V.A. CODE ANN. § 2.1 - 20.1 (LEXIS 2000).

⁷⁹See <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>.

⁸⁰These additional requirements include that the entity seeking coverage must post electronically an up to date list including: the phase for which the trial is approved, the entity approving the trial, the type of cancer being studied in the trial, and the estimated number of participants.

In 2000 Arizona joined the list of states that mandate third party payer coverage for routine patient care in cancer clinical trials. Arizona's law is the broadest of the "for/cancer/only" clinical trial legislation; it mandates coverage for Phases I, II, III, and IV. Arizona does not provide for any coverage beyond cancer. California,⁸¹ Delaware,⁸² Massachusetts⁸³ and New Mexico⁸⁴ have all followed suit with mandates that are broad in terms of sponsorship but cover only cancer clinical trials. New Mexico's law sunsets July, 2004.

Three states, Georgia,⁸⁵ Missouri,⁸⁶ and Illinois⁸⁷ have passed even more cautious forms of "for/cancer/only" mandated clinical trial coverage. Georgia mandates coverage only for pediatric oncology trials, Illinois allows a benefit limit, and Missouri offers coverage severely limited by phase.

Georgia's statute requires third party payers to cover routine patient care only in Phases II and III. The requirement applies to *drug* trials in pediatric oncology—no devices, no adults. While the horror of child cancer is undeniable, the logic of this policy is unclear. It may be justifiable to offer additional support for children, but there does not seem to be a reason to cover drug but not device trials, nor does it seem sensible to deny this coverage for other devastating pediatric diseases. Missouri only covers phases II and III but is broad by sponsor.

Illinois takes a different tack in further limiting the mandated coverage. It requires that third party payers must offer coverage for routine patient care in Phases II, III, and IV of cancer clinical trials. However, the insurers can set benefit limits at \$10,000 per year. Additionally, the law has a sunset provision which repeals the law on January 1, 2003, unless the legislature acts to provide for its continuation. The Illinois legislature is obviously concerned about the potential effects of these provisions and has sought to limit the effect and scope.

Vermont and Ohio limit their coverage in ways that favor the specific state. Vermont⁸⁸ passed legislation that covers trials administered at a Vermont hospital, a qualified Vermont cancer care provider, and clinical trials under the auspices of two specified cancer care centers. The law sunsets in 2005. Ohio⁸⁹ has a very limited

⁸¹See *supra* note 77. See also <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>.

⁸²SB 181 of 2001 session effective January, 2002. See also <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>.

⁸³HB 4376 of 2002 session. Chapter 257 of 2002 session. Effective January 2003. See also <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>.

⁸⁴SB 240 effective March 14, 2001. See also <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>.

⁸⁵2000 GA. LAWS 33-24-59.1 (West 2000). See also <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>.

⁸⁶SB 1026 effective August 28, 2003. See also <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>.

⁸⁷215 ILL. COMP. STAT. ANN. 5/356y (West 2000).

⁸⁸HB 255 effective March 1, 2002. See also <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>.

plan. It mandates coverage only for Ohio state employees who are insured by Ohio Med Plan and are enrolled in phase II and III NCI sponsored trials.

New Jersey has tried a new approach for states: A voluntary agreement by the insurers in the state to provide coverage for routine patient care in all phases of cancer clinical trials.⁹⁰ This agreement was signed in the fall of 1999 and the effects are not yet known. The agreement does not offer the protection that legislation would; the only protection would come from language in the policies offered by the state's insurers. The insurers may be hesitant to violate the agreement for fear that violations could lead to more demanding legislation on this issue. More recently Michigan has also negotiated a voluntary agreement.⁹¹

Nationally, there has been some effort at voluntary agreements between insurers and the government. The American Association of Health Plans in a 1998 agreement with NIH recommended that its member plans cover routine patient care in cancer trials.⁹² There are a number of plans that have forged agreements with NIH perhaps as a result of this recommendation.⁹³ These voluntary agreements tend to limit the risk to the third party payer.

VII. WORDS OF CAUTION ON RESEARCH REGARDING HUMAN SUBJECTS

The possibilities raised by increasing the number of clinical trials for rare diseases is exciting, but it is important not to lose sight of the sometimes frightening history of research on human subjects. This history suggests that there must be sufficient oversight of any research on human beings.

