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Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies

Prepared by Battelle Technology Partnership Practice

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Executive Summary

Developing a new medicine is a long and complex process, with risk of failure at every step. The R&D process from basic science to preclinical and clinical research to approval of new treatments for patients is shared across a robust R&D ecosystem in the U.S. Industry, government, academia, non-profit organizations, patient advocacy groups, health care providers and others engage all play complementary roles in bringing new medical advances to patients.

The innovative biopharmaceutical industry accounts for the vast majority of investments in clinical trials of potential new medicines at the clinical site level. As there has been interest in better understanding how the conduct of clinical trials at the site level generates economic activity in states, this report provides state-level estimates of industry-sponsored clinical trial activity across the country, including the number of trials, the number of trial participants, and the economic impact. Each state's economic impact estimate includes the annual direct investment companies have made to run clinical trial sites in the state, as well as the indirect economic effects that rippled through these local economies as a result of that investment in 2013.

This report focuses solely on investments at clinical trial sites, which are only a portion of the full economic impact of the R&D enterprise supported by the U.S. biopharmaceutical industry. In addition to excluding pre-discovery and preclinical research and other activities related to clinical trial design, management coordination, and analysis, as well as any other activities occurring beyond the operations at the site level in specific states were beyond the scope of this research. The report also excludes the large nationwide economic impact associated with non-R&D activities such as manufacturing and distribution.[1]

Key findings from this report include:

- **In 2013 the biopharmaceutical industry sponsored 6,199 clinical trials of medicines in the U.S., involving a total of 1.1 million participants.** Trials occurred in all 50 states and the District of Columbia.
- **The biopharmaceutical industry spent nearly $10 billion directly in the conduct of clinical trials at the site level across the U.S. in 2013.** These amounts are *in addition to* the significant resources invested in clinical trial-related activities occurring outside the individual trial sites, either within biopharmaceutical company facilities or by their contractors and vendors.
- **When considering the overall impact of site-specific clinical trial activity across states, i.e., the ripple effect of expenditures by clinical trial vendors and contractors and spending by industry and vendor employees, biopharmaceutical industry sponsored clinical trials generated a total of $25 billion in economic activity in communities throughout the U.S.**
- **The five states with the highest number of active clinical trial sites were California (3,111), Texas (2,799), Florida (2,571), New York (2,476), and Pennsylvania (1,972).** Only 7 states plus the District of Columbia had fewer than 200 clinical trial sites. Industry sponsored clinical trial investments

[1] The industry's total nationwide economic impact, including clinical trials and the many other activities conducted or supported by U.S. biopharmaceutical companies, have been documented elsewhere. For example, see Battelle Technology Partnership Practice, *The Economic Impact of the U.S. Biopharmaceutical Industry*, July 2013.

were distributed throughout the 50 states, with sizable spending in some states not typically associated with a large biopharmaceutical industry presence, e.g., Ohio and Tennessee.

Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies

Introduction

The U.S. innovative biopharmaceutical continues to lead the world in the development of new medicines. Over the past 20 years, the industry has continued to harness the potential of new scientific and technological advances, including using new learnings from the mapping of the human genome to expand possibilities for treating disease. The potential of the research and development (R&D) pipeline has never been greater at the same time the need for new treatments against some of our most costly and challenging diseases has never been greater.

While many important activities help advance potential medicines to the clinical testing stage in human volunteers, this report focuses on the clinical trials process. The potential medicines in clinical trials today are the therapies that have the potential to drive new treatments and potential cures over the next 5 to 10 years for a range of diseases and conditions, from addressing the substantial unmet medical need in diabetes and cardiovascular diseases to rare diseases for which there are few or no effective treatments. Clinical trials, the rigorous and highly controlled process required to demonstrate a medicine's safety and efficacy for approval by the U.S. Food and Drug Administration (FDA) for use by patients represent the most resource intensive part of the R&D process. Beyond the often profound value to society created by medicines themselves, the major resource investments required to identify clinical trial sites; hire staff and contractors; recruit, retain, and treat patients; and conduct various other clinical trial activities at the clinical site level create significant value for local communities across the United States. These economic impacts or value also typically have a wider geographic reach than any other stage of the R&D process.

The innovative biopharmaceutical industry accounts for the vast majority of investments in clinical trials of potential new medicines at the clinical site level. As there has been interested in better understanding how the conduct of clinical trials at the site level generate economic activity in states, this report provides state-level estimates of industry-sponsored clinical trial activity across the country, including the number of trials, the number of trial participants, and the economic impact.

This report provides an overview of the R&D process, describing the clinical testing phases that are the focus of the report, provides background and discussion on how we estimated the number of industry-sponsored clinical trials and trial participants by state, describes the approach to estimating the costs of conducting clinical research at local trials sites, and then reports estimates of the economic impact of industry-sponsored research at the site level and discusses the implications for policymakers.

Overview of the Clinical Trials and the R&D Process

We found that in 2013 alone the biopharmaceutical industry sponsored 6,199 clinical trials of medicines in the U.S., involving more than 1 million participants. A recent study found that there are more than 5,000 medicines in the drug development pipeline worldwide with the potential to aid U.S. patients. About 70% of the potential medicines in development represent novel approaches to addressing disease in such areas as neurology, cancer, diabetes, and immunology.[2] New scientific approaches representing the cutting edge of research are being explored across a range of therapeutic areas in clinical trials around the country, including new cell and gene therapies, and targeted therapies often referred to as precision medicines or personalized medicines.

These potential medicines are all in some stage of clinical testing, that is, controlled trials in volunteer participants designed to demonstrate whether they are safe and effective. While the clinical trials process is long, complex and costly, the drug discovery and development process begins even earlier, with initial discovery (discovering a potential target and then an investigational compound to impact that target), followed by pre-clinical testing in the lab and with animals to determine if the potential new medicine is safe for human testing. The key elements of the R&D process are described below, with particular attention paid to the clinical trials process. This material is adapted from the U.S. Food and Drug Administration (FDA) website.

Discovery and Preclinical Testing

Companies initiate particular drug development programs after they have identified a disease or clinical condition where there are few or no effective treatments or for which there remains unmet medical need. Researchers generate a hypothesis that the inhibition or activation of a particular protein or pathway will have a therapeutic effect in a particular disease or condition. This activity generally results in selection of a potential target which will require further research to validate in order to justify further drug discovery and development efforts. Extensive research is required to identify a potential small or large molecule therapeutic for further development, also known as a development candidate.

