Wyoming Healthcare Commission Clinical Trials Study

Final Report

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EXECUTIVE SUMMARY

Clinical trials are the only mechanism for new therapies to come to market in the United States. Their purpose is to provide evidence on the efficacy and safety of the new treatments. Most clinical trials in the United States are for the treatment of cancer. However, enrollment in these studies has been extremely low for a number of reasons. One assumed barrier to participation has been the ineligibility of coverage by insurance companies; in particular, the payment for the routine costs incurred by participants in clinical trials. This report examines the literature and stakeholder comments to make a recommendation on the need for a legislative mandate for private insurance coverage of routine medical costs for cancer patients enrolled in clinical trials.

Legislated insurance mandates only apply to private fully insured policies. They may be applied to self-insured plans that are political subdivisions of the state, but other self-insured plans are governed by the Employee Retirement Income Securities Act (ERISA) and are not affected by Insurance Commission mandates. Federal programs are also not affected by state mandates.

METHODS

A literature search was conducted to identify identify information regarding

- the incidence and prevalence of cancer in Wyoming
- insurance coverage of vulnerable populations such as children,
- the drug approval process including the probability of medications progressing through clinical studies to market approval, the role of the Food and Drug Administration and the National Institutes of Health, and
- the cost of clinical trials to patients and insurance companies, coverage policies and practices including federal regulation as well as legislative approaches and insurance regulations in other states.

Existing health care coverage mechanisms within federal, state, and private programs for funding claims for routine patient care costs of patients participating in cancer clinical trials were obtained from publicly available documents or interviews with key contacts within insurance companies that provide the majority of the insurance coverage for Wyoming, Medicare, Medicaid, The Department of Veteran's Affairs, the Department of Defense (TriCare/CHAMPUS), and the Wyoming Department of Insurance. When interviews with key contacts were conducted, specific questions were developed and sent ahead of time to facilitate the interviews.

Interviews with other stakeholders were also conducted to identify preferred coverage approaches in Wyoming. These stakeholders included the American Cancer Society, The Wyoming Insurance Department Commissioner, The National Association of State Comprehensive Health Insurance Plans (NASCHIP), a co-chair of a relevant Wyoming state legislative committees, and organizations conducting cancer clinical trials in Wyoming. When interviews with key contacts were conducted, specific questions were developed and sent ahead of time to facilitate the interviews.

A list of cancer clinical trials being conducted in the state was compiled from http://www.clinicaltrials.gov/. Copies of the consent forms were requested from the organizations conducting the cancer clinical research.

RESULTS

The Wyoming Cancer Surveillance Program (WCSP) reported an incidence of 2,198 all-site cases in 2004. Of these, children 19 and under had 20 cases, elderly 65 and over had 1187 cases, and the remainder (991) were in adults age 20-64; Wyoming will have an estimated 2,340 new cases in 2007. Nationally, 0.5-3.3% (maybe as high as 5%) of adult cancer patients participate in clinical trials; an estimated 50% of children participate. Participation in clinical trials is often associated with therapeutic misconception; this over-assessment of benefit and under-appreciation of risks often adds to the emotional nature of discussions on clinical trials. Cost and insurance coverage were concerns expressed by about 20% of patients and numerous other reasons were documented for not participating.

Employer and individual private insurance plans cover 72% of adults 20-64 year old and 63% of children in Wyoming; however, an estimated 40.6% are in self-insured programs. Wyoming has a large proportion of small group and individual insurance plans, which are price sensitive. The largest employed group in Wyoming is the 45-54 year olds, who are entering the age groups where the highest incidence of cancer occurs.

Policies on coverage of routine medical costs for cancer patients participating in clinical trials varied widely. The federal programs of Medicare, the VA and DoD have broad coverage and highly encourage participation as does one large insurer in Wyoming. Other insurers and Medicaid use the "Medical Necessity" or "Experimental" clauses to determine coverage; most do have a system of prior authorization and case review. The actual current payment for routine medical costs was considered an unknown, since most stakeholders had difficulty identifying patients enrolled in clinical trials. A total of 23 states now have mandated coverage at some level.

Enrollment in clinical trials was not noticeably higher after the Medicare policy was implemented in 2000 nor after implementation of state mandates for coverage of routine costs.

One hundred nineteen (119) cancer clinical trials are currently being conducted in Wyoming according to the National Cancer Institute's (NCI) website, www.clinicaltrials.gov. One hundred thirteen (113) out of the 119 cancer trials are sponsored by NCI, an institute of the National Institutes of Health. Most of the Wyoming studies are being conducted by a single research consortium and are outpatient studies. We were able to obtain 101 consent forms for review.

Determining the costs of cancer clinical trials or, even, of cancer treatment is very difficult and results of studies need to be considered preliminary.[27] Costs can be considered in two ways; one is the additional cost of treating cancer if the patient is involved in a clinical trial; the other is the actual cost per participant enrolled in a study.

Non-pediatric NCI cancer clinical trials cost about 6.5% more than treatment for non-study patients (pediatric studies are usually more expensive because of the small numbers and rare types); those who died early or were in earlier phases had more expensive courses.[28] The cost differences are more pronounced early in the treatment cycle. Bennett et. al reviewed five studies that compared costs in phase II and III clinical studies to treatment costs of non-enrolled cancer patients. Costs for the trials at 6 months were 17-23% more expensive [about $2,000 to $6,000]. Results at 12 and 24 months were not really different. The one study that reported costs at 60 months found that the difference was only 1% (about $300). One study using charges rather than costs found the trials to be about $6,000 less expensive at six months for patients enrolled in trials compared to those not enrolled (but the totals for both groups were much higher).[22] Chirikos et.al, in another study, found that after adjusting for age and stage of disease, the differences in total charges between the groups were not statistically different.[29] Wagner et. al found an increase of less than 10% ($2,000) over five years.[30]

The cost per participant has been reported in several studies, statements and reports. The average non-labor costs reported by C-Change were $3,091 to $6,094 from a literature review. C-Change also conducted a survey that found costs ranges from $2,000 to $9,849.[32] Love in his affadavit to the South African court states that cancer studies in the U.S. cost $2,000 to $7,000 per subject.[25]

One of the themes emerging from interviews is that participation in clinical trials is often not easily detected and routine costs are very difficult to define. Bennett et. al. estimates that Medicare paid for 50-90% of billed routine patient care costs for those enrolled in clinical trials during the 1990s even though they excluded routine costs under their "experimental" clause.[22] When asked how they knew if a patient was in a clinical trial, most insurers (especially those without strict networks) stated that they did not know unless the investigational drug or device was billed. Most of the stakeholders were comfortable with insurance providers paying for routine medical costs associated with clinical trials, with the exception of payment for investigational treatment-induced injury or toxicity.

CONCLUSION AND RECOMMENDATIONS

Given the likelihood that a bill to mandate insurance coverage for cancer patients enrolled in clinical trials will be introduced into the 2008 Wyoming Legislative, the recommendations being made are for considerations by the legislators concerning whether or not to pass the bill. The options for the legislature are to make no changes, to pursue voluntary coverage (especially by the large self-insured employers), to mandate coverage of routine care costs borne by patients enrolled in clinical trials, to mandate coverage of all costs borne by patients enrolled in clinical trials, or to establish a special pool to cover trial-related costs for all citizens, children, or the uninsured. If the option to mandate coverage of routine costs is selected, then a mechanism needs to be put into place for the insurance company to obtain documents (i.e. consent forms or study protocols) to determine routine costs. If an insurance mandate or a special pool is created, the legislature could also consider allowing insurers or the state the right of subrogation to recoup costs if an investigational drug or device is eventually marketed for the indication studied in a trial.

Legislators should consider the following findings in their deliberation:

- Clinical trials are not major drivers of cost in cancer therapy (and are of public health interest).
- Insurance premiums may increase anywhere from 0-10% based on published studies. However, any increase in premiums may cause decreased insurance participation.
- Mandated coverage of routine medical costs for subjects participating in clinical trials has not made a large impact on trial enrollment.
- General agreement exists among stakeholders that routine medical costs associated with trials could be covered. However, payment for treatment of toxicities from the investigational agent is controversial.
- An insurance mandate would not affect all the citizens of Wyoming since 40.6% (S.E. 3.9%) of Wyoming employees work for employers who are self-insured and others work for federal agencies which would not be impacted by the mandate; 14% are uninsured.
- The numbers of cancer patients from Wyoming who would be participating in clinical trials is small, but distribution may occur outside of statistics and impact the fully insured market disproportionately.

Wording of the bill is critical. Berlyn states clearly that "the wording of the mandate should be careful not to shift costs that are rightfully borne by the trial sponsor to others."[33]

If a bill is introduced, consideration should be given to the following suggestions for language and concepts:

- Careful review of the proposed changes to the Medicare policy and the components of the various state laws is recommended.
- Include definitions.
- The federal bills included cancer only; this was believed by many to be harmful to progress against other diseases (but the impact would be greater). The final Clinton declaration that resulted in the 2000 Medicare coverage does not limit to cancer.[33]
- Consider what "other life-threatening diseases" implies or excludes.
- Consider whether to include only effectiveness phase IV studies, all phase IV studies, or no phase IV studies.
- Non-covered costs need to be specified; remembering that sponsors, by regulation, may charge for devices and procedures, but not investigational drugs.
- Do not try to identify trial sponsors by name, but state the trial must be an approved trial (by the NIH or other government agencies, such as the VA).
- Coverage for all types of investigational treatments should be considered (not just drugs or devices).
- Be prepared to amend rules
- Exclude "reasonable expectation of benefit" clause. Several states specify that an agent have a reasonable expectation of benefit, but the benefit of agents in clinical trials is unknown; this is the purpose of clinical trials.

Coverage of routine medical costs for patients enrolled in clinical trials has potential benefit for patients with minimum impact on payers. Regardless of the result concerning legislation to mandate payment for routine costs, the Wyoming legislature is encouraged to join the Council of State Governments to lobby the US government to maintain or increase funding for research.

BACKGROUND

Evidence, or what really works in healthcare, is based on well designed, carefully conducted research.[1] Clinical trials of drugs, devices or procedures are very important to the advancement of health care and patient care. Individuals who participate in clinical trials are benefiting future patient care by helping determine what works and what does not. The reason for doing research is to find out if a treatment (drug, device, or procedure) is effective or if it is more effective than a current therapy. Side effects are relatively unknown, especially in early phases of study, but safety of the patient is still of highest priority.[1]

The costs associated with medical care covered in the study protocol and those associated with the disease state have not always been differentiated by the patient's insurance company or managed care organization. Historically, when subjects participate in clinical trials, the medical procedures, laboratory tests, and medications specified in a study protocol (costs directly related to the drug or procedure under study) were considered non-routine patient care costs and were covered by the organization or company conducting the study. In the past 10 years, the procedures provided to subjects free of charge under the protocol have been scaled back. Thus, some medical care may not be included in the study protocol or covered by the insurance company, leaving the patient or patient's family to bear the expense.

Clinical trials are of special importance in cancer therapy, because of the terminal nature of the disease and the lack of curative treatments for most cancers. Adequate enrollment in clinical trials is often difficult to achieve because of many factors including the actual or perceived lack of health care insurance or managed care organizations to cover health care costs that are associated with the disease (but not the drug or procedure under study) should the patient be enrolled in a clinical study. One proposed method to increase participation is to have routine costs paid by insurance providers. Mandated coverage is one potential way to achieve this objective.

Several states have laws or regulations mandating coverage of insurance claims associated with clinical trials, using various language. Medicare also instituted a policy in 2000 and is currently in the process of clarifying their policy.

A bill to mandate coverage of insurance claims associated with participation in a clinical trial was debated in committee during the 2007 Wyoming Legislative session. Although the bill never made it out of committee, the Wyoming Legislature appropriated funds for the Wyoming Health Care Commission to study the issues further. The four distinct areas of the study specified in the request for proposals were:

1. A comparison of existing health care coverage mechanisms within federal, state, and private programs for funding claims associated with routine patient care costs of subjects participating in the clinical trial of a new pharmaceutical drug or clinical procedure.
2. A literature review of best practices for such coverage.
3. Interviews with stakeholder organizations, including individual members of such organizations, to identify preferred approaches in Wyoming.

4. An analysis of the ways in which options for coverage fall within the current policies and regulations of the State of Wyoming and its private insurance carriers.

The following research questions address these four distinct areas.

RESEARCH QUESTIONS

1. What are the current trends for covering insurance claims associated with routine patient care costs of subjects participating in the clinical trial of a new pharmaceutical drug or clinical procedure among federal, state, and private insurance programs or managed care organizations?
2. Are best practices for covering insurance claims associated with routine patient care costs of subjects participating in the clinical trial of a new pharmaceutical drug or clinical procedure reported in the literature?
3. What are the preferred approaches in Wyoming for covering insurance claims associated with routine patient care costs of subjects participating in the clinical trial of a new pharmaceutical drug or clinical procedure according to key stakeholders in the state?

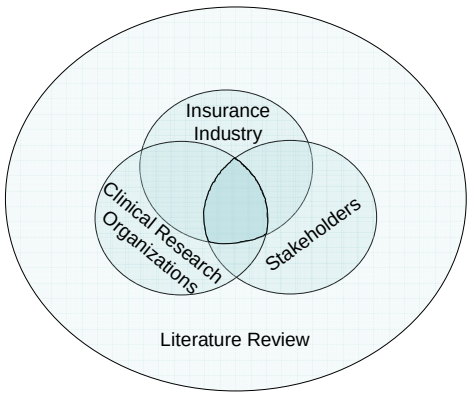
4a. How do the identified best practices and preferred approaches fit within current state insurance regulations and current coverage policies of insurers in the state?

4b. What impact would the identified best practices and preferred approaches have on access to and premiums for insurance coverage in the state?

METHODS

The study design and procedures used to address the research questions are diagrammed and described below.

Figure 1: Study Design Diagram



STUDY DESIGN

This is a descriptive study. Data was gathered through interviews and literature reviews.