A. A Brief History

Two of the most notorious ethical violations in research on human subjects, each of which led to reform are: The Nazi doctors convicted at Nuremberg who had performed unthinkable "experiments" on concentration camp prisoners,⁹⁴ and the Tuskegee Human Syphilis study in the United States from 1932 to 1972, in which the course of untreated syphilis was observed in 400 African-American men—the "study" continued and the subjects were not offered treatment even after effective treatment was available.⁹⁵

⁸⁹See <http://www.state.oh.us/das/dhr/hcb/hcb14.html>. See also <http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs>.

⁹⁰Available at <http://www.state.nj.us/governor/news/p91217a.htm>.

⁹¹See www.nci.nih.gov/clinicaltrials/developments/law-about-clinical-trial-costs-michigan.

⁹²AAHP Board of Directors Agreement Between AAHP and NIH for Support of Clinical Trials (1998), available at <http://aahp.org>.

⁹³Available at <http://www.clinicaltrials.gov>.

⁹⁴See *United States v. Karl Brandt*, Military Tribunal Case No. 1, 1947 (Nuremberg). See Also ALBERT JONSEN, *The Ethics of Research with Human Subjects: A Short History*, 5-10 in SOURCE BOOK IN BIOETHICS (Albert R. Jonsen et al., eds), Georgetown University Press, 1998).

⁹⁵In 1972, the story of the Tuskegee Syphilis Study was exposed to the public by the media. From 1932 until the story broke in 1972, 400 African-American men with syphilis living in rural Georgia were denied treatment so that researchers could watch the progression of this disease untreated. The horrified reaction to the truths of the Tuskegee study led to the

Internationally, the origin of the rules and regulations that govern modern research on human subjects can be traced back to the ten point Nuremberg Codes which originated from the verdict against the Nazi doctors. The Nuremberg Codes led to the Helsinki Declaration which generalized the Nuremberg Codes to make them more relevant to general research. The Helsinki Declaration emphasizes informed consent, respect for persons, and risk-benefit analysis.⁹⁶

After World War II, there was an extraordinary increase in government funding of research in the United States, but there was no organized and uniform review mechanism.⁹⁷ The prevailing sentiment in the medical community was that patient interests were best served by the inherent ethics of the researchers; the medical community did not view the Nuremberg Codes as relevant to the research in the United States. A few lone voices dissented, and history has shown these voices to be prophetic.⁹⁸

More recently, there was an additional discovery: from 1944 to 1974 the government had sponsored a number of radiation experiments on citizens. Once again, an advisory panel was convened to research the scope of these ethical violations and recommend changes in the oversight mechanisms.⁹⁹ Again, this came at a time of extraordinary growth in the experimentation on human subjects, and the panel made suggestions not only regarding classified research but also specifying the need for reform in research on human subjects generally. It is clear that the ethical struggles in research on human subjects are not resolved. The report on the Human Radiation Experiments¹⁰⁰ in combination with the recent ethical violations in gene

creation of the Tuskegee Syphilis Study Ad Hoc Advisory Panel and ultimately the Belmont Report which recommended specific reforms to the oversight of research on human subjects. A significant number of the suggested reforms were enacted, and these constitute the core of 46 CFR 45 which governs the ethics of research on human subjects. One of the most important pieces of these regulations is the requirement that research of human subjects be approved by an Institutional Review Board (IRB). The regulations include requirements regarding the kind of monitoring the IRB must perform after approval of a project and also provide requirements regarding IRB membership.

⁹⁶*Id.* The Helsinki Declaration was the product of the World Medical Association in 1964. It has been amended several times. *See also* GEORGE ANNAS, *THE RIGHTS OF PATIENTS* 144-45 (Southern Illinois University Press 1989) and Furrow *et al.* *Health Law*, ch. 21 § 6 (Hornbook Series, 2nd ed. West 2000).

⁹⁷ALBERT JONSEN, *SOURCE BOOK IN BIOETHICS* 13 (1998).

⁹⁸*Id.*

⁹⁹Many of these experiments did not fall under the requirements of 46 CFR 45 because they were “classified.” The panel was stunned by the large number and variety of experiments and ultimately produced approximately 5,000 pages of reports. *Available at* <http://tis/eh/doe.gov/ohre/roadmap/achre>.