Prior to testing in humans, the investigation compound or development candidate is considered to be in the preclinical testing phase versus the development phase. The focus of preclinical testing is to assess whether the drug development candidate is safe for human volunteers and whether it exhibits pharmacological activity to merit further investigation. If the investigational compound meets these criteria, the company files an investigational new drug application with the FDA to pursue clinical testing in humans. Companies generally also initiate patent fillings with the U.S. Patent and Trademark Office at this stage..

Clinical Testing in Human Volunteers

Potential new drugs must undergo extensive study in human volunteers in order to demonstrate safety and efficacy to theFDA. Clinical trials comprise the most lengthy and costly portion of the R&D process. The clinical trials process occurs in several phases and takes many years. Biopharmaceutical industry-sponsored clinical trials are conducted around the country and in a variety of settings, including academic medical centers, dedicated clinical trial testing centers, and physician offices.

Drug development is viewed in several distinct phases as outlined below:

Phase 0 clinical trials are a fairly new designation identifying exploratory studies involving very limited human exposure to a drug, with no therapeutic or diagnostic goals (for example, screening studies, microdosing studies). These studies are designed to understand the cellular level effects of a potential

[2] *Innovation in the Biopharmaceutical Pipeline: A Multi-Dimensional View*, The Analysis Group, Report prepared for PhRMA, 2012.

new drug (also known as an investigational drug or compound) by working with extremely low level dosing unlikely to cause any therapeutic or adverse results.

Phase I clinical trials typically are conducted with a small number of health volunteers, typically less than 100, to determine the safety, tolerability, and pharmacokinetics and pharmacodynamics of the potential drug (i.e., researchers assess how the potential drug behaves in the body and relationship between the compound's molecular structure and its effects on volunteers).

Phase II clinical trials begin if the drug successfully passes Phase I testing. This phase generally involves between 100 and 500 human volunteers to assess the efficacy and dose response of the investigational drug in development, including identification of common, short-term potential side effects.

Phase III clinical trials are initiated if the potential new medicine is found to be both safe and efficacious through Phases I and II testing. Phase III trials may enroll 1,000 to 5,000 patients or more across numerous clinical trials sites across states and around the world. From enrollment to completion, these trials take many years to complete and can cost hundreds of millions of dollars. These randomized, controlled trials generate large amounts of data to support submission to the FDA for approval.

A recent study released by the Tufts University Center for the Study of Drug Development found that less than 12 percent of investigational compounds entering Phase I are ultimately approved the FDA, a reflection of the challenges inherent in the R&D process. The same study found that the average time and costs to develop a new medicine were more than 10 years and a total of $2.6 billion.[3]

FDA regulatory review and approval involves the submission of the data collected from preclinical studies and the full set of clinical trial data if the trials are successful. The data are submitted to the FDA in the form of a new drug or biologic license application. If the drug is approved, the company may market the drug for its approved indications.

Post-approval research and monitoring may include requirments to conduct extensive post-approval research in the form of **Phase IV clinical trials** to monitor safety and long-term side effects in patients using the medicine. Under certain circumstances, the FDA may also require companies to conduct risk evaluation and mitigation strategies (REMS) to ensure that the benefits continue to outweigh the risks of a particular medicine.

Research on the medicine does not end once the medicine reaches patients. Companies may also conduct post-approval studies to assess the benefits of a medicine for different populations or in other disease areas. In some cases, they may also develop improved delivery systems or dosage forms. Post-approval research is critical to improving researchers' and clinicians' understanding of a medicine's potential uses and full benefits to patients. In many cases, a medicine may reveal itself over time to have an even greater impact on outcomes when used earlier in the progression of a disease, in combination with other medicines, in different disease indications, or in combination with specific biomarkers.

As noted above, while many potential compounds may be investigated in the discovery and pre-clinical phase, very few will eventually become approved medicines. The vast majority are eliminated prior to human testing via laboratory and pre-clinical screening. As the clinical testing phase is lengthy, costly and filled with uncertainty, companies continue to assess how to improve the effectiveness and efficiency of the clinical trials process, including in some cases increasing their use of clinical or contract research organizations and other vendors with specialized skills and expanding partnerships with academic medical researchers, nonprofit research organizations, and with health care providers and others involved at the clinical trial site level.

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[3] Tufts Center for the Study of Drug Development. Briefing: Cost of Developing a New Drug, November 18, 2014. Tufts Center for the Study of Drug Development & Tufts School of Medicine.

Approach to Estimating the Number of Industry-Sponsored Trials and Trial Participants by State

This report provides estimates of the state-level economic impact associated with biopharmaceutical industry-sponsored clinical trials occurring in a single year. Because a single source of state-level data on total biopharmaceutical industry-sponsored clinical trial investments does not exist, estimates were produced by combining elements from several data sources. As with any estimation methodology, there are limitations to the approach used for this analysis resulting from limitations of the source data. The methodology and potential limitations are described in more detail below and in the Appendix. Generally, these estimates are likely underestimates of the number of all industry-sponsored clinical trials active in the U.S. in 2013.

In developing the state-level data, one of the most critical elements was the number of industry-sponsored clinical trials active at any time during a one year period in each state and the corresponding number of volunteer participants enrolled in these trials. The number of trials and participants in each state are themselves important indicators of the wide geographic reach of the industry's R&D activities.

The number of industry-sponsored clinical trials was tabulated directly from data available in ClinicalTrials.gov. Clinicaltrials.gov is a registry maintained by the U.S. National Institutes of Health, as required under Food and Drug Administration Modernization Act of 1997, and contains data on publicly and privately supported clinical studies of human participants conducted around the world. While ClinicalTrials.gov is the most comprehensive single source of clinical trials data, it does not contain data for all clinical studies conducted in the United States because not all studies are required by law to be registered. The number of studies registered each year has increased markedly over time as more policies and laws requiring registration have been enacted and as more sponsors and investigators voluntarily register their studies.[4] It is nevertheless likely that ClinicalTrials.gov understates total industry-sponsored clinical trial activity and that the estimates reported here are conservatively low.

Totals were generated for each state representing the number of trials that were active for at least one day of the one-year period ending September 30, 2013, using address data included in ClinicalTrials.gov for target trial site(s) for each clinical trial.[5] The size of trials varies greatly, from small trials listing only one site to large multinational trials listing many sites in the U.S. and abroad. For trials with sites both within and outside of the U.S., only the U.S-based sites were included. Reported totals are unduplicated. That is, trials with multiple sites in a state are counted only once in that state's total number of trials, and, similarly, trials with sites in multiple states are counted only once in the total number of trials in the U.S. Data in ClinicalTrials.gov also allowed each trial and trial site to be categorized by phase (0 through IV) and, through analysis of categorical and text fields, by select disease area.