PROCEDURES

1. A search of the following literature databases: Medline (PubMed), LexisNexis, EconLit, CINAHL, Academic Search Premiere, Health Source Consumer Edition, Health Source Nursing, and Business Source Premiere Edition was conducted in addition to an internet search. The purpose of these searches was to identify information regarding
    - the incidence and prevalence of cancer in Wyoming
    - insurance coverage of vulnerable populations such as children,
    - the drug approval process including the probability of medications progressing through clinical studies to market approval, the role of the Food and Drug Administration and the National Institutes of Health, and
    - the cost of clinical trials to patients and insurance companies, coverage policies and practices including federal regulation as well as legislative approaches and insurance regulations in other states.

    The major findings and trends regarding best practices are reported in the results section.

2. Existing health care coverage mechanisms within federal, state, and private programs for funding claims for routine patient care costs of subjects participating in cancer clinical trials were obtained from publicly available documents or interviews with key contacts within insurance companies that provide the majority of the insurance coverage for Wyoming, Medicare, Medicaid, The Department of Veteran's Affairs, the Department of Defense (TriCare/CHAMPUS), and the Wyoming Department of Insurance. When interviews with key contacts were conducted, specific questions were developed and sent ahead of time to facilitate the interviews. The themes and findings generated from the review of documents and policies are summarized in the results section.

3. Interviews with other stakeholders were also conducted to identify preferred coverage approaches in Wyoming. These stakeholders included the American Cancer Society, The Wyoming Insurance Department Commissioner, The National Association of State Comprehensive Health Insurance Plans (NASCHIP), a co-chair of a relevant Wyoming state legislative committee, and organizations conducting cancer clinical trials in Wyoming. When interviews with key contacts were conducted, specific questions were developed and sent ahead of time to facilitate the interviews.

4. A list of cancer clinical trials being conducted in the state was compiled from http://www.clinicaltrials.gov/. Copies of the consent forms were requested from the organizations conducting the cancer clinical research.

5. The themes and findings generated from the stakeholder interviews are summarized in the results section along with a table identifying the types of cancers being studied, the phase of study, the costs covered by the protocol and the costs borne by the subject.

6. An analysis of the data is presented in the results and discussed in the discussion and conclusion/recommendation sections.

RESULTS

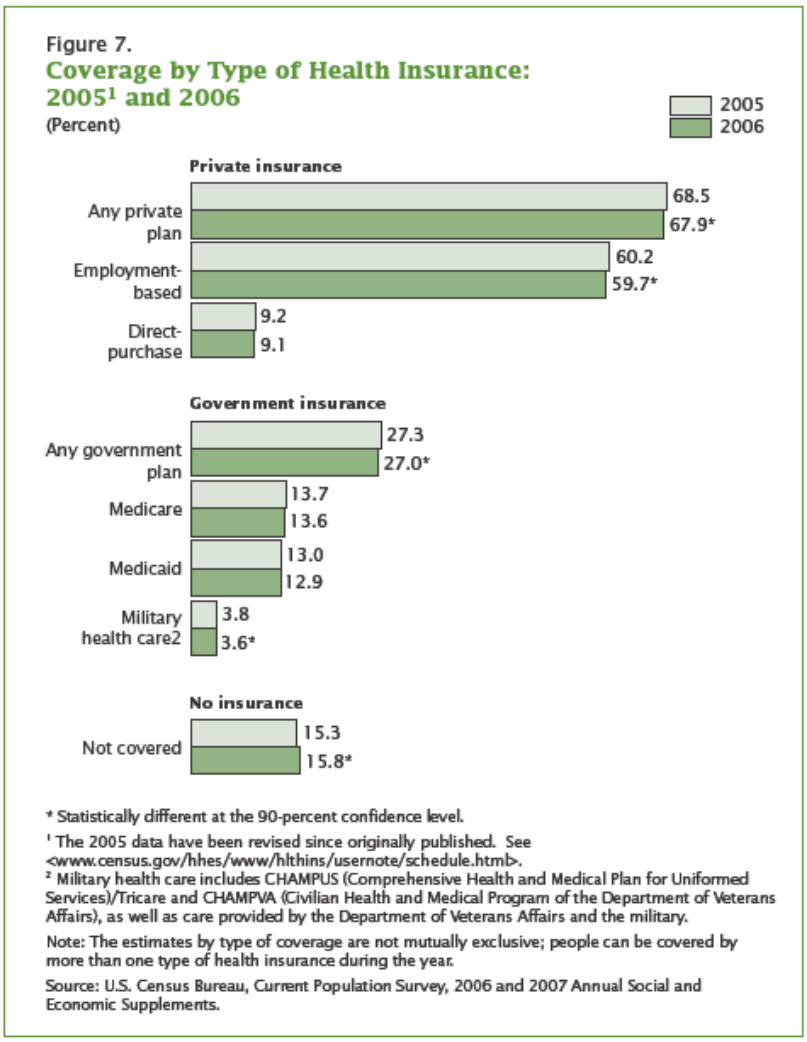
The results of the literature review and interviews are combined into related topics and presented below.

INCIDENCE AND PREVALENCE OF CANCER IN WYOMING

Cancer is a reportable disease in Wyoming. The Wyoming Cancer Surveillance Program (WCSP) reported an incidence of 2,198 all-site cases in 2004. Of these, children 19 and under had 20 cases, elderly 65 and over had 1187 cases, and the remainder (991) were in adults age 20-64.[2] The American Cancer Society estimates that Wyoming will have 2,340 new cases in 2007.[3] The estimated U.S. prevalence of all-site cancers was 10,762,214 in 2003 (compared to an average incidence of 1,671,579 for 2000-2004). The number of persons with a history of cancer (prevalence) who were receiving therapy was not available.[4] If extrapolated to Wyoming, a total of 15,066 persons will be living in Wyoming with a history of cancer during 2007. The WCSP also reported that 884 persons died from cancer in 2004.[2]

INSURANCE COVERAGE

The U.S Census Bureau released a report in August 2007 that found that, in 2006, the real median income of in the United States increased, the poverty rate decreased, and the number of both insured and uninsured increased (with the percentage of uninsured also increasing) over 2005. The number of insured increased from 249.0 million to 249.8 million with no statistical change in the numbers insured by private versus government sources. The percent covered by any type of private insurance decreased from 68.5 to 67.9 and employment-based insurance decreased from 60.2 to 59.7. The number of uninsured increased from 44.8 to 47.0 million (percentage increase from 15.3 to 15.8); the only age group that did not have a percentage increase was the 18-24 year olds. The number of uninsured children (less than 18) increased from 8.0 million to 8.7 million (10.9% to 11.7%). Figure 7 from the Census report is reproduced below. Only the rolling average (2004-2006) for uninsured in Wyoming was presented and was 14% (as in the Kaiser table).[5]



Statistics for Wyoming from the Kaiser Family Foundation from 2005 are probably the most current available and are presented in the table below:

TABLE 1: DISTRIBUTION OF HEALTH INSURANCE COVERAGE IN WYOMING

Health Insurance Coverage in Wyoming by Provider (2005)			
PROVIDER TYPE	ALL AGES [%]	CHILDREN (0-18) [%]	ADULTS (19-64) [%]
Employer	54	58	63
Individual	7	5	9
Medicaid*	11	24	6
Medicare	12		
Other Public**	2	3	4
Uninsured**	14	10	18
Total Number	501,921	124,604	314,614
*Includes dual eligibles **VA, Military, Non-elderly Medicare ***Includes those who only have access to Indian Health Insurance			
Adapted from Kaiser Family Foundation State Health Facts[6]			

In 1993, a research report indicated that 23.9% (S.E. 2.7%) of Wyoming employers covering 40.6% (S.E. 3.9%) of Wyoming employees were self-insured.[7] Search of the National Employer Health Insurance Survey (NEHIS) did not reveal any more recent numbers. Insurance Commissioner Ken Vines estimated 38-40% of Wyoming employers are currently self-insured/self-funded. The self-insured/self-funded plans are either political subdivisions (which can be included in legislation involving insurance mandates) or subject to the Employer Retirement Income Security Act (ERISA); ERISA employers are not subject to insurance mandates.

Workers In the United States and Wyoming

Although it may occur at any age, cancer is generally a disease of older adults (61% of all new cancer cases are in people aged 65 and older).[8] Toosi described that the percentage of U. S. workers in three groups (45-54, 54-64, 65 and older) will each have a greater percent increase than that of the younger workers over the next five years (and the 34-44 group will decrease significantly). Since people are tending to stay in the work force longer, this does have implications for costs associated with cancer treatment and, ultimately, costs of payment for clinical trial participants. In 2012, the youngest baby boomers will be just 48 years old, so this trend will continue for several more years into the future.[9]

In 2002, the largest group of employees in Wyoming was aged 45-54 and large numbers were older than that. The implications for employer-sponsored insurance and costs to treat cancer are similar to those of the United States. See the table below.

TABLE 2: EMPLOYMENT STATUS IN WYOMING BY AGE

Employment status of the civilian noninstitutional population by sex, age, race, and Hispanic origin, 2002 annual averages

Wyoming

(Numbers in thousands)

Population group	Civilian non-institutional population	Civilian labor force		Employment		Unemployment		
		Number	Percent of Population	Number	Percent of Population	Number	Rate	Error range of rate[1]
Total								
16 to 19 years	29	18	62.9	16	55.0	2	12.6	9.7 - 15.5
20 to 24 years	29	24	82.5	22	76.4	2	7.4	5.3 - 9.5
25 to 34 years	60	50	83.9	48	80.0	2	4.6	3.4 - 5.8
35 to 44 years	72	65	89.6	63	86.8	2	3.1	2.2 - 4.0
45 to 54 years	79	70	88.0	68	85.7	2	2.6	1.8 - 3.4
55 to 64 years	52	33	64.1	32	62.4	1	2.7	1.5 - 3.9
65 years and over	62	10	16.0	10	15.6	([3])	2.4	.4 - 4.4

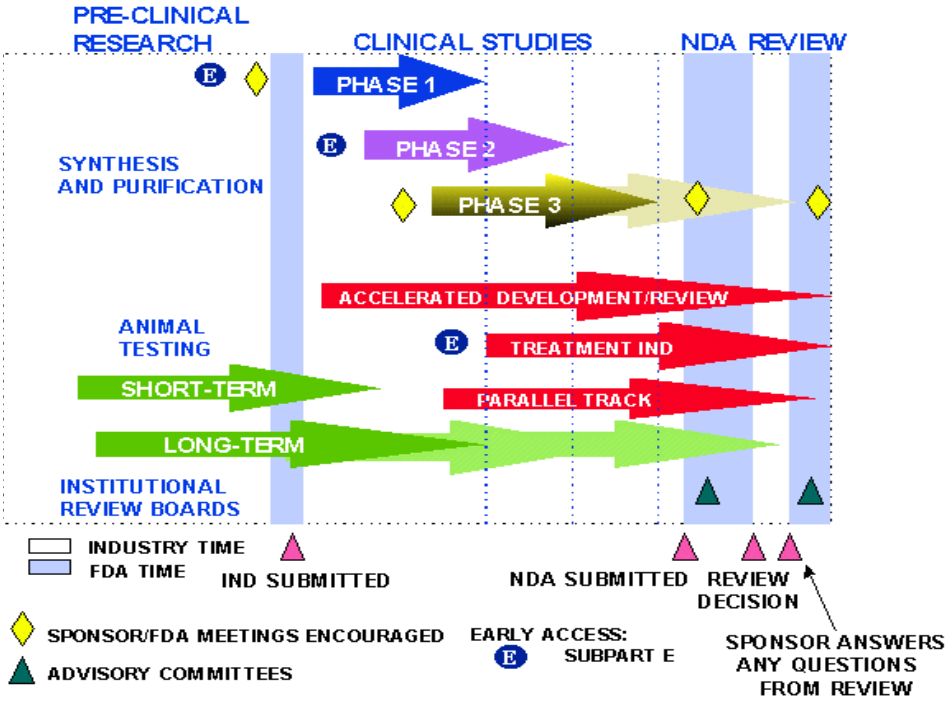
Bureau of Labor Statistics[10]

CLINICAL TRIALS AND THE DRUG APPROVAL PROCESS

A clinical trial is intended to test the hypothesis that no difference exists between the intervention and the control for whatever is being tested (efficacy, toxicity, costs). The researchers want to determine if their intervention is better than the control.

Clinical trials are usually at the end of a process intended for marketing approval. This process begins with discovery of a potential chemical compound or idea for a device or procedure. Although devices have a slightly different process, it is similar to the drug approval process which is diagrammed in figure 2.

FIGURE 2: THE DRUG APPROVAL PROCESS[11]



The approval process is long and complicated. For every 10,000 chemicals discovered, only 250 survive the 6.5 years of pre-clinical testing to go into clinical trials. Compounds spend an average of 6 years in phase I-III (see below) and only 5 are submitted as a New Drug Application (NDA), the submission to the FDA for its approval. The FDA approves one out of the 5 NDAs and takes an average of 1.5 years for review.[12]

The FDA and the National Institutes of Health (NIH) through the National Cancer Institute (NCI) play specific roles in clinical trials. The NCI is a component of the NIH and was established in 1937 to be the main source of cancer research and training for the U.S. government. It provides funding for studies by outside sources before human testing (pre-clinical) as well as clinical studies; NCI also conducts research and clinical trials in its own facilities.[13] Other organizations, including advocacy groups and the pharmaceutical industry,

also participate in the research funding and clinical trials process outside of the government arena.

Conduct of all clinical trials is generally divided into four phases. For oncology trials, definitions of these phases are as follows[14]:

- **Phase 1** studies are conducted in subjects with advanced disease and, generally, for whom no therapy is available. The purpose of a Phase 1 study is to (1) determine dosing and preliminary safety information for investigational drugs, (2) test the use of a new drug in combination with a marketed drug, or (3) test new doses or combinations of already marketed drugs.

- **Phase 2** studies examine preliminary efficacy at the dose and dosing schedule determined in Phase 1 in specific cancer types and provide further safety information. These trials are usually single-arm studies (i.e., a single treatment regimen is studied) with a response rate endpoint (i.e., a measure of study outcome). If activity can be demonstrated in Phase 2, further clinical development proceeds in Phase 3.