¹⁰⁰The release of this report has also spawned a number of court cases, some of which have been successful, brought by the unsuspecting victims of these experiments. *See e.g.*, *In Re Cincinnati Radiation Litigation*, 874 F. Supp 796 (S.D. Ohio 1995); *Craft v. Vanderbilt Univ.*, 18 F. Supp. 2d 786 (M.D. Tenn. 1998); *and Bibeau v. Pacific Northwest Research Found. Inc.*, 188 F.3d 1105 (9th Cir. 1998). The earlier rulings that soldiers cannot recover damages for experiments performed on them have not yet been overturned. *See Jaffee v. United States*, 663 F.2d 1226 (3rd Cir. 1981) and *United States v. Stanley*, 483 U.S. 669 (1987). There were strong dissents in both cases.

therapy (which led to the death of a young man who should not have been enrolled in the trial at all)¹⁰¹ and cancer research¹⁰² led the 106th Congress to propose reforms which unfortunately did not pass.¹⁰³ There have been a few even more recent problems such as the violations of required protocol at the Fred Hutchinson Cancer Research Center that were exposed by the Seattle Times,¹⁰⁴ and the recent death in an Asthma Study funded by NIH and conducted at Johns Hopkins¹⁰⁵ as well as the recent Johns Hopkins study that exposed healthy children to lead paint.¹⁰⁶ Policy changes that are likely to increase the number of clinical trials such as mandating coverage of routine patient care costs must be watched closely to prevent potential ethical lapses.

B. Contemporary Issues

The remarkable growth in experiments on human subjects has left the current system of regulation unable to perform adequately. The ethical issues of informed consent by patient enrollees and respect for the patients as well as complete disclosure of risks to them remain at the forefront of the ethical requirements of clinical trials, but there are also new issues. Currently, the IRBs are overworked and are not able to monitor adequately all the trials for which they are responsible.¹⁰⁷ This is a direct result of the dramatic increase in clinical research. One of these new ethical issues is the problem of doctors with financial conflict-of-interest (doctors who are researchers and have an equitable interest in the sponsor company¹⁰⁸ or who get a bonus from the company-sponsor for enrolling their own patients in the trial).¹⁰⁹ The increasing involvement by private companies in new drug development created the potential for this conflict of interest. This problem could become even more difficult to regulate with an increased number of trials which could be a result of mandating coverage of routine care in clinical trials.

Additionally, a new type of IRB has evolved due to the private for-profit sponsorship of clinical trials: The independent IRB. This kind of IRB is increasing in number. Independent IRBs are not local and are not attached to a specific

¹⁰¹Eliot Marshall, *Gene Therapy on Trial*, 288 SCIENCE 951-57 (2000).

¹⁰²David Malakoff, *Flawed Cancer Study Leads to Shake-up at Univ. of Oklahoma*, 289 SCIENCE 706-07 (2000).

¹⁰³H.R. 4605, 106th Cong. (2000).

¹⁰⁴Duff Wilson, *Uninformed Consent*, SEATTLE TIMES, Mar. 11-15, 2001 at A1. (Doctors in these studies had financial conflicts of interest with the pharmaceutical companies that were the trial sponsors).

¹⁰⁵Susan Levine, *FDA Cites Flaws in Hopkins Asthma Study*, WASH. POST, July 3, 2001, at B03.

¹⁰⁶Grimes v. Kennedy Krieger Institute, 782 A.2d 807 (MD. 2001)

¹⁰⁷Beverly Woodward, *Challenges to Human Subject Protections in US Medical Research*, 282 JAMA 1947, 1947-52 (1999).

¹⁰⁸Philip Hilts, *U.S. Weighs Changes on Rules in Drug Research Conflicts*, N.Y. TIMES, August 16, 2000, at A28.

¹⁰⁹Office of the Inspector General, *Recruiting Human Subjects: Pressures in Industry Sponsored Research*, OEI-01-97-00195 (June, 2000).

institution, as are traditional IRBs. Many of these independent boards are for-profit entities.¹¹⁰ These entities create the possibility for numerous ethical conflicts not the least of which is the possibility of IRB “shopping.” This possibility, that a for-profit company sponsor can search for a for-profit IRB that will permit the protocol most favorable to the sponsor, raises obvious concerns. If both the sponsor and the monitoring board are for-profit entities, is patient protection anyone’s top priority? One of the reforms that the 106th Congress proposed but did not pass would have required all IRBs to be accredited by a not-for-profit entity.¹¹¹

The lure of care and treatment within the context of clinical trials to the uninsured and underinsured patients with serious diseases presents ethical issues of increasing magnitude as the number of available clinical trials expands and our nation does not provide universal health care coverage. This is a concern not only for those with involvement in clinical trials but also for our entire society — it is unethical to place a disproportionate burden for drug discovery on those who have limited treatment options.¹¹²

VIII. CONCLUSION

The need to find new and better treatment options seems an obvious one, and it is clear that clinical trials are an important part of this process. The question remains, what is the best public policy to encourage this?