Summary counts of trials and trial participants by phase are shown in Table 1. The ClinicalTrials.gov data show 6,199 active clinical trials in the U.S. sponsored by the biopharmaceutical industry in 2013, accounting for a total enrollment of more than 1.1 million volunteer clinical trial participants. Phase III trials not surprisingly involved the largest number of trial participants (644,684), accounting for more than half of all participants in industry-sponsored clinical trials in the database. At the same time, the largest number of trials (2,562) was in Phase II.

[4] https://clinicaltrials.gov/ct2/resources/trends.

[5] Data were extracted for this analysis from ClinicalTrials.gov in December of 2013. The one-year window ending September 30, 2013 was chosen due to concerns that the U.S. federal government shutdown in late 2013 might have interfered with updates made in the last quarter of 2013, affecting completeness.

Table 1. Estimated Number of Industry-Sponsored Clinical Trials and Trial Participants by Phase, 2013

Phase	Number of Active Clinical Trials	Estimated Total U.S. Enrollment
Phase 0	35	3,222
Phase I	1,392	119,536
Phase II	2,562	215,740
Phase III	1,680	644,684
Phase IV	530	165,158
Total	6,199	1,148,340

Source: Battelle estimates based on information from ClinicalTrials.gov. Represents industry-sponsored trials testing a potential medicine and active for at least one day during the one-year period ending September 30, 2013.

Summary counts of trials and trial participants by selected disease area are shown in Table 2. Oncology accounted for both the largest number of trials (2,560 trials, or more than 40 percent of industry-sponsored trials) and the largest number of trial participants (215,176, or nearly 19 percent of participants). Large enrollment numbers were also seen in infectious disease trials (210,466 participants) and cardiovascular/circulatory trials (191,336). The large number of trials and participants categorized as "other" suggest that the industry is engaged in clinical research on potential treatments across a wide range of therapeutic areas beyond those listed here and/or may be researching treatments in a number of different therapeutic areas and not yet finalized the indication they will be pursuing for initial approval.

Table 2. Estimated Number of Industry-Sponsored Clinical Trials and Trial Participants by Selected Disease Area, 2013

Disease Area	Number of Active Clinical Trials	Estimated Total U.S. Enrollment
Cardiovascular/Circulatory	361	191,336
Central Nervous System/Brain/Pain	525	107,321
Hematology	180	15,454
Infectious	513	210,466
Metabolic/Diabetes/Nutrition	352	78,485
Oncology	2,560	215,176
Respiratory	208	87,498
Other	1,500	242,604
Total	6,199	1,148,340

Source: Battelle estimates based on information from ClinicalTrials.gov. Represents industry-sponsored trials testing a potential medicine and active for at least one day during the one-year period ending September 30, 2013.

Estimating the Costs Related to Conducting Clinical Research at the Trial Site Level

To estimate total industry clinical trial spending in each state, the data on the number of clinical trial participants summarized above need to be combined at the state level with estimates of the average cost per trial participant. This section describes the typical and average site-based costs of conducting a clinical trial. There are many sources of cost involved in running a clinical trial. Some of these are specific to the trial sites where clinical trial participants are seen, while other functions are more centralized, typically located at biopharmaceutical company offices or facilities or at contract research organizations working in partnership with these companies. The costs included in this analysis are only those related to activities occurring at the trial sites themselves, and are not intended to capture all of the costs related to the drug discovery and development process.

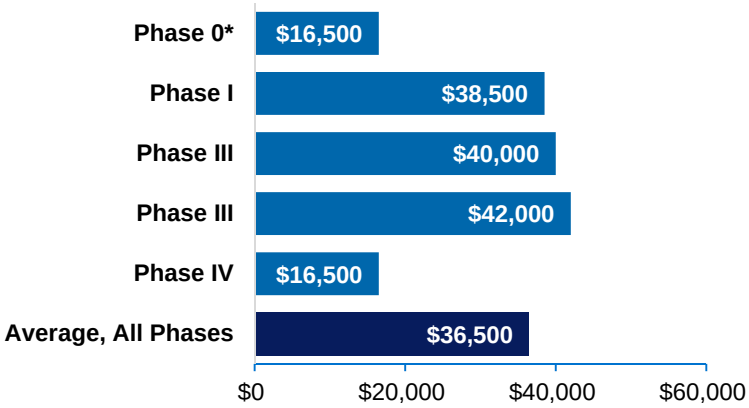
The resources required to conduct clinical research at a single site location of a clinical trial can vary significantly. Costs naturally vary due to the number of volunteer trial participants enrolled at a site, but they can also vary considerably due to a number of other factors including but not limited to the number of staff required to staff and conduct clinical trials, the complexity of the condition being studied, the requirements of the particular clinical trial protocol, and the phase of the clinical trial.

The cost data used in this analysis provide insight into the types of activities that must occur at a clinical trial site to effectively conduct a trial. Per-patient cost data was obtained from Cutting Edge Information (CEI), a clinical trials data and operations consultancy. While there is no one agreed-upon objective source for trial site cost data, the CEI survey-based data, was one of the most robust available sources providing detailed cost information for a range of clinical trial activities, including the following:[6]

- Investigator and site: Institutional overhead, investigator honoraria and fees, ethics review, Institutional Review Board , investigator meetings (travel)
- Patient enrollment: Recruitment costs (advertising, travel stipend, etc.), screening, office visits (equipment, diagnostics, etc.)
- General trial procedures: Initial exam, physical exam, vital signs, detailed medical history
- Materials: Drug supply, comparator drug, other equipment, shipping, etc.
- Efficacy assessments: MRIs, CT scans, other diagnostic tests
- Laboratory: Local lab fees, storage, shipping of samples, etc.
- Site-based IT/data management: Trial master file, electronic data capture, Interactive Voice/Web Response System
- Site-specific CRO expenses: Monitoring, randomization, biostatistics, travel, meetings, etc.

We used the CEI survey data to develop the per-patient cost assumptions by phase and disease area used in this analysis (see Appendix for a description of the methodology used to derive these estimates). Site-based costs per trial participant averaged $36,500 among trials of any phase or condition (Figure 1). Phases I through III showed similar average costs per study participant, ranging from $38,500 to $42,000 in total costs per participant for that phase of an investigational medicine's clinical testing. The highest of these was Phase III, which as shown earlier also typically involve much larger numbers of participants, making them significantly more resource-intensive than the other phases of the clinical trial process.