- **Phase 3** studies usually compare a new treatment regimen with best available treatment to determine which is the better therapy (i.e., a controlled clinical trial). Controlled clinical trials with protocols that have undergone appropriate external scientific review have been critical in determining the most effective therapies. Congress recognized the value of such evidence-based medicine in the 1962 Amendments to the Food, Drug, and Cosmetic Act, which require "substantial evidence of effectiveness based on adequate and well-controlled clinical investigations." Adequate and well-controlled investigations are defined in the Code of Federal Regulations (21 CFR 314.126).

- **Phase 4** trials are studies performed after a drug is marketed to further define safety and efficacy. (See law in box below) "Studies in Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication."[15] A company must file an investigational new drug application (IND) to conduct a study of an approved drug to support a new indication, a significant change in labeling, or a significant change in advertising (i.e. becomes subject to the appropriate phases I-III).[14, 16]

The information derived from the phases of clinical trials is required for approval of the intervention by the FDA. The FDA has roles in regulating many aspects of cancer therapy (through its Centers for Drug Evaluation and Research (CDER), Biological Evaluation and Research (CBER), Devices and Radiologic Health (CDRH), and (to some degree) Food Safety and Applied Nutrition (CFSAN). If a clinical trial is conducted with a dietary supplement (which is a food by law) or biological agent, they become new drugs for regulatory purposes. Thus, CDER and CDRH are the areas responsible for reviewing clinical trials. The FDA does not conduct any clinical trials on its own, but uses information from trials to approve drugs and devices.[11]

CODE OF FEDERAL REGULATIONS
TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 312 -- INVESTIGATIONAL NEW DRUG APPLICATION

Subpart E--Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

Sec. 312.85 Phase 4 studies

Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

Participation in Clinical Trials

People participate in clinical trials for a number of reasons. The ideal reason, which prevents unrealistic expectations, is altruism, the desire to help humankind. The next reason is that no effective therapies currently exist for the condition. On the other end of the spectrum is desperation, where, for various reasons, standard treatments have been ineffective for the individual. Although all persons entering clinical trials hope that their personal health will improve, this is not the purpose of the trial. A study by Lidz et.al found that 62% of the clinical trial participants (of 155 participating in 40 different trials) interviewed showed therapeutic misconception. Earlier papers have defined therapeutic misconception as the belief that an intervention would not be offered if it did not have some chance of benefit or if significant risks existed (despite reasonably clear informed consent statements). Lidz et.al clarified this to include "belief that the therapy would be individualized to the patient and an unreasonable assessment of benefit." This study found that most participants had only a minimal appreciation of the risks involved.[17] Therapeutic misconception may add to the emotional aspects of the discussion concerning clinical trials legislation.

On the other side, participation in clinical trials is extremely low. Less than 5% of adults participate in clinical trials (with most studies indicating less than 3%). Low participation leads to delays in achieving adequate numbers, ultimately delaying analysis of the results, cancellation of the trial, or publication of underpowered studies containing inconclusive results.[18] The large participation by children with cancer is related to the relatively few available therapies for childhood cancers.

A Harris Poll of 5,972 cancer patients in 2000 found that nearly 85% either were not aware (or were unsure) that participation in a clinical trial was an option.[19] In the study by Mills et.al, the reasons given by patients for deciding not to participate in a cancer trial are presented in the following table (in order of proportion of pooled responses; people may report more than one). Cost was mentioned fairly infrequently.[20] The Harris Poll also found that about 75% of those who were aware (the remaining nearly 16%) turned down participation, citing reasons similar to Mills. Belief that insurance would not cover the cost was cited by 20% and amount that would

have to be paid out-of-pocket was mentioned by 18%. Interestingly, of those who had participated, only 76% would recommend a clinical trial to a patient who had cancer, even though 97% felt they were treated with dignity and that the care was good or excellent. Insurance did cover costs for 86% of the participants.[19]

TABLE 3: REASONS FOR NOT PARTICIPATING IN CLINICAL TRIALS

REASON FOR NOT PARTICIPATING	PROPORTION
Quality of life might be reduced	55%
Dislike possibility of placebo	53
Potential side effects	45
Trial treatments not best option	44
Dislike randomization	38
Physician should make decisions	38
Inconvenience to everyday life	35
Preference for other treatment	34
Negative effect on patient-physician relationship	26
Trial not appropriate for diagnosis	24
Trial treatments offer no benefit	24
Not informed	23
Lose control of decision-making	23
Feels coerced to join	20
Dislike being experimented on	19
CONCERNS OVER COST OR HEALTH INSURANCE	**17**
Too uncertain	12
Lack of family support	10
Statistics from: Mills et. al, Lancet Oncol, 2006[20]	

Participation by Adults

Various numbers have been reported for participation in clinical trials by adults. The New Jersey alliance reported that 3.3% of cancer patients enrolled before they began the voluntary payment of routine costs in 2000. Approximately 1% of Medicare enrollees participated in 2000. The Department of Defense has an agreement with the NCI for covering TriCare/CHAMPUS insurees. In 1996 (before the agreement), only 0.5% of cancer patients participated in clinical trials.[22] Murthy et. al reported a study in 2004 on cancer patients age 30 and over enrolled in cooperative group therapeutic trials (surgical interventions were excluded). They found that about 1.7% of the total number of incident cancer cases diagnosed from 2000-2002 participated (1.8% of whites, less for other groups).[23] A recent study from Australia found that when offered a choice of participating in 5 types of randomized, controlled trials (RCTs), rectal cancer patients would choose to participate 19-31% of the time. Surgery plus experimental radiation therapy was more likely to interest patients. Surgeons and oncologists were not much more likely to recommend RCTs (ranging from 15-38%). Reasons patients would not participate were similar to Mills and the Harris poll (however, cost was not presented)[18] The guide for conducting clinical trials by C-Change and the Coalition of Cancer Cooperative Groups states that only 1 of 6-10 screened individuals will actually be enrolled in a trial (this is after willingness to participate and is based on the inclusion and exclusion criteria of the study).[21]

Participation by Children

The Best Pharmaceuticals Children Act of 2002 (BPCA) required the Secretary of Health and Human Services to report on pediatric patient access to new (investigational) therapeutic agents [Access report].[14] Investigational agents in pediatrics may include approved adult drugs that have not been approved for pediatric use.

The Access report indicated that 12,000 new cases of cancer are diagnosed in children each year and about 20,000 receive treatment in a year and 2,300 die. The report further states that 90% of children with cancer are treated at Children's Oncology Group (COG) or related institutions (212 in the United States). The report estimated that 50% of children (compared to less than 5% for adults) are enrolled in clinical trials and 4000 were enrolled in National Cancer Institute (NCI) trials. Of these NCI trials, 500 children were receiving one or more investigational agents.[14]

SPONSORS OF CLINICAL TRIALS FOR CANCER IN THE UNITED STATES

Who sponsors clinical trials and how they are sponsored is difficult to determine. The primary sponsor of the clinical trials can be determined by accessing websites such as www. clinicaltrials.gov. Using the clinical trials search engine at the NCI website allows searching by sponsor (NCI, other government agencies, pharmaceutical industry and other). Of the 5985 cancer clinical trials posted, 1778 were sponsored by the U.S. government (1721 of these by NCI), 1416 by the pharmaceutical industry, and 3027 by others (mostly foreign sponsors). A sampling of information on phase IV trials indicated that most were "Other" and were being conducted in a foreign country.[24]

However, indirect sponsoring is more difficult to identify. From an interview with the Chair of the research committee for the American Society of Clinical Oncology, pharmaceutical companies donate chemical agents (which they hope will eventually become drugs) to NCI for studies. Companies may also get chemical agents from government research to study in clinical trials; no mechanism exists to reimburse the government for these if they eventually become profitable drugs or devices.[25] Data from NCI studies is free to the company. Studies sponsored by NCI through the Coalition of Cancer Cooperative Groups enrolls about 50% of all clinical trial participants.[26]

Clinical Trials in Wyoming

One hundred nineteen (119) cancer clinical trials are currently being conducted in Wyoming according to the National Cancer Institute's (NCI) website, www.clinicaltrials.gov. One hundred thirteen (113) out of the 119 cancer trials are sponsored by NCI. Most of these studies are being conducted by a single research consortium and are outpatient studies. We were able to obtain 101 consent forms for review. Some of the consent forms are for studies being conducted by the research consortium in neighboring states. Most of the consent forms reviewed were for studies funded in part or in whole by the NCI. Thirsty six percent (36.1%) of the reviewed studies were jointly funded by NCI and pharmaceutical manufacturers. This was generally characterized by

the manufacturer providing the study medications free of charge and potentially having access to the study information.

None of the studies reviewed provided monetary compensation for participating subjects. The vast majority of studies involving medications provided the study medications to the subjects free of charge. However, few (3%) provided other medications free of charge including medications used by the control group (these were medications that are currently on the market). Three quarters of the other protocol costs, i.e. the costs of laboratory monitoring, were borne by the study subject and/or his/her insurance provider. While the investigational medications were often provided by the study sponsor, none of the sponsors paid to treat the adverse effects or toxicity associated with the study medications (the investigational or control medications).

The reviewed consent forms contained details about the study procedures that most likely could be used by an insurance provider in a prior authorization process. This is important because all subjects will have a copy of the consent form, but few if any would have access to the study protocol. (Table 4) Additional detail is covered in Appendix C.

COSTS OF PARTICIPATION IN CLINICAL TRIALS

Determining the costs of cancer clinical trials or, even, of cancer treatment is very difficult and results of studies need to be considered preliminary.[27] Goldman et.al later reported that non-pediatric NCI cancer clinical trials was about 6.5% more than treatment for non-study patients; those who died early or were in earlier phases had more expensive courses (pediatric studies are usually more expensive because of the small numbers and rare types).[28] Bennett et. al reviewed the literature on costs for subjects involved in clinical trials compared to treatment costs. They found that solid information was difficult to obtain because of small sample sizes, included and excluded items, costs at different sites, the length of the study and the selection of controls. The one study that found clinical trials less expensive used charges instead of costs (the impact of this on the results is unknown). Five studies covering phase II/III or III clinical studies were included. Costs at 6 months ranged from 17-23% more expensive [about $2,000 to $6,000]; the study using charges found the trials to be about $6,000 less expensive, but charge totals were approximately double the highest costs. Results at 12 and 24 months were not really different. The one study that reported costs at 60 months found that the difference between clinical trials and treatment costs was only 1% (about $300).[22] Chirikos et.al studied the charges for subjects at their institution enrolled in phase I-III or non-enrolled in clinical trials for 4 cancer types. They found that after adjusting for age and stage of disease, the differences in total charges between the groups were not statistically different (except for breast cancer subjects in "other protocols – non-phase I-III – which were higher).[29] Wagner et. al found an increase of cost in clinical trials of less than 10% ($2,000) over five years;[30] these subjects were matched for severity and lack of co-morbidity. The Chirikos study included patients who may have had more charges due to co-morbidity in the non-enrolled group. A study of all of the phase III trials of the National Institute of Neurological Disorders and Stroke (non-cancer trials) funded before 2000 (28 trials for a total cost of $335 million) found that the cost per quality adjusted life-year was $7,713 even though only 21% of the trials resulted in "measurable improvements" in health.[31]

Table 4: Summary of Consent Form Review

Category	Description	n (%)
Study Phase		
	I	4 (3.9%)
	II	43 (42.6%)
	III	50 (49.5%)
	IV	4 (3.9%)
	Total	101 (100%)
What is the Funding Source for the Study?		
	NCI*	51 (50.5%)
	NCI*/Pharmaceutical Manufacturer	37 (36.1%)
	Pharmaceutical Manufacturer	7 (7.2%)
	Other Consortium	6 (6.2%)
Are Subjects Compensated for Participation?		
	No	101 (100%)
	Yes	0 (0%)
Who Pays for Investigational Drugs?		
	N/A+	16 (15.4%)
	Sponsor	69 (68.3%)
	Subject	16 (16.3%)
Who Pays for Other Study Drugs?		
	N/A+	14 (13.5%)
	Sponsor	3 (2.9%)
	Subject	83 (82.7%)
	Sponsor & Subject	1 (1%)
Who Pays for Study Protocol Costs?		
	N/A+	1 (1.0%)
	Sponsor	20 (20.2%)
	Subject	76 (75.0%)
Who Pays for Treating Toxicity Resulting From Study?		
	N/A+	3 (2.9%)
	Sponsor	0 (0.0%)
	Subject	98 (97.1%)
Are Protocol Procedures Described in the Consent Form?		
	No	0 (0.0%)
	Yes	101 (100.0%)

* NCI = The National Cancer Institute

+ N/A = Not Applicable because the study does not include the specified costs

The cost per participant has been reported in several studies, statements and reports. The average non-labor costs reported by C-Change were $3,091 to $6,094 from a literature review. C-Change also conducted a survey that found costs ranges from $2,000 to $9,849.[32] Love in his affidavit to the South African court states that cancer studies in the U.S. cost $2,000 to $7,000 per subject.[25] Of course, these are actual costs and not the charges that a hospital or clinic might normally charge (which include overhead and profit).

One of the themes emerging from interviews is that participation in clinical trials is often not easily detected and routine costs are very difficult to define. Bennett et. al. estimates that Medicare paid for 50-90% of billed routine patient care costs for those enrolled in clinical trials during the 1990s even though they excluded routine costs under their "experimental" clause (see below).[22] When asked how they knew if a patient was in a clinical trial, most stakeholders (especially those without strict networks) stated that they did not know unless the investigational drug or device was billed.

Costs in clinical trials include the drug or device and administrative costs which are considered protocol costs; other costs have been extensively discussed as to whether or not they are routine.[33] The Bennett article states that routine costs (as derived from the Centers for Medicare and Medicaid and the Institute of Medicine) include or do not include the following:[22]

- Conventional care
- Items or services that are typically provided absent a clinical trial
- Administrative items
- Items or services required solely for the provision of the investigational item or service (such as administration of a non-covered chemotherapeutic agent)
- Clinically appropriate monitoring related to complications and treatment effects
- Reasonable and necessary care
- Items or services arising from the provision of an investigational item or service, including the diagnosis or treatment of complications

Routine patient care costs do not include the following:

- Items and services that are customarily provided by the research sponsors free of charge for individuals participating in the trial (such as investigational drugs or items)
- Tests or measurements conducted primarily for the purpose of the clinical trial involved
- Administrative costs associated with collecting research data

The category of costs that is the most controversial is the payment for "the diagnosis or treatment of complications." Hochauser states that even policies that use the "experimental" clause rarely state whether or not they cover research-related injury treatment.[34] So, the prospective subject must attempt to obtain information before they enroll. When a sponsor does not cover these costs, enrollment is often delayed or becomes inadequate. Reasoning behind commercial sponsors not covering these costs was not found, but the $2000 per enrollee[32] paid by the NCI and other government sponsors is the reason that these NCI-sponsored studies do not cover injury costs.