One current avenue of choice in mandating coverage — mandating coverage for cancer only is disturbing. This is poor public policy; it does not resolve the most pressing need first. While it would be most desirable to provide coverage for routine care for clinical trial enrollees for all qualified clinical trials, if there is a need to take a step by step approach, cancer-only is not the right first step. If an incremental approach is warranted, there are more rational cautious methods. Mandated coverage for routine patient care in clinical trials for rare diseases should come first.

Another possible cautionary provision would be a mandatory review of the legislation’s consequences after a set term of two or three years. An alternative possibility would be to limit the mandatory coverage to publicly sponsored trials, at least until there is clear data that this coverage did not present an unmanageable burden on the third party payers; that was Congress’ approach in its proposals. However, there does not appear to be evidence that the routine care costs are significantly higher for trial patients than for patients receiving standard treatment.

The promise of this policy is that if followed it will lead to more treatments (especially for rare diseases if they are included). This promise will need to be monitored both to ensure that the sponsors are not simply using this as easy money with no responsibilities attached and to ensure that it does not lead to an increased number of lower quality trials. This is particularly important if private trials are included in the mandate.

¹¹⁰Office of the Inspector General, *Institutional Review Boards: The Emergence of Independent Boards*, OEI-01-97-00182 (June, 1998).

¹¹¹H.R. 4605, 106th Cong. (1999).

¹¹²Sugarman, J. *et al.*, *What Patients Say About Medical Research*, 20 IRB 4, 107 (1998). (Presents data showing why patients enroll in clinical trials. Many of them feel it is their best or even their only disease specific treatment option).

A federal mandate on this issue would create the best public policy — a uniform law across country would satisfy the goal of reducing insecurity of trial patients regarding expenses. A national standard would provide one consistent definition of the terms such as routine patient care. The legislation should go beyond cancer to all qualified clinical trials or at least to trials for serious or life threatening conditions; insurers often cover routine care in cancer trials now anyway — through public private partnerships and NIH cooperative groups. There is serious need for clinical trials testing therapies for rarer diseases which often lack any treatment and do not have enough patients to make it profitable enough to encourage a drug company's effort—one of the unfortunate effects in this for-profit system. The trials may be prohibitively expensive for public research entities if they must pay all routine patient care costs.

Legislation would offer greater protection than voluntary agreements; legislation can be enforced and can include penalty provisions for companies that do not follow the requirements. It would be appropriate to monitor the effects of any legislation on this issue to discover whether the policy created an increased number of clinical trials and new therapies as well as to discover what the financial effects have been. This monitoring is easier with federal legislation because federal agencies fund or approve the trials. If Congress does not act on this and the states choose to act, or if the states choose to mandate broader coverage than Congress does, legislation is a better option for the same reason: Enforceability.

In the realm of Medicare, the administrative action option has many good qualities: the mandated coverage was broad and the effect was immediate. The problem with an administrative order is that if the next president does not agree with the policy, it could all be undone just as quickly and leave the Medicare recipients in their former conundrum. For this reason it would be rational to pass legislation to back up the Declaration.

While the move towards for-profit health care coverage appeared to decrease the third party payer coverage of routine care in clinical trials, the recent attention to problems in our healthcare system seems to have brought attention to this issue. In the next few years it is likely that the coverage for these costs will again increase as a result of some form of government action.

It is of extraordinary importance that patients know from the start what the expenses and risks are and that they know they will not be abandoned after participating in research studies. There must be no question that patient protection is the top priority for all research on human subjects. The system for assuring patient protection needs updating as well, especially if new requirements mandating third party payer coverage for routine care in clinical trials spawns an increased number of trials. Protection for clinical trial enrollees must include disclosure and understanding of risks, strict reliance on ethical practices and also security regarding how costs will be borne. One national standard could ensure the protection of subjects both medically and financially.