Figure 1. Estimated Average Per-Patient Clinical Trial Costs, by Phase, 2013

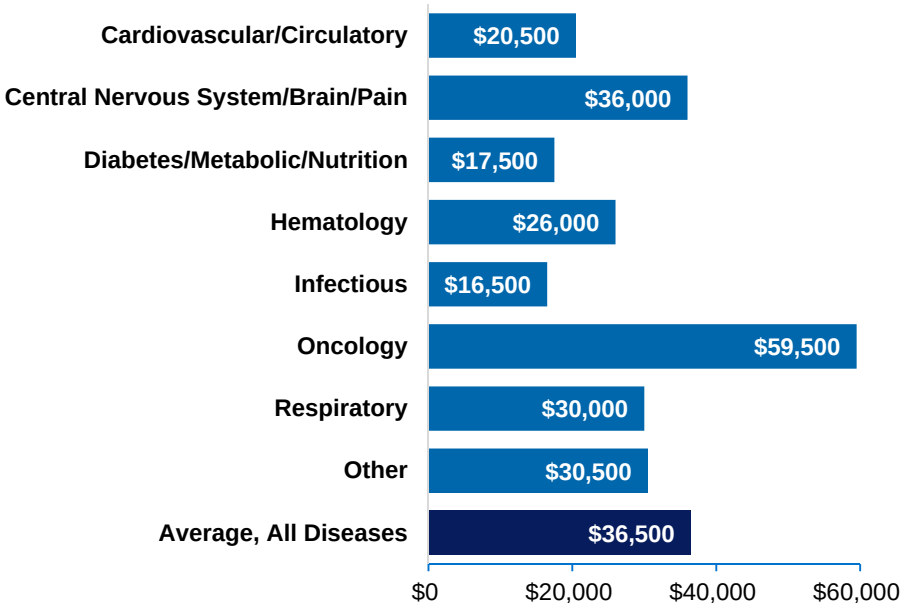


Source: Battelle, based on survey data from Cutting Edge Information. Because Cutting Edge Information did not develop estimates for Phase 0 studies, Phase 4 estimates, which were the lowest, were used for the very small number of Phase 0 biopharmaceutical trials included in the ClinicalTrials.gov database.

[6] Clinical Development and Trial Operations – Protocol Design and Cost per Patient Benchmarks, Cutting Edge Information, 2013.

Figure 2 summarizes the estimated average per-patient costs by the condition for which the potential new medicine is tested. Oncology trials show the highest average per-patient cost, with an average per-patient cost of $59,500. Oncology trials also typically require fewer participants than average, so any fixed costs are spread over a smaller number of participants. In contrast, infectious disease trials show relatively low costs per participant ($16,500), and generally require a larger number of participants.

Figure 2. Estimated Average Per-Patient Clinical Trial Costs, by Selected Condition, 2013



Source: Battelle, based on survey data from Cutting Edge Information.

Estimating the Economic Impact of Industry-Sponsored Research Across the U.S. and by State

Combining state-level ClinicalTrials.gov enrollment data with the CEI data on average site-based costs per trial participant produces state-level estimates of total industry clinical trial investments at clinical trial sites in each state. Appendix A provides a detailed description of the methodology for this calculation.

As with any estimation methodology, there are limitations to the approach used for this analysis resulting from limitations of the source data and the simplifying assumptions required to generate estimates at the level of detail reported here.

First, the ClinicalTrials.gov database likely understates the number of industry-supported clinical trials active in the U.S. in 2013, because not all studies are required by law to be registered. The estimates are therefore likely to be conservatively low.

Second, estimating the share of a trial's participants in each state is challenging. ClinicalTrials.gov provides target trial participation at the trial level, so participants were distributed equally across all target trial sites.

The Increasing Costs and Complexity of Drug Discovery and Development

On average, it takes more than 10 years for a new medicine to complete the journey from initial discovery to patients, with new research released by the Tufts Center for the Study of Drug Development indicating that the time from the start and successful completion of clinical testing to FDA review and approval is now more than 8 years. For every new drug that receives FDA approval, millions of compounds in company and other compound libraries may be screened early in development. According to new estimates released by the Tufts Center for the Study of Drug Development, the estimated average cost of developing a new medicine was $2.6 billion in 2013, with another $312 million for post-approval research.[1] The estimates represent the average cost of developing a new medicine, including the R&D costs of the majority of compounds which do not make it through clinical trials (less than 12 percent of investigational drugs or drug development candidates that reach clinical trials are likely to be approved, long after substantial time and financial investments have been made).*****

The Tufts research indicates that the costs of drug development have more than doubled over the past decade. Tufts identified the following as key cost drivers:

- **Much higher failure rates for drugs that are tested in human subjects.** The researchers noted an increase in the proportion of projects failing early, before reaching more costly Phase III trials. They reported that increases in failure rates may be due to:
  - Industry generally focusing more in areas where the science is difficult and failure risks are high as a result.
  - The substantial growth in identified drug targets, many of which may be poorly validated, may have encouraged companies to pursue clinical development of more compounds with an unclear likelihood of success than they otherwise would.
- **Increases in the real out-of-pocket costs of development for individual drugs.** The largest impact on the change in costs between the current and prior study was driven by changes in average out-of-pocket clinical phase costs, which resulted in an 82.5% increase in the full costs of drug development. Out-of-pocket clinical cost increases may be driven by a number of factors:
  - Increasing clinical trial complexity,
  - Larger clinical trial sizes,
  - A greater focus on targeting chronic and degenerative diseases,
  - Changes in protocol design to include gathering health technology assessment information
  - Testing on comparator drugs to accommodate payer demands for comparative studies
  - Inflation in the cost of inputs taken from the medical sector that are used for development.

The chart below provides additional detail on the increasing complexities and protocols related to clinical trials that are contributing to rising R&D costs related specifically to the clinical trial process:******

Complexity Indicator	2000-03	2008-11	Change
Median Clinical Trial Treatment Period	140 days	175 days	25%
Median Clinical Trial Site "Work Burden"	28.9 units	47.5 units	64%
Number of Eligibility Criteria (increases recruiting costs)	31 criteria	46 criteria	58%
Number of Case Report Form Pages per Protocol	55 pages	171 pages	227%
Number of Procedures per Trial Protocol	105.9	166.6	57%

***** *Tufts Center for the Study of Drug Development. Briefing: Cost of Developing a New Drug, November 18, 2014. Tufts Center for the Study of Drug Development & Tufts School of Medicine.*

****** *KA Getz, RA Campo, and KI Kaitin. "Variability in Protocol Design Complexity by Phase and Therapeutic Area." Drug Information Journal 2011; 45(4):413-420; Updated data provided through PhRMA correspondence with Tufts Center for the Study of Drug Development.*

However, evidence suggests that some sites over-enroll while others under-enroll. For example, according to 2006 data from the University of North Carolina at Chapel Hill[7]:

- 15-20% of sites never enroll a single patient
- 30% of sites under-perform (i.e., enroll 5% of evaluable patients)
- 20% of sites are average performers (i.e., enroll 25% of evaluable patients)
- 30% of sites are high performers (i.e., enroll 70% of evaluable patients)

To the extent that some target sites are less or more successful than others, the state-level estimates will overstate or understate enrollment, respectively. Also, in cases where trials fail to achieve overall target enrollment, our estimates will overstate enrollment and therefore costs. Mitigating this source of bias, however, is that sites that underperform have to bear similar costs of study start-up, regulatory management, and study closure as sites that accrue well. Thus, costs should not vary as much as enrollment.