HEALTHCARE COVERAGE MECHANISM FOR CLINICAL TRIALS

No standard for coverage of routine costs emerged from the literature review or the interviews. The coverage ranged from the very broad coverage of Medicare, the VA and DoD to a general policy of not covering investigational treatment. The states may restrict the coverage to cancer only or to life-threatening diseases. Some states limit the coverage to certain sponsors or to children only.

State Regulations

Twenty-three states have some form of mandated insurance coverage for clinical trials. All mandates include phase III trials, based on the assumption that states that do not specifically exclude phases would include coverage for participation in any phase of study so long as the patient met the other criteria. At least two states specify coverage for studies examining the detection of cancer, 13 specify coverage for studies examining the treatment of cancer, six specify coverage for palliative care studies and seven cover prevention studies. Five states include coverage for other life threatening diseases. Two of these states do not specifically specify coverage of cancer trials (they are included under trials for life threatening conditions).

Many states including CT, MA, NH, and VT specify coverage of "routine patient care." Connecticut defined "routine patient care" as medically necessary care that would be covered if the patient was not enrolled in the trial. At least three states specify that the trials should have a therapeutic intent to qualify for mandated coverage (toxicology and dose finding studies are excluded). While many states mandate coverage for medications currently approved by the FDA (for the control or standard of care group), at least one state (MO) mandates coverage for investigational medications that are not yet approved by the FDA. Some form of pre-approval is required by several states (including CT, OH and VT) before an insurance company is mandated to pay for clinical trial claims. CT specifies what documents may be requested of the subject by the insurance company. WV specifically excludes mandated coverage of trials that are intended to extend the patent life of a medication or studying the impact of a change in product formulation.

Table 5 Number of States with Mandated Coverage by Phase

Study Phase Included in Law	Number of States
Phase I Studies	14
Phase II Studies	22
Phase III Studies	23
Phase IV Studies	20
Total	23

A detailed summary of state legislation is presented in Appendix D.

Public Payers

Medicare is updating their current policy (310.1)[35] relative to clinical trial routine costs. Most, if not all of the costs considered routine in the list above are currently covered by Medicare. (Appendix A) The proposed changes will be a clarification of 310.1 and will be called a Clinical Research Policy[36]. (Appendix B) Both the Department of Veteran's Affairs and the Department of Defense (TriCare/CHAMPUS) have agreements with the NCI for their insurees to cover all costs not covered by the trial.[37, 38] The Railroad Employees plan generally does not cover clinical trials under the "experimental" clause. It does, however, allow for exceptions in "life-threatening conditions."[39] The Indian Health Service is the payer of last resort and has a system of priorities that change with funding.[40]

Private Payers

The largest private insurers in Wyoming (58.2% of market share) have various policies. UnitedHealth was not interviewed but has a policy of voluntarily covering routine costs.[22] Most insurance plans (public and private) in the United States currently use the American Medical Association's (AMA) definition of "medical necessity" adopted in 1999 as the basis of their general coverage.[41] This standard, also utilized by Wyoming providers, is as follows:

> Health care services or products that a prudent physician would provide to a patient for the purpose of preventing, diagnosing, treating or rehabilitating an illness, injury, disease or its associated symptoms, impairments or functional limitations in a manner that is: (1) in accordance with generally accepted standards of medical practice; (2) clinically appropriate in terms of type, frequency, extent, site and duration; and (3) not primarily for the convenience of the patient, physician, or other health care provider.[41] Many insurance policies include the "experimental clause" which may allow them to exclude coverage if the treatment is part of a clinical trial. An example of the definition is below.[42]

FIGURE 3: EXAMPLE OF THE EXPERIMENTAL CLAUSE

■ **Experimental or Investigational**

A drug, device, medical treatment or procedure which:

- Cannot be lawfully marketed without the approval of the Food and Drug Administration (FDA) or other governmental agency and such approval has not been granted at the time of its use or proposed use; or
- Is the subject of a current investigational new drug or new device application on file with the FDA; or
- Is being provided pursuant to:
  - A Phase I or Phase II clinical trial or as the experimental or research arm of a Phase III clinical trial; or
  - A written protocol which describes among its objectives, determinations of safety, toxicity, effectiveness, or effectiveness in comparison to conventional alternatives;
- Is being delivered, or should be delivered subject to the approval and supervision of an Institutional Review Board (IRB) as required and defined by federal regulations particularly those of the FDA or the Department of Health and Human Services (HHS);
- In the predominant opinion among experts:
  - As expressed in the published, authoritative literature, is substantially confined to use in research settings;
  - Is subject to further research in order to define safety, toxicity, effectiveness, or effectiveness compared with conventional alternatives; or
  - Is experimental, investigational, unproven or is not a generally acceptable medical practice; or
- Is not a covered service under Medicare because it is considered investigational or experimental as determined by the Centers for Medicare and Medicaid (CMS);
- Is provided concomitantly to a treatment, procedure, device or drug which is experimental, investigational, unproven treatment; or
- Has not been performed at least ten (10) times and reported on in United States peer review medical literature.

Table 6 provides a summary of relevant points collected during the stakeholder interviews.

TABLE 6: INTERVIEW DATA ON SPECIFIC POLICIES

Do You Have a Specific Clinical Trial Coverage Policy?

- No policy dealing specifically with this issue
- WY Medicaid program has no official policy for processing claims associated with clinical trials. Typically don't cover investigational drug but do cover the wrap around claims by default as long as they are part of usual care for the specific cancer
- This company covers routine care associated with clinical trials by default

What is Your Current Screening / Payment Process

- Use Medicare's policy as a guide
- Cover off-label use if medically necessary.
- Medically necessary care is provided to children up to age 21 (so most wrap around costs would be covered)
- Often don't know if patient is in clinical trial or not
- Coverage for toxicity from investigational drug probably wouldn't be discovered unless there was an audit. Then a 3rd party recovery agency would be used.
- Medical Director screens claims, if it is a trial then it is sent for external review. Problems arise when there is a discrepancy between external review and the literature (as in BMT for Breast CA)
- Ultimate decision lies with claims department, but the Medical Director advises using the following to questions as a guide: 1. Is this the medically correct thing to do? Would I do this for my family; and 2. Under this contract is this something that we promised to cover? Formed special internal committee to review cases
- We have three options when considering claims associated with clinical trials: 1) reject all claims (often done on TPA Side); 2) pay all claims; 3) pay for non-experimental claims (general course for fully insured business – but difficult to determine)
- Hospitalization as part of a clinical trial is not covered, labs are not fought

EFFECT OF LAWS AND POLICIES MANDATING PAYMENT FOR ROUTINE COSTS ON CLINCIAL TRIAL ENROLLMENTS

Gross et.al conducted a study of enrollment by patients under age 65 with the four most common cancers in NCI-sponsored phase II and phase III trials before and after four states had mandated coverage (in 1999) of routine costs for patients enrolled in clinical trials. The study found that the difference between enrollment in any phase was not significant between coverage and noncoverage states. The coverage states had a significant increase in phase II enrollment (where noncoverage states had a decrease), but the reverse was true for phase III trials. Gross et. al explains that the states with coverage may have been more supportive of phase III trials at baseline (affecting ability to increase), but that phase II trials have been considered more experimental.[43] More impact was seen in a study by Martel et. al which studied participation in

clinical trials at UC Davis before and after the California law was passed. They found that although little difference in total enrollment occurred, the decreased enrollment by persons with private insurance (which was statistically different) no longer existed after the law went into effect (only 8% of persons declining enrollment was due to insurance limitations in the original study).[44] In an additional study, Gross et.al examined enrollment of cancer patients 65 years and over in the same types of studies, that included at least 5% elderly, before and after Medicare implemented the change in policy in 2000. The study found that, after the change in policy, cancer studies had either a decrease in enrollment by older adults or no change.[45] Unger et.al found that enrollment by older adults in clinical trials increased after the change in Medicare policy if the patient also had a supplemental (private) insurance policy, where no change was seen in patients with Medicare alone.[46] By 2001, participation by TriCare enrollees had increased to 2%; no information was found on why this group was less willing originally to participate than the average cancer patient.[22]

EFFECT OF INCREASE IN PREMIUMS ON INSURANCE COVERAGE

A primary concern of the insurance industry stakeholders and an important issue to policy makers is whether mandated coverage would increase insurance costs and premiums to the point where insured lives will be lost. In an insurance market like Wyoming where small employer groups and individuals make up a large part of the market share, price sensitivity can have a large impact. Buchmueller reviews his and others work in this area. In two studies where employees were offered a menu of plans with different premiums, employees were found to be extremely sensitive to price. They were willing to switch plans for a $5 decrease in monthly premium (1997-1998 prices) and that younger, healthier persons were the most sensitive. Adverse selection becomes important and premiums would then increase further. Older insurees are impeded more by the cost of switching (including the hassle factors).[47] A related study found that the loss of market share caused by a $5 premium increase ranged from about 4% in older persons with at least one health risk to nearly 16% for younger, healthy insurees.[48] California's law resulted in a 1% increase in premiums; the Lewin group has determined that a 1% increase in premiums results in at least 300,000 people who can no longer afford insurance.[49] Small companies (less than 50 employees) and companies insuring 50-500 employees have recently seen the highest premium increases.[50] Williams and Lee state that evidence suggests that mandates are not a significant factor in premium increases to small employer plans.[51] Royalty and Hagens investigated the effect of premiums on uptake of group health insurance, but they refer to studies showing that for the self-employed, a 1% increase in premium results in a 1.8% decrease in probability of having coverage.[52]

SUMMARY OF STAKEHOLDER INTERVIEWS

Content from interviews are summarized into themes below.

Patient or Clinical Trial Issues

General Statements

- Council of State Governments is lobbying the US government to maintain or increase funding for research. This is best done on a national level. If insurance companies are mandated to pay for research, then the US government won't have any incentive to pay.
- Groups like the Jason's Friends organization in Casper help pay for travel for families to receive treatment and participate in clinical trials (which can be a substantial burden).

Positives (related to trials)

- Clinical trials can save lives
- Clinical trials advance science and improve therapy

Negatives (related to trials)

- Clinical trials can give patients false hope since many agents aren't successful due to toxicity or lack of efficacy. Specifically insurance company coverage of trials seems like an endorsement and may add to the false hope.
- An insurance mandate in WY would affect a minimum market share since self-insured companies would be exempted by the ERISA laws, unless the self-insured entity is a political subdivision of the state.
- Mandating insurance companies to cover clinical trial claims limits recruitment and eligibility for trials which affects the generalizability of the results.
- There is no scientific screen to only fund studies with large incremental value
- It is difficult to determine the scientific value of a study.
- It is difficult to determine what is "worthy" research since we do not have a national technology research approval body.
- Indemnity clauses and financial changes in the mid 90s made investigators at risk and also decreased income for small investigators which concentrated research in to larger groups.

Negatives (related to dollars or insurance)

- The small employer group is one of the largest fully insured groups in the state and it is also extremely sensitive to changes in premiums; groups with 1-10 employees are most price sensitive.
- A state our size feels the impact of adverse selection quicker and more acutely. We have a lot of small employers who are most price sensitive. They'll hang onto coverage as long as possible, but may decrease benefit plan.
- Money to cover care has to come from somewhere -- someone is going to get charged. State mandates unintendedly ignore the fact that as premiums increase then access to insurance market is limited or decreased.

Insurance Issues

Insurance: The Big Picture

- Insurance was not designed to finance clinical research. Insurance companies must manage resources to maximize utility. Insurance companies don't sign up for infinite liability.
- No insurance company wants unhappy clients, but they have to manage resources in light of contracts with clients.
- Insurance is a risk contract so you end up arguing contract issues.
- Historically, it has not been the states responsibility to pay for clinical research.
- If a state mandate was passed then the self-insured business in the state (typically large employers) would end up benefiting from small business that are not self-insured.
- If insurance companies are mandated to pay for trials then they have to pay for the drug once it is on the market, they are paying at both ends with no recouping of costs or share in the drug company's profits.
- It is important to determine costs of care with and without clinical trial to determine financial impact of mandate.
- It is difficult to determine routine care from protocol costs.
-

Coverage Issues

- ERISA plans are exempt from state insurance mandates.
- ERISA laws forbid state from imposing regulations on self-insured organizations in the state.

Special Pool to Cover Trial-Related Costs

- Using a state-wide mechanism such as high risk health insurance pools to fund clinical trial claims could be problematic since each state funds their programs differently and some states are having problems funding these programs.
- Creating a state wide pool such as WHIP could create a huge moral hazard problem and additional bureaucracy.
- Medicaid administers the colonoscopy, breast cancer, and cervical cancer screening programs for the uninsured in the state. If a similar program were established to cover claims associated with cancer clinical trials then WY Medicare would be a likely candidate to administer the program.

Other Issues

- Insurance companies that administer contracts, finance care, and provide care are most at risk of being sued for covering procedures that harm.
- If legislators passed a mandate then WY Medicaid would have to write a new state plan (Contract with the federal government) with projections of the number of people and dollars involved. This would require a lot of paperwork, but this would be minimized if the state mandate followed Medicare policies.

Alternatives / Potential Solutions

- If insurance companies are mandated to pay for claims associated with clinical trials then study sponsors should be mandated to cover medical services and medications that are above and beyond normal clinical practice amounts.
- If insurance companies are mandated to pay for claims associated with clinical trials then they should have the right of subrogation to recoup costs if the drug is successfully marketed.
- Consider excluding types of claims rather than reviewing every claim.
- HMO's must be included in this legislation
- CO has an arbitration agreement to determine what claims are paid

DISCUSSION

The results above cannot be completely generalized to Wyoming and they are, at best, inconclusive. However, the information suggests that clinical trials are not major drivers of cost in cancer therapy, that premiums may be minimally impacted (but that insurance participation does decrease with even a small premium increase), and that mandated coverage of routine medical costs for subjects participating in clinical trials has not made a large impact on study enrollment.