Another limitation is the limited number of specific diseases for which we have average clinical trial costs. For a relatively large number of trials, an overall average trial cost for "all other" diseases had to be used. To the extent the actual cost per participant for these trials are above or below the average of "all other" trials within the Cutting Edge Information data, trial costs will be over or understated. However, this would not introduce significant bias to the aggregate cost estimates.

These limitations notwithstanding, the estimates in this report provide a useful snapshot of the wide human and economic reach of industry-sponsored clinical trials in the U.S.

The industry's investment in clinical trials around the country has an impact on local economies that goes beyond the amounts spent conducting the trials. Standard input-output (I/O) analysis indicates that the nearly $10 billion spent by industry at clinical trial sites supported a total of nearly $25 billion after including the economic ripple-effects created in the communities where trials are located (Table 3). These ripple effects include the flow of funds to vendor companies that supply or support clinical trial sites in some way (i.e., indirect impact), as well as dollars that are re-circulated into the local economy through purchases from wages (induced impact).

Table 3. Estimates of Overall Economic Impact of Industry-Sponsored Clinical Trial Activities at U.S. Trial Sites, 2013

Source of Impact	Economic Impact (Billions)
Direct – *Research activities at clinical trial sites around the country*	$9.818
Indirect and Induced – *Vendors and suppliers to trial sites; Consumer purchases by researchers and workers engaged in or supporting the clinical trial process*	$15.132
Total	**$24.950**

Source: Battelle analysis.

State-level estimates show how industry-sponsored clinical trials were distributed around the country and provide an indication of what these industry clinical trial investments meant for the local economies in those states. Using this aggregated database, each clinical trial's total enrollment and distribution of administration sites throughout the country was used to develop estimates of trial enrollment per state. The number of trial participants in each state was estimated based on total reported enrollment per trial, apportioned by state proportionally based on the number of sites in each state.

[7] *Budgeting at the Investigative Site*, University of North Carolina at Chapel Hill, Office of Clinical Trials Newsletter. July/August 2006.

Table 4 shows the 25 states with the largest economic impact, and Figure 3 maps summary data for all 50 states. The five states with the highest number of active clinical trial sites were California (3,111), Florida (2,571), Texas (2,799), New York (2,476), and Pennsylvania (1,972). Industry sponsored clinical trial investments were distributed throughout the 50 states, with sizable spending in some states not typically associated with a large biopharmaceutical industry presence, e.g., Ohio and Tennessee.

Because clinical trials occur "in the field" where hospitals, doctors, trial centers, and volunteer participants are located, the list of top 25 states include some states that may not typically be associated with a large biopharmaceutical industry presence.

Table 4. Estimates of Industry-Sponsored Clinical Trial Activity and Related Economic Impacts at Trial Sites, Top 25 States, 2013

State	Number of Trials Active in State in 2013	Estimated Total Trial Enrollment	Estimated Total Site-Based Trial Investments ($ millions)	Total Economic Impact ($ millions)
California	3,111	125,613	$1,112	$3,083
Texas	2,799	99,934	$974	$2,623
Florida	2,571	119,256	$963	$2,682
New York	2,476	59,095	$553	$1,338
Pennsylvania	1,972	47,538	$401	$1,020
Ohio	1,928	41,051	$331	$848
North Carolina	1,779	45,524	$400	$1,008
Illinois	1,701	29,294	$250	$678
Tennessee	1,578	42,895	$283	$706
Massachusetts	1,577	33,346	$364	$910
Georgia	1,572	29,460	$239	$633
Michigan	1,456	23,600	$192	$488
Maryland	1,405	25,291	$222	$527
Missouri	1,371	20,316	$189	$470
Arizona	1,311	29,291	$237	$618
Washington	1,295	19,407	$164	$411
Colorado	1,251	20,997	$164	$428
New Jersey	1,234	25,127	$246	$617
Virginia	1,197	23,656	$183	$429
Indiana	1,111	19,659	$187	$442
South Carolina	1,097	36,104	$239	$540
Alabama	1,069	32,776	$244	$531
Minnesota	932	13,855	$119	$318
Utah	865	18,928	$171	$461
Kansas	755	15,001	$137	$307

Source: Battelle analysis.

Figure 3. Estimate of Economic Impact of Industry-Sponsored Clinical Trials Activity Across the U.S., 2013

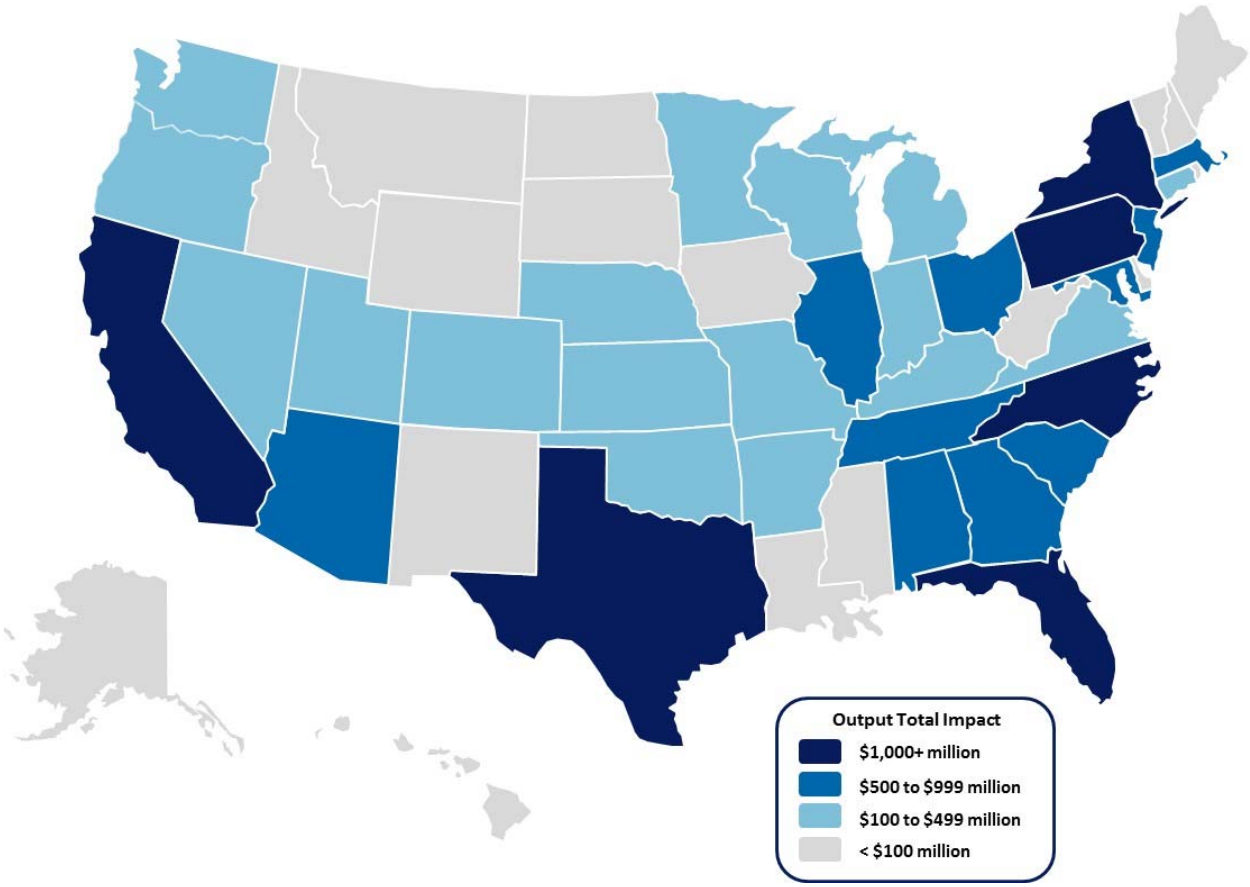


Table 5, on the next page, provides estimates on clinical trial activity and the related economic impacts generated by industry-supported clinical trials for all 50 states and the District of Columbia. Only 7 states plus the District of Columbia had fewer than 200 clinical trial sites.

Table 5. Estimate of Industry-Sponsored Clinical Trial Activity and Related Economic Impacts at Trial Sites by State, 2013

Region	Number of Trials Active in State in 2013	Estimated Total Trial Enrollment	Estimated Total Site-Based Trial Investments ($ millions)	Total Economic Impact ($ millions)	Leading Clinical Trial Disease Area by Enrollment
Alabama	1,069	32,776	$243.9	$531.3	Infectious
Alaska	45	1,417	$12.2	$24.9	Respiratory
Arizona	1,311	29,291	$237.2	$618.4	Infectious
Arkansas	627	8,648	$70.0	$151.9	Oncology
California	3,111	125,613	$1,112.2	$3,082.8	Oncology
Colorado	1,251	20,997	$164.0	$428.4	Infectious
Connecticut	841	13,105	$124.7	$292.0	Cardiovascular/Circulatory
Delaware	133	1,544	$10.4	$23.6	Cardiovascular/Circulatory
District of Columbia	474	4,948	$41.4	$68.1	Oncology
Florida	2,571	119,256	$963.0	$2,681.7	Infectious
Georgia	1,572	29,460	$238.7	$632.7	Infectious
Hawaii	162	2,729	$35.8	$81.1	Infectious
Idaho	364	5,959	$38.1	$85.7	Infectious
Illinois	1,701	29,294	$249.5	$678.4	Oncology
Indiana	1,111	19,659	$187.1	$441.6	Oncology
Iowa	444	4,948	$39.6	$86.9	Oncology
Kansas	755	15,001	$137.4	$307.1	Infectious
Kentucky	886	15,575	$113.2	$252.7	Infectious
Louisiana	787	12,724	$93.0	$214.0	Infectious
Maine	222	3,376	$22.1	$52.4	Cardiovascular/Circulatory
Maryland	1,405	25,291	$221.8	$526.7	Oncology
Massachusetts	1,577	33,346	$364.1	$910.5	Oncology
Michigan	1,456	23,600	$191.7	$488.2	Oncology
Minnesota	932	13,855	$119.2	$318.3	Oncology
Mississippi	343	3,725	$28.9	$61.7	Cardiovascular/Circulatory
Missouri	1,371	20,316	$188.9	$470.2	Oncology
Montana	256	3,264	$22.6	$51.2	Cardiovascular/Circulatory
Nebraska	677	11,412	$96.1	$219.6	Infectious
Nevada	570	8,459	$68.6	$149.9	Infectious
New Hampshire	236	2,210	$17.6	$41.8	Oncology
New Jersey	1,234	25,127	$245.9	$617.5	Oncology
New Mexico	382	5,430	$42.6	$87.7	Infectious
New York	2,476	59,095	$552.7	$1,337.6	Oncology
North Carolina	1,779	45,524	$400.3	$1,007.7	Oncology
North Dakota	179	2,737	$19.5	$38.8	Infectious
Ohio	1,928	41,051	$330.9	$848.1	Cardiovascular/Circulatory
Oklahoma	735	8,589	$75.3	$173.2	Cardiovascular/Circulatory
Oregon	904	10,620	$107.5	$264.1	Oncology
Pennsylvania	1,972	47,538	$400.6	$1,020.1	Oncology
Rhode Island	341	4,563	$38.5	$90.4	Infectious
South Carolina	1,097	36,104	$238.9	$540.2	Cardiovascular/Circulatory
South Dakota	165	2,485	$21.0	$45.6	Cardiovascular/Circulatory
Tennessee	1,578	42,895	$282.5	$705.6	Respiratory
Texas	2,799	99,934	$974.1	$2,623.0	Oncology
Utah	865	18,928	$171.2	$460.7	Infectious
Vermont	161	1,403	$11.8	$25.6	Central Nervous
Virginia	1,197	23,656	$183.1	$429.5	Infectious
Washington	1,295	19,407	$164.2	$410.7	Oncology
West Virginia	198	1,721	$13.3	$26.3	Oncology
Wisconsin	725	9,712	$90.8	$223.3	Oncology
Wyoming	6	22	$0.2	$0.4	Oncology
United States	**6,199**	**1,148,340**	**$9,817.7**	**$24,949.8**	**Oncology**

Source: Battelle analysis.