EXTRAPOLATION OF POTENTIAL SUBJECTS FROM WYOMING

If the total expected new Wyoming cancer cases in 2007 equal 2340, then the expected cases would be 1055 adults aged 20-64 and 22 children (rounded up). If 72% of the adults aged 19-64 are insured by employer or individual policies and 59.4% are fully insured, then 451 adults would be potentially eligible under a mandate. If the enrollment in clinical trials would be at the high end (5%), then 23 of these adults would enroll in a clinical trial. Employer and individual insurance covers 63% of children (59.4% fully insured), so 9 children would be eligible. If the average enrollment in clinical trials is 50% for children, then 5 children would be enrolled. Therefore, an insurance coverage mandate would affect less than 30 people. Costs could be similarly extrapolated, but the numbers are too inconclusive to be informative.

PAYMENT FOR OFF-LABEL USE OF DRUGS FOR CANCER

This report was not intended to cover such topics as off-label use, continued use of a drug after a clinical trial is completed (but before approval), or treatment Investigational New Drug (IND) applications (for persons not eligible for the clinical trial). Relative to off-label (indications not covered in the FDA approved labeling) use, the National Cancer Institute (NCI) states that, since standard of care of many cancers is use of drugs outside of their labeling, denial of payment is denial of care under medical necessity (not experimental or investigational use). The Omnibus Budget Reconciliation Act (OBRA) of 1993 required Medicare to cover off-label uses of drugs to treat cancer if the use was published and stated to be an acceptable use in one of three compendia (American Hospital Formulary Service, United States Pharmacopoeia Drug Information [renamed DrugTopics in 2007], and the out-of-publication AMA Drug Evaluations). The expansion to include Medicaid added the DrugDex information system as the third source. Medicare Part D language also includes the Medicaid compendia. Most states have included the

provisions of OBRA 93 to cover private plans (excluding ERISA plans). A call has been made for the Secretary of Health and Human Services to officially recognize peer-reviewed journals in addition to the recognized compendia due to the time lag involved in publication.[53]

THE ABIGAIL ALLIANCE CASE

The recent (August 7, 2007) decision by the United States Court of Appeals in the Abigail Alliance case to uphold the lower court decision that "there is no fundamental right 'deeply rooted in this Nation's History and tradition' of access to experimental drugs for the terminally ill" may affect thinking about access to experimental therapies and the right to clinical trials (reimbursed or not).[54]

CONCLUSION AND RECOMMENDATIONS

Given the likelihood that a bill to mandate insurance coverage for cancer patients enrolled in clinical trials will be introduced into the 2008 Wyoming Legislative, the recommendations being made are for considerations by the legislators concerning whether or not to pass the bill. The options for the legislature are to make no changes, to pursue voluntary coverage (especially by the large self-insured employers), to mandate coverage of routine care costs borne by patients enrolled in clinical trials, to mandate coverage of all costs borne by patients enrolled in clinical trials, or to establish a special pool to cover trial-related costs for all citizens, children, or the uninsured. If the option to mandate coverage of routine costs is selected, then a mechanism needs to be put into place for the insurance company to obtain documents (i.e. consent forms or study protocols) to determine routine costs. If an insurance mandate or a special pool is created, the legislature could also consider allowing insurers or the state the right of subrogation to recoup costs if an investigational drug or device is eventually marketed for the indication studied in a trial.

Legislators should consider the following findings in their deliberation:

- Clinical trials are not major drivers of cost in cancer therapy (and are of public health interest).
- Insurance premiums may increase anywhere from 0-10% based on published studies. However, any increase in premiums may cause decreased insurance participation.
- Mandated coverage of routine medical costs for subjects participating in clinical trials has not made a large impact on trial enrollment.
- General agreement exists among stakeholders that routine medical costs associated with trials could be covered. However, payment for treatment of toxicities from the investigational agent is controversial.
- An insurance mandate would not affect all the citizens of Wyoming since 40.6% (S.E. 3.9%) of Wyoming employees work for employers who are self-insured and others work for federal agencies which would not be impacted by the mandate; 14% are uninsured.
- The numbers of cancer patients from Wyoming who would be participating in clinical trials is small, but distribution may occur outside of statistics and impact the fully insured market disproportionately.

Wording of the bill is critical. Berlyn states clearly that "the wording of the mandate should be careful not to shift costs that are rightfully borne by the trial sponsor to others."[33]

If a bill is introduced, consideration should be given to the following suggestions for language and concepts:

- Careful review of the proposed changes to the Medicare policy and the components of the various state laws is recommended.
- Include definitions.
- The federal bills included cancer only; this was believed by many to be harmful to progress against other diseases (but the impact would be greater). The final Clinton declaration that resulted in the 2000 Medicare coverage does not limit to cancer.[33]
- Consider what "other life-threatening diseases" implies or excludes.
- Consider whether to include only effectiveness phase IV studies, all phase IV studies, or no phase IV studies.
- Non-covered costs need to be specified; remembering that sponsors, by regulation, may charge for devices and procedures, but not investigational drugs.
- Do not try to identify trial sponsors by name, but state the trial must be an approved trial (by the NIH or other government agencies, such as the VA).
- Coverage for all types of investigational treatments should be considered (not just drugs or devices).
- Be prepared to amend rules
- Exclude "reasonable expectation of benefit" clause. Several states specify that an agent have a reasonable expectation of benefit, but the benefit of agents in clinical trials is unknown; this is the purpose of clinical trials.

Coverage of routine medical costs for patients enrolled in clinical trials has potential benefit for patients with minimum impact on payers. Regardless of the result concerning legislation to mandate payment for routine costs, the Wyoming legislature is encouraged to join the Council of State Governments to lobby the US government to maintain or increase funding for research.

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APPENDIX A: CURRENT MEDICARE POLICY
See attached document

APPENDIX B: PROPOSED MEDICARE POLICY 2007

Proposed Decision Memo for Clinical Trial Policy (CAG-00071R2) COMMENT

Proposed Decision Memo

TO: Administrative File: CAG-00071R2
Clinical Research Policy

FROM: Steve Phurrough, MD, MPA
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DATE: July 19, 2007

SUBJECT: Proposed Decision Memorandum for Second Reconsideration of the Clinical Trial Policy, Renamed the Clinical Research Policy (CAG -00071R2)

I. Proposed Decision Summary

This memorandum announces the proposed determination of the Centers for Medicare & Medicaid Services (CMS) on whether items and services delivered as part of a clinical research study are reasonable and necessary. We propose the following revisions to the current Medicare Clinical Trial Policy (CTP), which we will rename as the Clinical Research Policy (CRP) in order to make clear the full scope of the policy.

1. Setting forth the scope of the policy by defining “clinical research” and renaming the overall NCD to clearly include all clinical research.
2. Replacing the requirements and other necessary characteristics for qualifying clinical trials under the Clinical Trial Policy with scientific and technical standards for certified clinical research studies.
3. Preserving CMS authority to permit Coverage with Evidence Development (CED) when appropriate.
4. Redefining coverage for qualifying clinical research studies or CED to avoid confusion with terms used in other contexts, using the term “usual patient care.”
5. Defining “routine clinical services” that are included in “usual patient care.”
6. Clarifying the extent to which “investigational clinical services” are included in “usual patient care.”
7. Clarifying that coverage does not include “administrative services” required to carry out studies but not required to furnish usual patient care.
8. Establishing a process that clinical research study sponsors/principal investigators must use to certify to CMS that their study meets the standards described in this policy.
9. Enumerating types of clinical research studies that are excluded from this policy.
10. Clarifying the relationship between coverage under this policy and local coverage determinations (LCDs).

These proposed changes are described in more detail below. The proposed NCD language is in the Appendix.
This second reconsideration proposed determination builds upon the input from the previous reconsideration. We are requesting public comments on this proposed determination pursuant to Section 731 of the Medicare Modernization Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

II. Background

On September 19, 2000, the Health Care Financing Administration (now CMS) implemented a CTP through the NCD

process. The CTP was developed in response to a June 7, 2000 Executive Memorandum. The NCD was set forth in the NCD Manual at section 310.1 (the 2000 NCD).
That 2000 NCD limited the payment for items and services provided to Medicare beneficiaries in qualified trials to routine costs. In general, the policy defined "routine costs" as those items and services that would generally be covered for Medicare beneficiaries outside a trial. As noted by commenters on the April 10, 2007 proposed decision memorandum, this definition contained language that was read as ambiguous with respect to the items or services that were the subject of the investigation.
In July 2006, CMS began a reconsideration of the 2000 NCD. CMS convened a Medicare Evidence Development & Coverage Advisory Committee (MedCAC) to obtain public input and provide recommendations to CMS; asked AHRQ to provide recommended changes, and received public comments on the proposed decision. After the publication of our proposed decision memorandum on April 10, 2007, we received several comments from hospitals and others suggesting that Medicare contractors had been paying claims involving patients in various types of clinical research outside the terms of the clinical trial policy. These claims may not have always been identified as clinical trial items or services. The commenters sought an assurance that funding will continue for the usual patient care associated with research in a hospital.
In addition, commenters identified additional Medicare policies and statements that are not identical to the coverage provided under the 2000 NCD, and the existence of these policies may have been confusing or ambiguous. As a result, in the initial reconsideration, CMS adopted only the following two proposed changes:

1. The addition of Coverage with Evidence Development (CED).
2. Clarification that the item under investigation was considered a routine cost if covered outside the trial.

III. Authority
In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, must not be otherwise excluded from coverage, and must be reasonable and necessary as defined in section 1862(a)(1)(A). Section 1862(a)(1)(A) is an exclusion of items and services that do not meet the reasonable and necessary standard which states:
Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—which, except for items and services described in a succeeding subparagraph, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member…
A succeeding subparagraph, section 1862(a)(1)(E), provides additional authority for coverage of items and services under certain federally funded or supported clinical research. This section states:
In the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section.
Generally, when making a national coverage determination, CMS evaluates whether or not items or services falling within Medicare benefit categories are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. We customarily review specific evidence to determine whether the item or service is reasonable and necessary in the specific intervention at issue and, as part of that review, whether the intervention will improve health outcomes for Medicare patients.
Evidence-based review is not feasible for the broad range of items or services that can be furnished to patients enrolled in a clinical research trial. As discussed below, CMS therefore relies on the integrity of the clinical research protocol in lieu of our usual evidence-based review. In this policy we extend Medicare coverage only to clinical research that is likely to result in evidence that we would accept to demonstrate that the specific interventions are reasonable and necessary, and that contain protections to maximize the improvement of health outcomes for Medicare patients. To that end, this policy includes standards for clinical research that are a condition of Medicare coverage.
IV. Discussion
During the two 30-day public comment periods of the initial reconsideration when CMS was first reconsidering the CTP, the Agency received public comments from 90 different groups and individuals. The comments originated from academic health centers, specialty research groups, the medical device and pharmaceutical industry, professional societies, advocacy and interest groups, and lawyers.
We discuss below the comments received during the initial reconsideration that led to this second reconsideration and the significant changes that are proposed in this second reconsideration. We will fully address all comments in our final decision memorandum.
A. GENERAL ISSUES
CMS received many comments stating that it appeared that the April 10, 2007 proposed decision would limit privately funded trials that were being paid prior to the announcement of that policy. This concern was based on an interpretation

that the 2000 Clinical Trial Policy established a second path to Medicare coverage of items and services within Federally funded trials, but did not restrict or otherwise affect Medicare coverage under privately funded trials. Because of this apparent confusion concerning the applicability of the 2000 NCD, we are proposing to set forth the scope of the policy by defining "clinical research" and renaming the overall NCD to include all clinical research. We are further proposing to replace the requirements for qualifying clinical trials with new standards that ensure that coverage for Medicare beneficiaries participating in research studies is consistent across all types of studies, including Federally funded and privately funded trials. We are also proposing to define the items or services that would be covered in qualifying clinical research to maintain consistency across the Medicare program (and making clear that coverage does not include administrative costs of the clinical research). We have reviewed the Medicare regulations, manual instructions, and other policy statements to ensure that this definition will be consistent with other Medicare policies. CMS is considering rulemaking to resolve these issues.

In addition to ensuring consistency of wording, we are proposing a process that will allow study sponsors/principal investigators to certify to CMS that their study meets the standards described in this policy. This modification will ensure that all qualifying clinical research studies, whether publicly funded or privately funded, will be eligible for coverage under the final NCD. More details of the proposed changes are discussed below.

B. SCOPE OF CLINICAL RESEARCH POLICY -- DEFINITION OF CLINICAL RESEARCH

Comments on the initial reconsideration indicated that the 2000 CTP was not clear in setting forth its overall scope; in particular, there was uncertainty as to whether its scope was limited to federal funded clinical trials. To clarify the scope of the policy, we propose to rename the policy as the Clinical Research Policy, and we propose to define clinical research. We had numerous requests for a definition during the previous reconsideration. We are proposing the following:

Clinical research, for purposes of this NCD, means any systematic investigation involving human participants which is designed to contribute to generalizable knowledge and which involves a clinical intervention, care delivery strategy, or diagnostic technique designed to potentially improve predefined health outcomes.

Some examples of the types of clinical research studies that might be supported follow, but this list should not be considered exhaustive:

- Randomized controlled trials and other comparative clinical studies of effectiveness and comparative effectiveness;
- Observational clinical studies of outcomes of specific interventions, primary and secondary prevention strategies, or of implemented strategies related to delivery of care or testing of hypotheses regarding health services research; and
- Clinical studies of diagnostic tests, including measurements of sensitivity and specificity, and impact on physician decision making and patient outcomes.

C. STANDARDS FOR CLINICAL RESEARCH TO SUPPORT MEDICARE COVERAGE OF ITEMS AND SERVICES

The purpose of technical and scientific standards is twofold; 1) to ensure that all sponsors and investigators conduct clinical research so that Medicare covered items and services are reasonable and necessary to obtain valid research outcomes and for treating research participants, and 2) to maximize the health outcomes (and minimize risk) for Medicare beneficiaries.