Conclusion

This report identifies the significant investment biopharmaceutical companies make every year in supporting clinical trial activities across the U.S. This work is critical to bringing new medicines to patients that will improve their health and quality of life. Clinical trial activity also provides significant benefits to state and local economies in terms of economic impact generated through activities as development of clinical trial protocols; selection of clinical trial sites; implementation trials including the recruitment of staff, contractors, vendors, and patient volunteer; manufacture of small batches for testing; care to patients, including lab tests and ongoing health monitoring; and analysis of the enormous amount of data generated –just to name some of the activities occurring at particular trial sites which require significant expenditures by biopharmaceutical companies and their vendors and contractors.

Using conservative data sources and assumptions, we were able to identify 6,199 industry-sponsored clinical trials involving 1.1 million volunteer trial participants in 2013. Biopharmaceutical companies invested $10 billion in these trials, with an overall economic impact of nearly $25 billion across the communities where the trials were located. Clinical trial sites are operating in all 50 states and the District of Columbia reflecting the broad reach of the biopharmaceutical industry as well as the substantial unmet medical needs across the U.S. Supporting continued medical innovation and a thriving life sciences ecosystem that impacts state and local economies across the country requires a long-term view, with policies and regulatory structures that are consistent, predictable, and focused on meeting the needs of patients.

APPENDIX: Methodological Considerations

Because detailed state-level data on total biopharmaceutical industry-sponsored clinical trial spending do not exist, estimates were produced by combining several data sources. The number of industry-sponsored clinical trials was tabulated directly from the data available in ClinicalTrials.gov. The number of trial participants in each state was estimated based on total reported enrollment per trial, apportioned by state proportionally based on the number of sites in each state. Total site-based trial costs were estimated by applying survey-derived estimates of average per-participant costs by phase and condition to the state-level enrollment estimates, which were grouped into the same phase/condition categories. Total state-level economic impacts were then estimated using standard input-output analysis, reflecting the economic multiplier effect in the communities in which the clinical trials were located. The sections below describe these steps and the data used in more detail.

Estimating the Number of Industry-Sponsored Clinical Trials by State

The number of industry-sponsored clinical trials was tabulated directly from the data available in ClinicalTrials.gov. Clinicaltrials.gov is a registry maintained by the U.S. National Institutes of Health, as required under Food and Drug Administration Modernization Act of 1997, and contains data on publicly and privately supported clinical studies of human participants conducted around the world. ClinicalTrials.gov does not contain all clinical studies conducted in the United States because not all studies are required by law to be registered. While the number of studies registered each year has increased over time as more policies and laws requiring registration have been enacted and as more sponsors and investigators voluntarily register their studies, it is reasonable to assume that the total number of trials and trial participants generated from ClinicalTrials.gov is a conservative, lower-bound estimate.

Each trial listed in the ClinicalTrials.gov database contains information in the form of free-text entries listing the addresses of the target clinical trial sites. The size of trials varies greatly, from small trials listing only one site to large multinational trials listing many sites in the U.S. and abroad. For trials with sites both within and outside of the U.S., only the U.S-based sites were included.

Totals were generated for each state representing the number of trials that were active for at least one day of the one-year period ending September 30, 2013.

Obtaining Clinical Trial Records from ClinicalTrials.gov

Detailed records of clinical trials are available to the public through the U.S. National Institutes of Health that and include information on funding sources, trial sites, and numbers of enrolled participants. Using the ClincalTrials.gov website search interface to access trial records, a query was used to identify the records of all clinical trials funded by industry sources.

Among the information provided for each clinical trial listed in the ClinicalTrials.gov database include:

- Title, description, and design of the study
- Disease or condition
- Intervention (for example, the medical product, behavior, or procedure being studied)
- Requirements for participation (eligibility criteria)
- Description of study participants (number starting and completing the study and their demographic data)
- Locations where the study is being conducted

Groups of trial records containing structured text field information on trial protocol details are available for large batch downloading in the form of XML files. Extensible Markup Language (XML) is a type of text file format that contains text fields that are tagged with labels to identify various portions of the larger text document. In the case of the clinical trials records, these tags identify parts of the individual trial protocol records that correspond to information like the locations of trial sites and sponsors.

Records for all active industry clinical trials (one XML file for each trial) were downloaded at the beginning of October 2013, with a total of 59,786 industry trial records present at that time. Each trial record's text structure was parsed and data fields of interest were read and stored in an aggregated database file.

For each record, the state locations of all U.S. trial sites (a single trial often has many administration sites in different states) were identified and summed using this method to create a database of total number of trial sites per state for each clinical trial. Trial recruitment status, phase, and total enrollment data as well as relevant information about conditions, interventions (if any), collaborators, and important trial dates were also captured the clinical trial records database.

Using this aggregated database, each clinical trial's total enrollment and distribution of administration sites throughout the country was used to develop estimates of trial enrollment per state.

Mapping Clinical Trials to Key Disease Areas

Using keywords from ClinicalTrials.gov as well as additional keywords generated by Battelle and found within the clinical trial information provided by Cutting Edge Information, Inc., a broad list of keywords were developed to classify each clinical trial into one of the seven disease-specific areas or other.

These keywords were searched against the text of the clinical trials title and condition fields, obtained from the ClinicalTrial.gov record.

For those trials with keywords reflecting more than one disease area, Battelle made a judgment call regarding which category the particular clinical trial would be placed by examining the title of the clinical trial.

Establishing Trial Phase for Calculation Purposes

Certain valid trials are included in the ClinicalTrials.gov database with a phase designation of "N/A". The purpose and structure of these trials were examined and in every case they were reclassified as Phase 4 trials for calculation purposes.

Certain valid trials are included in the ClinicalTrials.gov database with a multi-phase designation (e.g., Phase I/Phase II or Phase II/Phase III. Given the broader, more comprehensive nature of these trials they are treated as the later phase for calculation purposes.

Estimating the Number of Volunteers Enrolled in Industry-Sponsored Clinical Trials by State

Conceptually, the number of trial participants in each state was estimated based on total reported enrollment per trial in ClinicalTrials.gov, apportioned by state based on the number of trial sites listed for each state.

Most records within ClinicalTrials.gov have a sponsor provided "estimated enrollment" value. Many trials' final number of enrollees does not reach this level, while some at times actually exceed it. For the purposes of this estimation study, Battelle used these values as representative of overall clinical trial enrollment activity. Using the site and location information parsed out of the ClinicalTrials.gov records, Battelle developed a count of the number of sites by country and for the U.S. by state. If a state had more than one location where patients could be enrolled in the trial, the number of distinct locations was captured. The total estimated enrollment value was divided by the total number of sites to yield a "per site enrollment" figure.