All bona fide disciplines that conduct research have standards that describe good research practices -- whether the research is in the field of management, health care, clinical trials, or marketing. It is imperative that all researchers adhere to the highest standards of integrity. In order for researchers to adhere to high standards, the standards must be credible and designed to apply to all research within the specific discipline. The rule at 42 CFR § 52(h) describes the scientific peer review of research grant applications and research and development contract projects for The National Institutes of Health.[1] In addition, 42 CFR § 52(h)(8) provides the specific criteria by which the peer review members must assess the study protocol for its overall impact on the research subject. Eight matters are specifically addressed as shown below:

(a) The significance of the goals of the proposed research, from a scientific or technical standpoint;
(b) The adequacy of the approach and methodology proposed to carry out the research;
(c) The innovativeness and originality of the proposed research;
(d) The qualifications and experience of the principal investigator and proposed staff;
(e) The scientific environment and reasonable availability of resources necessary to the research;
(f) The adequacy of plans to include both genders, minorities, children and special populations as appropriate for the scientific goals of the research;
(g) The reasonableness of the proposed budget and duration in relation to the proposed research; and

(h) The adequacy of the proposed protection for humans, animals, and the environment, to the extent they may be adversely affected by the project proposed in the application.

As with other federal agencies, CMS believes minimum standards for Medicare supported clinical research are needed to ensure that items and services furnished to Medicare beneficiaries in clinical research are reasonable and necessary, and for the protection of participants who volunteer to participate in studies, in this case Medicare beneficiaries. Any study that removes the ability of physicians and patients to make choices as to their healthcare exposes that patient to increased risks. In addition, there are numerous studies that are of little benefit to patients or to the Medicare program. Furthermore, CMS believes, in concert with other federal agencies, that appropriate study design is critical to ensure that not only are participants in research studies exposed to the least risk possible, but also to ensure that the results from the study will be useful in improving healthcare delivery. Poorly designed studies will likely produce results of little benefit in improving outcomes.

Thus, CMS is proposing to set forth scientific and technical standards for clinical research to be applied to clinical research in which providers, practitioners, or suppliers are requesting payment for usual patient care provided to Medicare beneficiaries participating in the study.

These standards were crafted purposely to update the 2000 CTP with input from other Federal Agencies that conduct health research, the MedCAC, and AHRQ. We are proposing that they be established as standards of a clinical research study in this revised Clinical Research Policy:

- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- The research study does not unjustifiably duplicate existing studies.
- The research study design is appropriate to answer the research question being asked in the study.
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated, it also must be in compliance with 21 CFR Parts 50 and 56.
- All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
- The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
- The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Studies of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- The clinical research study is registered on the ClinicalTrials.gov website by the study sponsor/principal investigator prior to the enrollment of the first study subject.
- The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

D. EXCLUSIONS FROM CLINICAL RESEARCH STANDARDS FOR MEDICARE COVERAGE OF ITEMS AND SERVICE.

During the initial reconsideration that resulted in the policy issued on July 9, 2007, commenters suggested that certain research studies that do not influence physician or patient behavior do not increase the risk to patients and, as such, should not be required to meet the clinical research standards outlined in the proposed CRP. We agree. Therefore, we propose the following language:

A number of data collection processes, while meeting the broad definition of a clinical research study, are based upon previously collected data, or data collected in such a manner as to not influence current patient management or health outcomes. The clinical items and services that are provided as the basis for these data collection processes may be determined to be reasonable and necessary under §1862(a)(1)(A).

These include:

- Simple non-comparative case reports and case series;
- Retrospective studies that evaluate events that have already occurred including studies that rely exclusively on previously collected administrative records, medical data or other available data;
- Quality assessment, quality improvement, or performance improvement studies; and
- Prospective studies in which natural human behavior is observed in a way that does not intentionally or unintentionally change or potentially change the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; in which there is no assigned or pre-specified intervention that intentionally or unintentionally changes or potentially changes the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; and in which there is no assigned or pre-specified intervention that changes or potentially changes medical care, medical decision-making or any medical treatments.

These studies are not required to meet the standards or approval processes outlined in this policy. All human subject protections and patient privacy rules continue to apply.

E. COVERED ITEMS AND SERVICES

The CTP provided for coverage of "routine costs" under a clinical trial, and contained certain specific included categories of covered items or services. The July 9, 2007 NCD amended the 2000 CTP to clarify that investigational items and services that would be covered outside a clinical trial would also be covered as routine costs, and also added coverage for items and services in clinical research trials for which there is some evidence of significant medical benefit, but for which there is insufficient evidence to support a "reasonable and necessary" determination (CED). The July 9, 2007 NCD provided that CED is determined through the NCD process, and is conditional on meeting standards for clinical research that ensures patient protection and the development of evidence to evaluate coverage.

In the initial reconsideration that led to the policy announced on July 9, 2007, we received numerous comments and recommendations to expand coverage to the item under investigation if it was covered outside the study. We had proposed in that reconsideration to define two (2) types of services that were eligible for coverage: routine clinical services and investigational clinical services. We learned from public comments that there was some confusion about the meaning of the term "routine care" and the proposed terms, in light of other definitions of those and similar terms in Medicare regulations and manuals.

To prevent confusion and provide consistency, we are proposing to adopt the term "usual patient care" in this NCD to define those items and services that are covered by Medicare in clinical research studies. The definition of usual patient care will include both routine and investigational clinical services.

Thus, CMS is proposing the following definitions:

Administrative services: Administrative services are defined as all non-clinical services, such as investigator or coordinator salaries; protocol development; recruiting participants; data quality assurance activities; statistical analyses; dissemination of findings; and study management. Administrative services also include clinical services provided to solely satisfy data collection and analysis needs that are not used in the direct clinical management of the patient.

Investigational clinical services: Investigational clinical services are defined as those items and services that are being investigated as an objective within the study. Investigational clinical services may include items or services that are approved, unapproved, or otherwise covered (or not covered) under Medicare.

Routine clinical services: Routine clinical services include items and services that:

- are covered for Medicare beneficiaries outside of the clinical research study;
- are used for the direct patient management within the study; and,
- do not meet the definition of investigational clinical services.

For example, routine clinical services include:

- items or services required solely for the provision of the investigational clinical services (e.g., administration of a chemotherapeutic agent);

- clinically appropriate monitoring, whether or not required by the investigational clinical service (e.g., blood tests to measure tumor markers); and
- items or services required for the prevention, diagnosis, or treatment of research related adverse events (e.g., blood levels of various parameters to measure kidney function).

Usual Patient Care: Usual patient care includes routine clinical services and investigational clinical services in clinical research when the investigational clinical services would be covered outside of the clinical research and the clinical research meets the standards for a clinical research study outlined in this policy.

In addition, we are proposing the following coverage determination:

Medicare covers usual patient care in qualified clinical research. Medicare does not cover usual patient care when such care is provided free to the Medicare beneficiary or when the study sponsor agreement with investigator sites or the informed consent documents provided to the patient specify that the care will be provided free to participants (§1862(a)(2); 42 CFR 411.4).

This proposal does not change any coverage requirement that has been developed through regulation, NCD or CMS manual instructions. Any restrictions that are applied to patient care through an NCD or local policies (including LCDs or claim adjudication) must be followed within a clinical research study unless modified through an NCD that provides CED. For more information on LCDs, see Section G below.

F. APPROVAL PROCESS

The 2000 CTP outlined two processes for ensuring that research studies enrolling Medicare beneficiaries met the standards of that policy: deeming and self-certification. Deeming allowed other Federal agencies to deem that the standards had been met through their funding and review process. Self-certification, in which trial sponsors could certify that the standards had been met, was never implemented.

During the last reconsideration of this policy, it became apparent that significant confusion existed about the deeming process and whether non-Federally funded trials were exempt from this process.

As an alternative to deeming or self-certification, many commenters recommended that Institutional Review Board (IRB) review is sufficient and that no approval process is necessary. The members of the MedCAC spent a considerable amount of time at the December 13, 2006 meeting discussing whether IRBs are appropriate mechanisms to approve clinical research studies for coverage by the Medicare program and recommended that IRB review is not sufficient to meet the goals of this policy. IRB review and CMS standards are aimed at different objectives. CMS standards are aimed to ensure that the research will generate evidence that can be used for determining Medicare coverage while IRB review is focused on informed consent and patient protection. IRBs have also expressed concern that they are underfunded to do scientific reviews of protocols, or assure that trials are registered at ClinicalTrials.gov. Thus, we do not believe it is appropriate for CMS to consider burdening IRBs to perform a more rigorous and time-consuming review that is beyond their primary purpose.

We received many comments during the initial reconsideration urging the Agency to implement the self-certification process outlined in the 2000 policy. We believe that until we clarify policy issues around coverage of usual patient care in clinical research studies through rulemaking, a self-certification process that allows study sponsors/principal investigators to certify that their study meets these standards will add appropriate protection for our Medicare beneficiaries.

Therefore, we are proposing the following:

CMS will cover usual patient care for beneficiaries enrolled in clinical research studies in which the study sponsor/principal investigator has certified to CMS that the standards in this policy have been met. CMS will notify beneficiaries, providers, and practitioners of those research studies that have certified compliance with this policy by posting the research study title and ClinicalTrials.gov registry number on our website and in the Federal Register. The ClinicalTrials.gov registry will also annotate this in its registry. Providers and practitioners will add appropriate information to their claims forms indicating that usual patient care provided to beneficiaries in research studies occurred in research studies that were listed on these sites as meeting the standards of the CRP.

Study sponsors/principal investigators wishing to have their research study listed as certified on our website, in the Federal Register and on ClinicalTrials.gov may send a letter to CMS describing the scope and nature of the clinical research, discussing each of the standards in this policy, and certifying that all standards in this policy have been met. CMS will only review this letter for completeness. Following approval of a Paperwork Reduction Act form, it will be provided on the CMS website to facilitate this submission. To be added to the list of certified studies, the letter should include the following information:

- Name of the research study
- ClinicalTrials.gov registry number ("NCT" followed by eight numbers)
- Study start date
- A point of contact with telephone number for questions if the letter is not complete.

- Discussion as to how the study meets each of the standards in this policy.

Letters should be submitted to:
Centers for Medicare & Medicaid Services
Office of Clinical Standards & Quality
Director, Coverage & Analysis Group
ATTN: Clinical Study Certification
Mailstop: C1-09-26
7500 Security Blvd
Baltimore, MD 21244

Additionally, CMS determined in the initial reconsideration that, through the national coverage determination (NCD) process, CMS may determine, through an individualized assessment of benefits, risks, and research potential, that certain items and services for which there is some evidence of significant medical benefit, but for which there is insufficient evidence to support an evidence-based determination, are reasonable and necessary only when provided in a clinical trial that meets the requirements defined in that NCD. This implemented the CED concept outlined in a previously published guidance document.[2] We will maintain this policy in this proposed decision.

G. LOCAL COVERAGE DETERMINATIONS

The 2000 CTP stated that local coverage determinations (LCDs) were not affected by the CTP. The language used resulted in confusion. Therefore, we are proposing that the CRP explain that items and services provided within clinical research studies are subject to local policies including LCDs and claim adjudication. We propose the following language:

Items and services provided within clinical research studies are subject to local policies including LCDs and claim adjudication. For information about LCDs, refer to http://www.cms.hhs.gov/DeterminationProcess/04_LCDs.asp#TopOfPage, a searchable database of Medicare contractors' local policies.

H. INVESTIGATIONAL DEVICE EXEMPTION (IDE)

The rule at 42 CFR Part 405 Subpart B specifically outlines the coverage criteria applicable to medical devices that have been provided an IDE by the FDA. This policy does not alter those criteria.

I. TRANSITION

This policy will not apply to any clinical research study that was covered under any previous policy that has begun enrollment prior to the effective date of this decision.

J. HUMANITARIAN DEVICE EXEMPTIONS

Since humanitarian use devices (HUDs) with an FDA approved humanitarian device exemption (HDE) are not addressed in this policy, local contractors may continue to make determinations about the coverage of HUDs.

V. Summary of Changes

In summary, CMS is proposing the following revisions to the current Medicare Clinical Trial Policy.

1) Setting forth the scope of the policy by defining “clinical research” and renaming the overall NCD to clearly include all clinical research.
2) Replacing the requirements and other necessary characteristics for qualifying clinical trials under the Clinical Trial Policy with scientific and technical standards for certified clinical research studies.
3) Preserving CMS authority to permit Coverage with Evidence Development (CED) when appropriate.
4) Redefining coverage for qualifying clinical research studies or CED to avoid confusion with terms used in other contexts, using the term “usual patient care.”
5) Defining “routine clinical services” that are included in “usual patient care.”
6) Clarifying the extent to which “investigational clinical services” are included in “usual patient care.”
7) Clarifying that coverage does not include “administrative services” required to carry out studies but not required to furnish usual patient care.
8) Establishing a process that clinical research study sponsors/principal investigators must use to certify to CMS that their study meets the standards described in this policy.
9) Enumerating types of clinical research studies that are excluded from this policy.
10) Clarifying the relationship between coverage under this policy and local coverage determinations (LCDs).

The proposed NCD language is in the Appendix.

Finally, CMS is considering rulemaking to resolve some of the issues uncovered during this NCD reconsideration process. We hope to issue a Notice of Proposed Rulemaking on this subject shortly.

NCD Manual 310.1: Clinical Research Policy

Effective for items and services furnished on or after XXX XX, 2007, Medicare covers usual patient care in a clinical research study, under the circumstances described more fully below. The subject or purpose of the study must be the

evaluation of an item or service that falls within a Medicare benefit category under Part A or Part B (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids). In addition, Medicare covers reasonable and necessary items and services used to prevent, diagnose, and treat complications arising from participation in these research studies.
Items and services furnished to Medicare beneficiaries in clinical research studies that do not meet the requirements of this policy are not covered.

1. Definitions.

Administrative services: Administrative services are defined as all non-clinical services, such as investigator and coordinator salaries; protocol development; recruiting participants; data quality assurance activities; statistical analyses; dissemination of findings; and study management. Administrative services also include clinical services provided to solely satisfy data collection and analysis needs that are not used in the direct clinical management of the patient.

Clinical research: Clinical research, for purposes of this NCD, means any systematic investigation involving human participants which is designed to contribute to generalizable knowledge and which involves a clinical intervention, care delivery strategy, or diagnostic technique designed to potentially improve predefined health outcomes.

Investigational clinical services: Investigational clinical services are defined as those items and services that are being investigated as an objective within the study. Investigational clinical services may include items or services that are approved, unapproved, or otherwise covered (or not covered) under Medicare.

National Coverage Determination Coverage with Evidence Development (CED) standards*:* Using the national coverage determination (NCD) process, the Centers for Medicare & Medicaid Services may determine, through an individualized assessment of benefits, risks, and research potential, that certain items and services for which there is some evidence of significant medical benefit, but for which there is insufficient evidence to support an evidence-based determination, are reasonable and necessary only when provided in clinical research that meets the requirements defined in that NCD.

Routine clinical services: Routine clinical services include items and services that:

- are covered for Medicare beneficiaries outside of a clinical research study;
- are used for the direct patient management within the study; and
- do not meet the definition of investigational clinical services.

For example, routine clinical services include:

- items or services required solely for the provision of the investigational clinical services (e.g., administration of a chemotherapeutic agent);
- clinically appropriate monitoring, whether or not required by the investigational clinical service (e.g., blood tests to measure tumor markers); and
- items or services required for the prevention, diagnosis, or treatment of research related adverse events (e.g., blood levels of various parameters to measure kidney function).

Usual Patient Care: Usual patient care includes routine clinical services and investigational clinical services in clinical research when the investigational clinical services would be covered outside of the clinical research and the clinical research meets the standards of a clinical research study defined in this policy.

2. Standards for clinical research to support Medicare coverage of items and services.

Medicare will cover items and services furnished through clinical research only when the following standards are met:

- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- The research study does not unjustifiably duplicate existing studies.
- The research study design is appropriate to answer the research question being asked in the study.
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated, it also must be in compliance with 21 CFR Parts 50 and 56.

- All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
- The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
- The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Studies of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR 312.81(a) and the patient has no other viable treatment options.
- The clinical research study is registered on the ClinicalTrials.gov website by the study sponsor/principal investigator prior to the enrollment of the first study subject.
- The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Exclusions from Required Standards: A number of data collection processes, while meeting the broad definition of a clinical research study, are based upon previously collected data, or data collected in such a manner as to not influence current patient management or health outcomes. The clinical items and services that are provided as the basis for these data collection processes may be determined to be reasonable and necessary under §1862(a)(1)(A).
These include:

- Simple non-comparative case reports and case series;
- Retrospective studies that evaluate events that have already occurred including studies that rely exclusively on previously collected administrative records, medical data or other available data;
- Quality assessment, quality improvement, or performance improvement studies; and
- Prospective studies in which natural human behavior is observed in a way that does not intentionally or unintentionally change or potentially change the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; in which there is no assigned or pre-specified intervention that intentionally or unintentionally changes or potentially changes the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; and in which there is no assigned or pre-specified intervention that changes or potentially changes medical care, medical decision-making or any medical treatments.

These studies are not required to meet the standards or approval processes outlined in this policy. All human subject protections and patient privacy rules continue to apply.

3. Coverage of Usual Patient Care and Coverage with Evidence Development.

Using processes outlined in this policy, Medicare covers usual patient care as defined in this policy. Medicare does not cover usual patient care when it is provided free to the Medicare beneficiary or when the study sponsor agreement with an investigator site or the informed consent documents provided to the patient specify that the clinical service will be provided free to all enrollees (§1862(a)(2); 42 CFR 411.4).

Through the national coverage determination (NCD) process, CMS may determine, through an individualized assessment of benefits, risks, and research potential, that certain items and services for which there is some evidence of significant medical benefit, but for which there is insufficient evidence to support an evidence-based determination, are reasonable and necessary only when provided in a clinical study that meets the requirements defined in that NCD.

4. Non-Coverage of Administrative Services.

Administrative services, as defined in this policy, in a clinical research study are not covered by Medicare.

5. Approval Process.

Effective XXXX, XX, 2007, CMS will cover usual patient care for beneficiaries enrolled in clinical research studies in which the study sponsor/principal investigator has certified to CMS that the standards as defined in this policy have been met. CMS will notify beneficiaries, providers, and practitioners of those research studies that have certified compliance with this policy by posting the research study title and ClinicalTrials.gov registry number on our website and in the Federal Register. The ClinicalTrials.gov registry will also annotate this in its registry. Providers and practitioners will add code modifiers and the ClinicalTrials.gov registry number to their claims forms indicating that usual patient care provided to beneficiaries in research studies occurred in research studies that were listed on the above sites as meeting the standards of the CRP.

Study sponsors/principal investigators wishing to have their research study listed as certified on our website, in the Federal Register and on ClinicalTrials.gov may send a letter to CMS describing the scope and nature of the clinical research, discussing each of the standards in this policy, and certifying that all standards in this policy have been met. CMS will only review this letter for completeness. Following approval of a Paperwork Reduction Act form, it will be provided on the CMS website to facilitate this submission. To be added to the list of certified studies, the letter should include the following information:

- Name of the research study
- ClinicalTrials.gov registry number ("NCT" followed by eight numbers)
- Study start date
- A point of contact with telephone number for questions if the letter is not complete.
- Discussion as to how the study meets each of the standards in this policy.

Letters should be submitted to:
Centers for Medicare & Medicaid Services
Office of Clinical Standards & Quality
Director, Coverage & Analysis Group
ATTN: Clinical Study Certification
Mailstop: C1-09-26
7500 Security Blvd
Baltimore, MD 21244

Clinical research studies required under CED will meet the approval process outlined in that NCD.

6. Exceptions.

Medicare will pay for covered services in clinical research studies where the study sponsor/principal investigator has certified that the study meets the standards as defined in this policy unless the CMS' Chief Medical Officer finds that the study does not meet the criteria outlined in this policy or the study jeopardizes the health or safety of Medicare beneficiaries.

7. Local Coverage Determinations.

Items and services provided within clinical research studies are subject to local policies including LCDs and claim adjudication. For information about LCDs, refer to http://www.cms.hhs.gov/DeterminationProcess/04_LCDs.asp#TopOfPage, a searchable database of Medicare contractors' local policies.

8. Investigational Device Exemption (IDE).

This policy is not applicable to, and does not change Medicare coverage according to the regulations on category A and category B investigational device exemptions (IDE) found in 42 CFR 405.201-405.215, 411.15, and 411.406.

9. Humanitarian Device Exemptions.

Since humanitarian use devices (HUDs) with an FDA approved humanitarian device exemption (HDE) are not addressed in this policy, local contractors may continue to make determinations about the coverage of HUDs.

10. Medicare Prescription Drug Benefit.

This policy is not applicable to and does not propose any changes to Medicare policies for coverage of prescription drugs under Medicare Part D.

11. Transition Plan.

This policy will not apply to any clinical research study that was covered under any previous policy that has begun enrollment prior to the effective date of this decision.

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[1] http://www.access.gpo.gov/nara/cfr/waisidx_05/42cfr52h_05.html

[2] http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8

APPENDIX C: CANCER CLINICAL TRIAL CONSENT FORM REVIEW

Appendix C: Cancer Clinical Trial Consent Form Review

Cancer Type	Study Number	Study Phase	Funding Source	Patient Payment	Study Drugs	Other Study Drugs	Study Protocol Costs	Study Toxicity	Protocol Procedure Described
Bladder	1	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Brain	1	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Brain	2	I/II	NCI	No	Prot	Pt	Prot	Pt	Yes
Brain	3	II	NCI	No	Prot	Pt	Prot	Pt	Yes
Brain	4	III	NCI	No	NA	NA	Pt	Pt	Yes
Breast	1	III	NCI	No	Pt	Pt	Pt	Pt	Yes
Breast	2	IV	NCI	No	NA	NA	Prot	Pt	Yes
Breast	3	III	NCI / Pharma	No	Prot	Prot	Pt	Pt	Yes
Breast	4	III	NCI / Pharma	No	Prot	Prot	Pt	Pt	Yes
Breast	5	III	NCI	No	NA	NA	Prot	Pt	Yes
Breast	6	III	Other Consortium	No	NA	Na	Pt	Pt	Yes
Breast	7	III	Other Consortium	No	Prot	Pt	Prot	Pt	Yes

Cancer Type	Study Number	Study Phase	Funding Source	Patient Payment	Study Drugs	Other Study Drugs	Study Protocol Costs	Study Toxicity	Protocol Procedure Described
Breast	8	III	Other Consortium	No	Prot	Pt	Pt	Pt	Yes
Breast	9	III	Other Consortium	No	Prot	Pt	Pt	Pt	Yes
Breast	10	III	Other Consortium	No	Prot	Pt	Pt	Pt	Yes
Breast	11	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Breast	12	II	NCI	No	Pt	Pt	Pt	Pt	Yes
Breast	13	II	NCI / Pharma	No	Pt	Pt	Prot	Pt	Yes
Breast	14	II	NCI / Pharma	No	Prot	Pt	Prot	Pt	Yes
Breast	15	II	NCI	No	Prot	Pt	Pt	Pt	Yes
Breast	16	III	NCI	No	NA	Pt	Prot	Pt	Yes
Breast	17	III	NCI	No	Prot	Pt	Pt	Pt	Yes
Breast	18	III	NCI	No	Prot	Pt	Pt	Pt	yes
Cervical	1	III	NCI	No	Prot	Pt	Pt & Prot	Pt	Yes

Cancer Type	Study Number	Study Phase	Funding Source	Patient Payment	Study Drugs	Other Study Drugs	Study Protocol Costs	Study Toxicity	Protocol Procedure Described
Colon - Rectal	1	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Colon - Rectal	2	II	Pharma	No	Prot	Pt	Prot & PT	Pt	Yes
Colon - Rectal	3	III	NCI / Pharma	No	Prot	Prot / Pt	Pt	Pt	Yes
Colon - Rectal	4	II	NCI	No	Pt	Pt	Pt	Pt	Yes
Colon - Rectal	5	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Colon - Rectal	6	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Colon - Rectal	7	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Colon - Rectal	8	III	NCI	No	Prot	Pt	Pt	Pt	Yes
Endometrial	1	III	NCI	No	Pt	Pt	Pt	Pt	Yes
Esophageal	1	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Esophageal	2	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Head & Neck	1	III	NCI	No	Prot	Pt	Pt	Pt	Yes
Head & Neck	2	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Head & Neck	3	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes

Cancer Type	Study Number	Study Phase	Funding Source	Patient Payment	Study Drugs	Other Study Drugs	Study Protocol Costs	Study Toxicity	Protocol Procedure Described
Leukemia	1	I	NCI	No	NA	NA	Prot	Pt	Yes
Leukemia	2	IIb	NCI	No	Prot	Pt	Pt	Pt	Yes
Leukemia	3	II	NCI	No	Pt	Pt	Pt	Pt	Yes
Leukemia	4	III	NCI	No	NA	NA	Pt	Pt	Yes
Leukemia	5	I	NCI	No	NA	NA	Pt	Pt	Yes
Leukemia	6	II	NCI	No	Prot	Pt	Pt	Pt	Yes
Leukemia	7	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Leukemia	8	II	NCI / Pharma	No	Pt	Pt	Pt	Pt	Yes
Leukemia	9	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Leukemia	10	IV	NCI	No	NA	NA	NA	Pt	Yes
Leukemia	11	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Leukemia	12	I	NCI	No	Prot	Pt	Pt	Pt	Yes
Leukemia	13	III	NCI	No	Pt	Pt	Pt	Pt	Yes
Leukemia	14	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Leukemia	15	III	NCI	No	Prot	Pt	Prot	Pt	Yes
Leukemia	16	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes

Cancer Type	Study Number	Study Phase	Funding Source	Patient Payment	Study Drugs	Other Study Drugs	Study Protocol Costs	Study Toxicity	Protocol Procedure Described
Leukemia	17	III	NCI	No	Pt	Pt	Prot	Pt	Yes
Leukemia	18	III	Pharma	No	Prot	Pt	Pt	Pt	Yes
Leukemia	19	II	NCI	No	Prot	Pt	Pt	Pt	Yes
Leukemia	20	II	Pharma	No	Prot	Pt	Pt	Pt	Yes
Leukemia	21	III	NCI	No	NA	NA	Prot	Pt	Yes
Lung	1	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Lung	2	II	Pharma	No	Prot	Pt	Prot	Pt	Yes
Lung	3	II	NCI	No	NA	NA	Prot	NA	Yes
Lung	4	III	NCI	No	NA	NA	Prot	NA	Yes
Mantle Cell	1	II	Pharma	No	Prot	Pt	Prot	Pt	Yes
Mantle Cell	2	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Melanoma	1	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Melanoma	2	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes

Cancer Type	Study Number	Study Phase	Funding Source	Patient Payment	Study Drugs	Other Study Drugs	Study Protocol Costs	Study Toxicity	Protocol Procedure Described
Melanoma	3	III	NCI	No	Prot	Pt	Pt	Pt	Yes
Melanoma	4	II	NCI	No	Prot	Prot	Prot	Pt	Yes
Myeloma	1	III	NCI	No	Prot	Pt	Pt	Pt	Yes
Myeloma	2	II	NCI	No	Pt	Pt	Pt	Pt	Yes
Myeloma	3	IV	NCI	No	NA	NA	Pt	Pt	Yes
Myeloma	4	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Non-Hodgkin's	1	III	NCI	No	NA	Pt	Pt	Pt	Yes
Non-Hodgkin's	2	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Non-Hodgkin's	3	II	NCI	No	Pt	Pt	Pt	Pt	Yes
Non-Hodgkin's	4	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Non-Hodgkin's	5	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Non-Hodgkin's	6	II	NCI / Pharma	No	Prot	Pt	Prot	Pt	Yes
Non-Hodgkin's	7	III	NCI	No	Pt	Pt	Prot	Pt	Yes
Non-Hodgkin's	8	III	NCI	No	Pt	Pt	Prot & Pt	Pt	Yes