To estimate U.S. trial impact only, locations and per site enrollment values for non-U.S. sites were removed from subsequent data and calculations. For each specific trial-specific state (trial-state pair) record, a value equal to the average per site enrollment multiplied by the number of sites within that state was calculated.

For example, if a trial within ClinicalTrials.gov shows that it expects 100 enrollees and includes 5 sites in Canada, 3 sites in Massachusetts, and 2 sites in Rhode Island the specific trial-specific state records would include one record with 30 enrollees for Massachusetts and one record with 20 enrollees for Rhode Island and the remaining 50 enrollees assigned to Canada would be removed from subsequent data and calculations.

Estimating Total Industry Spending on Clinical Trials by State

The information obtained from CEI allowed for the development of Phase-based per-patient cost estimates for seven specific disease areas and an eighth "other" category for trials not related to one of the disease areas (Table A-1). These initial per-patient cost estimates by phase and disease area were then examined by industry representatives and adjustments were made to these figures to account for outliers among the CEI survey responses as well as to better reflect industry experience for certain disease areas. For the overall analysis specific costs related to disease area and trial phase are used to develop the overall economic impact assessment.

This information combined with the disease- and phase-specific cost information, yields the following estimated annual (12 month period ending September 30, 2013) site-based patient total by phase and disease area. The principal driver of these activities and costs are often the level of professional resources and physical infrastructure that exists to support the geographically dispersed activities. This combination of trial phase, disease or condition, and trial site (e.g., doctor's office, outpatient clinic, stand-alone trial centers, and hospitals) all combine to generate site-based expenditures.

Table A-1. Estimated Locally-Based Per Patient Costs by Selected Disease Areas and Phase

Disease Area	Phase 0*	Phase I	Phase II	Phase III	Phase IV	Avg. All Phases
Cardiovascular/Circulatory	$9,500	$21,500	$25,000	$26,000	$9,500	$20,500
Central Nervous System/Brain/Pain	$15,000	$34,000	$39,500	$40,500	$15,000	$36,000
Diabetes/Metabolic/Nutrition	$7,000	$16,000	$18,500	$19,000	$7,000	$17,500
Hematology	$11,500	$26,000	$30,000	$31,000	$11,500	$26,000
Infectious	$6,500	$15,000	$17,500	$18,000	$6,500	$16,500
Oncology	$25,500	$57,500	$67,500	$69,000	$25,500	$59,500
Respiratory	$11,500	$26,000	$30,500	$31,000	$11,500	$30,000
Other	$13,000	$29,500	$34,500	$35,000	$13,000	$30,500
Avg. All Diseases	$16,500	$38,500	$40,000	$42,000	$16,500	$36,500

Source: Battelle, based on survey data from Cutting Edge Information.

Estimating "Annual" Trial Duration

Most records within ClinicalTrials.gov have a sponsor provided "start date" and "completion date" indicated the expected duration of the clinical trial, with significant variability in duration depending on the trial phase. These dates include the full extent of the trial's activities, not just the core period where ongoing participant or patient involvement is occurring. For example, if the trial requires 12 months to recruit a suitable participant group, these 12 months are also included in the trial duration. Start dates for active clinical trials can begin many months or years prior to the date the records were captured. Additionally, completion dates for active clinical trials can be months or years in the future from when the records were captured.

To provide a controlled, single year measure of economic impact a specific 12 month active "window" was used to filter the trials' durations. This window corresponded with the federal government 2013 fiscal year

(October 1, 2012 to September 30, 2013). It should be noted that this specific year was chosen primarily due to the U.S. federal government shutdown and the uncertainty on whether the site was going to be updated starting October 1, 2013. This 12 month filter was applied to the timeframe established by each trial's start and completion dates, to estimate what share of the trial's timeframe occurred within the specific 12 months used for this analysis.

For example, if a Phase 1 trial started October 1, 2012 and was completed on December, 31, 2012, all three months of this trial fall within the window, and hence, 100% of the trial's impact is captured as part of the analysis. If a Phase 3 started on October 1, 2011 and will complete on September 30, 2014, only 12 months of the total 36 months of the trial fall within the window, and hence, 33% of the trial's total impacts are captured as part of the analysis.

Calculating Total Trial- and Duration-Weighted Cost by State

Having established a per patient cost to be assigned to each clinical trial record based upon its disease area and phase, this value is multiplied by the estimated number of trial participants for each state involved in the trial. This creates a "total patient cost" estimate for each trial-state pair. For each trial-state pair, a share of these "total patient costs" are captured with regard to the to the 12 month active window to establish a duration-weighted trial cost estimate for each trial-state pair.

For each state, all of the duration-weighted trial-state pair values are summed to establish a single state-level clinical trial activity value. These state-level activity values are used as the direct effect in modeling the overall annual (2013) economic impacts of these clinical trials.

Estimating Total Economic Impact of Industry-Sponsored Clinical Trials by State

Economic impact broadly consist of three types of effects: ***direct effects*** (the specific impact of the actual "first round" spending on clinical trials activities by the biopharmaceutical companies and/or contract research organizations spent with clinical trial service providers), ***indirect effects*** (the impact of expenditures by suppliers to these clinical trial service providers), and ***induced effects*** (the additional economic impact of the spending of clinical trial service provider employees and suppliers' employees in the overall economy that can be attributed to the actual "first round" expenditures). Taken together, these three combine to form the ***total impact***.

Economic impacts are measured using the well-established regional economic analysis technique of input/output analysis (I/O) which tracks the revenues of a sector and the related economic activity of suppliers to the sector and its personnel through the earning of wages and spending of those wages throughout the economy. Output, sometimes referred to as business volume, is defined as the dollar value of sales, goods, and services produced in an economy. Output represents the typical measure expressed as the ***economic impact*** in a standard economic impact study.

To estimate the economic impacts of the biopharmaceutical-related clinical trials activities on overall output in the U.S. and state economies, the analysis in this report employed separate, customized IMPLAN (Impact analysis for Planning) I/O models for the U.S. and each state for 2012, the most recent models available. Economic values for 2013 activities were entered into the model as current dollars.

The model incorporates employment and other details of the economic sectors encompassing hospitals (IMPLAN Sector 397), outpatient medical centers (396), and physician offices (394) where the overwhelming majority of state-level clinical trial activity (e.g., patient interactions and clinical trial costs) occur. For modeling purposes these three sectors were aggregated to represent all the location types and variations within each state and for each trial.

The state-level clinical trial spending totals estimated from ClinicalTrials.gov and other data serve as the "direct" economic impact used as input into the I/O analysis. The model then estimates the impact and "ripple effect" of this spending on the U.S. and each state level economies leading to a total economic impact metric (i.e., total output impacts) for the U.S. and each state.