Cancer Type	Study Number	Study Phase	Funding Source	Patient Payment	Study Drugs	Other Study Drugs	Study Protocol Costs	Study Toxicity	Protocol Procedure Described
Ovarian	1	III	NCI	No	Prot	Pt	Pt	Pt	Yes
Ovarian	2	III	NCI	No	Prot	Pt	Pt & Prot	Pt	Yes
Ovarian	3	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Pancreas	1	II	NCI	No	Prot	Pt	Pt	Pt	Yes
Prostate	1	II	NCI	No	Prot	Pt	Pt	Pt	Yes
Prostate	2	II	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Prostate	3	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Prostate	4	III	NCI	No	Prot	Pt	Pt	Pt	Yes
Prostate	5	III	NCI / Pharma	No	Prot	Pt	Pt	Pt	Yes
Prostate	6	III	NCI	No	Prot	Pt	Pt	Pt	Yes
Prostate	7	III	NCI	No	Prot	Pt	Pt	Pt	Yes
Prostate	8	II	NCI	No	Pt	Pt	Pt	Pt	Yes
Prostate	9	III	NCI	No	NA	NA	Pt	Pt	Yes
Prostate	10	III	NCI	No	Prot	Pt	Pt	Pt	Yes

Cancer Type	Study Number	Study Phase	Funding Source	Patient Payment	Study Drugs	Other Study Drugs	Study Protocol Costs	Study Toxicity	Protocol Procedure Described
Renal	1	III	Pharma	No	Prot	Pt	Prot	Pt	Yes
Sarcoma	1	II	NCI	No	Prot	Pt	Pt	Pt	Yes
Sarcoma	2	II	Pharma	No	Prot	Pt	Pt	Pt	Yes
Sarcoma	3	IV	NCI	No	NA	NA	Prot	NA	Yes
Stomach	1	II	NCI	No	Pt	Pt	Pt	Pt	Yes
Stomach	2	III	NCI	No	Pt	Pt	Pt	Pt	Yes

APPENDIX D: STATE LEVEL INSURANCE MANDATES

Appendix D: State-Level Insurance Mandates

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
AZ	2001	Private insurers and managed care plans		I-IV	• National Institutes of Health (NIH) • NIH cooperative group or center • U.S. FDA (in the form of an Investigational New Drug Application) • U.S. Department of Defense • U.S. Department of Veterans Affairs • A qualified research entity that meets NIH criteria for grant eligibility • A panel of qualified clinical research experts from academic health institutions in the state.	Yes	treatment, palliation (supportive care) (supportive care) or prevention of cancer	
CA	2001	All California insurers, including the state's Medicaid program and other medical assistance programs.		I-IV	• National Institutes of Health (NIH) • U.S. Food and Drug Administration • U.S. Department of Defense • U.S. Department of Veterans Affairs	Plan may restrict coverage to services in California	treatment of cancer	

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
CT	2002	Private insurers, including individual and group health plans		Not specified, however treatment in any phase could be covered	• National Institutes of Health (NIH) • National Cancer Institute cooperative group or center • U.S. Food and Drug Administration • U.S. Department of Defense • U.S. Department of Veterans Affairs		treatment, palliation (supportive care), or prevention of cancer	• Prevention trials are covered only in Phase III and only if they involve therapeutic intervention. • Insurer may require documentation of the likelihood of therapeutic benefit, informed consent, protocol information and test results, and/or a summary of costs involved.
DE	2001	Every group or blanket policy		II-III	• National Institutes of Health (NIH) • NIH cooperative group or center • U.S. Department of Defense • U.S. Department of Veterans Affairs • Institutional Review Board that has a Multiple Project Assurance (MPA) from the U.S. Department of Health and Human Services' Office for Human Research Protections. • A qualified research entity that meets the criteria for NIH Center Support grant eligibility.		treatment, palliation (supportive care), or prevention of cancer	• The trial must have therapeutic intent and enroll individuals diagnosed with the disease. • The trial must not be designed exclusively to test toxicity or disease pathophysiology (the functional changes that accompany a particular syndrome or disease)

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
GA	2002	Kaiser, BCBS of Georgia, United Health Care, Aetna, Humana, Coventry, OneHealth, Cigna, The GA Dept of Community Health (the State Health Benefit Plan, Medicaid, and PeachCare).	Yes	I-IV	• National Institutes of Health (NIH) • an NIH-sponsored cooperative group or center • U.S. Department of Defense • U.S. Department of Veterans Affairs • U.S. Food and Drug Administration • An Institutional Review Board of any accredited school of medicine, nursing, or pharmacy in the State of Georgia OR • the trial must involve a drug that is currently exempt under federal regulations from a new drug application			
GA	1998	all health plans in Georgia	Yes	II-III	• U.S. Food and Drug Administration • U.S. National Cancer Institute			• Requires reimbursement of patient care costs associated with a dependent child's participation in a phase II or phase III cancer clinical trial that is testing prescription drugs. • The child has to have been diagnosed with cancer prior to his or her nineteenth birthday

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
LA	1999	Health maintenance organizations, preferred provider organizations, the State Employee Benefits Group Program, other specified insurers.		II-IV	• A cooperative group funded by a component of the National Institutes of Health • U.S. Food and Drug Administration • U.S. Department of Veterans Affairs • U.S. Department of Defense • A federally funded general clinical research center • The Coalition of National Cancer Cooperative Groups (Also, the clinical trial protocol must have been reviewed and approved by a qualified IRB operating within the state that has a multiple project assurance contract approved by the Office of Protection from Research Risks, U.S. Department of Health and Human Services).		treatment, supportive care, early detection, and prevention of cancer	
ME	1999	Managed care organizations and private insurers		Not specified	• National Institutes of Health (NIH) • An NIH-sponsored cooperative group or center • U.S. Department of Health and Human Services		treatment for a life-threatening or serious illness for which no standard treatment is effective.	• Participation must offer meaningful potential for significant clinical benefit to the enrollee. • Referring physician must conclude that trial participation is appropriate

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
MD	1998	Private insurers and other specified managed care plans		I-IV	• National Institutes of Health (NIH) • An NIH-sponsored cooperative group or center • U.S. Department of Veterans Affairs • U.S. Food and Drug Administration OR • The trial must be conducted by an academic medical center in Maryland		cancer & other life-threatening treatment, supportive care, early detection, and prevention trials	
MA	2003	All health plans issued or renewed after January 1, 2003.		I-IV	• National Institutes of Health (NIH) • An NIH-sponsored cooperative group or center • U.S. Department of Defense • U.S. Department of Veterans Affairs • U.S. Food and Drug Administration • A qualified non-government research entity (Trial must also be peer-reviewed)			• Insurers must provide payment for services that are "consistent with the usual and customary standard of care" provided under the trial's protocol and that would be covered if the patient did not participate in the trial.

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
MI	2002	Private insurance plans, HMOs and the Michigan Medicaid Program		II-III	• National Institutes of Health (NIH) • National Cancer Institute • U.S. Food and Drug Administration • U.S. Department of Defense • U.S. Department of Veterans Affairs • Centers for Medicare and Medicaid Services • Centers for Disease Control and Prevention			• Coverage for Phase I trials is under consideration
MO	2002	All health benefit plans operating in the state.		III-IV	• National Institutes of Health (NIH) • NIH Cooperative Group or Center • U.S. Food and Drug Administration • U.S. Department of Defense • U.S. Department of Veterans Affairs • An Institutional Review Board in Missouri that has been approved by the U.S. Department of Health and Human Services • A qualified research entitity that meets the criteria for NIH Center support grant eligibility		prevention, early detection, or treatment of cancer	• Requires coverage of FDA-approved drugs and devices used in cancer clinical trials even if those drugs and devices have not been approved for use in treatment of the patient's particular condition. • Coverage for Phase I and II cancer trials is under consideration.

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
NV	2004	Private insurers and managed care plans		I-IV	• National Institutes of Health (NIH) • NIH cooperative group • U.S. Food and Drug Administration (FDA) • U.S. Department of Veterans Affairs • U.S. Department of Defense	Yes	treatment of cancer	• Phase I clinical trials for the treatment of cancer, and phase II, III, and IV clinical trials for the treatment of cancer or chronic fatigue syndrome • Requirement that there is no medical treatment available that is considered more appropriate treatment than the treatment provided in the clinical trial. • Trial must be conducted in Nevada
NH	2001	Private insurers and specified managed care plans		I-IV (I on a case-by-case bases)	• National Institutes of Health (NIH) • NIH cooperative group or center • U.S. Food and Drug Administration • U.S. Department of Veterans Affairs • U.S. Department of Defense • An IRB of an institution in New Hampshire with a Multiple Project Assurance (MPA) from the U.S. Department of Health and Human Services' Office for Human Research Protections		cancer and other life-threatening conditions	• Trials are covered when standard treatment has been or would be ineffective or does not exist, or when there is no clearly superior noninvestigational alternative. • Coverage is also required for reasonable and medically necessary services to administer the drug or device under evaluation in the clinical trial.

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
NJ	1999	All insurers in the state, including those affiliated with the New Jersey Association of Health Plans.		I-IV	• National Institutes of Health (NIH) • NIH cooperative group or center • U.S. Food and Drug Administration • U.S. Dept of Defense • U.S. Dept of Veterans Affairs			
NM	2001	Private insurers, specified managed care plans, and Medicaid and other state medical assistance programs.		I-IV	• National Institutes of Health (NIH) • NIH cooperative group or center • U.S. Food and Drug Administration (under an Investigational New Drug application) • U.S. Dept of Defense • U.S. Dept of Veterans Affairs • Research entities meeting NIH grant standards.		early detection, treatment, palliation (supportive care), or prevention of recurrence of cancer	• Legislation is effective through July 1, 2009 (as per Senate Bill 73). • Trial must have therapeutic intent. • Payment is limited to in-state or in-network costs, unless the plan covers standard out-of-state or out-of-network treatment
NC	2002	All health insurance plans and the teachers' and state employees' comp major medical plan		II-IV	• National Institutes of Health (NIH) • NIH cooperative group or center • U.S. Food and Drug Administration • CDC • Agency for Healthcare Research and Quality • U.S. Dept of Defense • U.S. Dept of Veterans Affairs		treatment of a life-threatening condition	• Patients suffering from a life-threatening disease or chronic condition may designate a specialist to coordinate their health care needs as their primary care physician. The law also established an Office of Managed Care Patient Assistance.

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OH	1999	Ohio Med Plan (Ohio state employees)		II-III	• National Cancer Institute-sponsored Phase II and III cancer treatment clinical trials			• Preauthorization is required for clinical trial participation.
RI	1995 & 1998	Private insurers and specified managed care plans		II-IV	• National Institutes of Health (NIH) • A community clinical oncology program • U.S. Food and Drug Administration • U.S. Department of Veterans Affairs • A qualified nongovernmental research entity, as identified by an NIH support grant.			
TN	2005	Any health benefit plan offered by an employer; excludes individually underwritten health insurance policies		I-IV	• National Institutes of Health (NIH) • U.S. Food and Drug Administration (FDA) (in the form of an Investigational New Drug Application) • U.S. Department of Defense • U.S. Department of Veterans Affairs		treatment of cancer	• The subject of the trial must evaluate a drug, medical device or service that falls within a Medicare benefit category. • Limits coverage to those drugs, medical devices, and services that have been approved by the FDA and that are used in the clinical managment of the patient.

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
VT	2002 & 2005	All health insurance policies and health benefit plans issued in Vermont, including the Vermont Medicaid program.		Not specified	• The Vermont Cancer Center at Fletcher Allen Health Care • The Norris Cotton Cancer Center at Dartmouth-Hitchcock Medical Center. • If no suitable trial is available at the above locations, the law covers approved cancer clinical trials being administered by a hospital and its affiliated, qualified cancer care providers in or outside the state of Vermont.	Yes		• Participants in cancer trials located outside Vermont must provide notice to the health benefit plan prior to their participation. • Health insurers are permitted to require patients participating in a trial outside the provider network to receive routine follow-up care within the plan's network, unless the patient's cancer care provider determines this would not be in the best interest of the patient. • Cancer care providers and the state's four largest health insurers are required to participate in a cost analysis to determine the impact of the program on health insurance premiums

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
VA	1999	Private insurers, specified managed care plans, and public employee health plans.		II-IV (I on Case-by-Case basis)	• National Cancer Institute (NCI) • NCI cooperative group or center • U.S. Food and Drug Administration • U.S. Department of Defense • U.S. Department of Veterans Affairs • An Institutional Review Board of a Virginia institution with a Multiple Project Assurance (MPA) from the U.S. Department of Health and Human Services' Office for Human Research Protections.			

State	Year	Mandated Payers	Child Coverage Explicitly Stated	Phases Covered	Studies Must Be Approved or Run By:	Research Must be Conducted Within State	Type of Trial	Unique Features
WV	2003	Private insurers, managed care plans, Medicaid or state medical assistance, public employee health plans.		II-IV	• The clinical trial must be approved by one of the following:National Institutes of Health (NIH) NIH-sponsored cooperative group or center U.S. Food and Drug Administration (FDA) U.S. Department of Veterans Affairs The Institutional Review Board (IRB) of an institution in West Virginia that has a multiple project assurance contract approved by the NIH Office of Protection from Research Risks		prevention, early detection, or treatment of cancer, or for the treatment of any other life-threatening condition.	• The treatment must have therapeutic intent. • Does not require reimbursement for clinical trials intended to: o Extend the patent of any existing drug. o Gain approval of or coverage for a metabolite of an existing drug. o Gain approval or coverage relating to additional clinical indications for an existing drug. o Keep a generic version of a drug from coming to market. o Gain approval of or coverage for reformulated or repackaged version of an existing drug.
WI	2006	All health benefit plans operating in the state, including self-insured plans.		I-IV	• National Institutes of Health (NIH) • NIH Cooperative Group or Center • U.S. Food and Drug Administration • U.S. Department of Defense • U.S. Department of Veterans Affairs		treatment	• The cancer trial must have therapeutic intent, not exclusively testing toxicity or disease pathophysiology.
• **Source (http://www.cancer.gov/clinicaltrials/developments/laws-about-clinical-trial-costs-all-states) Accessed August 10, 2007**								