Biopharmaceutical Industry-Sponsored Clinical Trials:

Growing State Economies

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TECONOMY PARTNERS LLC
Innovating Tomorrow's Economic Landscape

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Executive Summary

Developing a new prescription medicine is a long and complex process, with risk of failure at every step. The research and development (R&D) process in the U.S., from basic science to preclinical and clinical research to approval of new treatments for patients, involves a robust R&D ecosystem. The R&D ecosystem includes biopharmaceutical companies large and small, government, academia, non-profit organizations, patient advocacy groups, health care providers and others who play complementary roles in helping develop and bring new medical advances to patients.

The U.S. innovative biopharmaceutical industry continues to lead the world in the development of new medicines, harnessing the potential of new scientific and technological advances to expand possibilities for addressing unmet medical needs. At a time when the need for new treatments against some of our most costly and challenging diseases has never been greater, the potential of the R&D pipeline has also never been greater.

America's biopharmaceutical companies account for more than half (53%) of all U.S. investments in health and biomedical research and development, including significant spending in clinical research.[1] This report specifically sheds light on the investments and additional economic activity generated by clinical trials funded across the country by the biopharmaceutical industry. The analysis provides updated state-level estimates of industry-sponsored clinical research at trial sites across the country, including the number of trials, the number of trial participants, and the total economic impact based on a review of clinical trial data included in www.clinicaltrials.gov, a database of privately and publicly funded clinical studies conducted around the world. Given that the time for development of a new medicine ranges from 10 to 15 years or more, this report should be viewed as a snapshot of the impact in 2017, the most recent year for which data were available.

Each state's economic impact estimate includes the annual direct investment companies have made to establish and operate 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 2017.

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. Beyond the scope of this report are pre-discovery and preclinical research (i.e., prior to testing in humans), as well as activities occurring beyond the operations at clinical trial sites themselves (e.g., clinical trial design, management, coordination, analysis, and related activities). The report also excludes the large nationwide economic impacts associated with non-R&D activities such as manufacturing and distribution, which comprise a substantial portion of industry's overall economic impact in the states.

Key findings from this report include:

- America's biopharmaceutical companies sponsored more than 4,500 clinical trials in 2017 alone.
- These sponsored trials involved more than 920,000 participants, with active trial sites in all 50 states, the District of Columbia, and Puerto Rico.

[1] Research!America, U.S. Investments in Medical and Health Research and Development: 2013 – 2017, Fall 2018.

- The biopharmaceutical industry invested more than $15 billion on clinical research at trial sites across the U.S. in 2017. These resources are in addition to the significant resources invested in clinical trial-related activities occurring outside the individual trial sites, such as trial design, coordination, and centralized data analysis.
- Including the ripple effect of expenditures by clinical trial vendors and contractors, such as clinical research organizations, and spending by industry and vendor employees, biopharmaceutical industry investments at U.S. clinical trial sites generated more than $42 billion in economic activity in communities throughout the U.S. (Table ES-1).

Table ES-1. Economic Impact of Industry-Sponsored Clinical Trials in the U.S., 2017

Source of Impact	Economic Impact ($ Billions)
Direct – *Research activities at clinical trial sites around the country*	$15.2
Indirect and Induced – *Vendors and suppliers to trial sites; Consumer purchases by researchers and workers engaged in or supporting the clinical trial process*	$27.4
Total	**$42.6**

Source: TEConomy analysis.

- The five states with the highest number of active clinical trials in 2017 were California (2,152), Texas (1,989), Florida (1,735), New York (1,707), and North Carolina (1,196). Because clinical trials occur "in the field" where doctors, trial centers, and volunteer participants are located, sizable investments often occur in states that may not typically be associated with a substantive biopharmaceutical industry presence, e.g., Ohio, Arizona, Tennessee, and Utah.

Biopharmaceutical Industry-Sponsored Clinical Trials: Growing State Economies

Introduction

The U.S. innovative biopharmaceutical industry continues to lead the world in the development of new medicines. Due to new scientific and technological advances that are expanding the 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 also never been greater.

To develop a new medicine, researchers and others involved in the R&D process work to piece together the basic causes of disease at the level of genes, proteins, and cells. Out of this understanding emerge "targets," which potential new drugs might be able to affect. Biopharmaceutical companies work to:

- validate these targets,
- discover the right molecule (potential drug) to interact with the target chosen,
- assess the safety and efficacy of investigational medicines in the lab and through clinical trials,
- submit to the FDA for review and approval,
- manufacturer and distribute new medicines, and
- conduct additional studies and monitoring for many years beyond Food and Drug Administration (FDA) approval.

This report focuses solely on the trial site-specific expenditures related to the clinical trials process, which is used to assess new methods of diagnosing, treating, or preventing health conditions and diseases. The potential new medicines in clinical trials today are the therapies that could result in new treatments or even cures for a range of diseases and conditions, from addressing substantial unmet medical need in cancer, 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 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 test these medicines – identifying and securing clinical trial sites; hiring staff and contractors including clinical investigators and laboratories for testing; recruiting, retaining, and treating trial volunteers; and conducting various other clinical trial activities – generate significant value for local communities across the United States.

The biopharmaceutical industry accounts for a significant share of the overall investments in clinical trial activities at trial sites. Given continued interest in 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 total 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 used to estimate 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 R&D Process

There are more than 7,000 medicines in the drug development pipeline. Considering that there may be clinical trials underway in more than one indication for a given molecule, these products correspond to over 9,500 projects (or unique molecule-indication combinations) in clinical development. Approximately 70% of the potential medicines in development represent novel, first-in-class 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 across the country, including new cell and gene therapies, small and large molecule drugs and therapeutics, and targeted therapies often referred to as precision or personalized medicine.

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 development process begins even earlier, with initial drug 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 testing (or "clinical trials" process). This material is adapted from FDA materials.

Discovery and Preclinical Testing

Biopharmaceutical companies will initiate a drug development program 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 specific protein or pathway will have a therapeutic effect on a certain 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 development efforts. Extensive research is required to identify a potential small or large molecule therapeutic, also known as a development candidate, for further development.

Prior to testing in humans, the investigation compound or development candidate is 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 (IND) application with the FDA to pursue clinical testing in humans.

An **Investigational New Drug (IND)** application must be submitted to FDA before beginning clinical research. Within the IND applications drug developers or sponsors must include information and any existing data related to any animal studies, toxicity, proposed manufacturing processes, and prior-related human research. Additionally, the submission must include the clinical protocols or plans for clinical studies and information about the PI and study team.

[2] *The Biopharmaceutical Pipeline: Innovative Therapies in Clinical Development*, The Analysis Group, July 2017.

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 (also referred to as participants) in order to demonstrate safety and efficacy to the FDA. Clinical trials comprise the most lengthy and costly portion of the R&D process. The clinical trials process occurs in several phases each with increasing levels of complexity in terms of the number of participants, duration, and other requirements. Biopharmaceutical industry-sponsored clinical trials are conducted around the country in a variety of settings, including physician offices and dedicated clinical trial testing centers.

Drug development consists of several distinct clinical trial phases leading to FDA review and approval as outlined below:

- **Phase I clinical trials** typically are conducted with a small number of healthy volunteers, typically fewer 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). Some trials are classified as Early Phase I (previously referred to as Phase 0) studies involving very limited human exposure to a drug, with no therapeutic or diagnostic goals (for example, screening studies, micro-dosing studies). Phase I studies typically last three months or less.
- **Phase II clinical trials** begin if the drug successfully passes Phase I testing. This phase generally involves between 100 and 500 participants to assess the efficacy and dose response of the investigational drug in development, including identification of common, short-term potential side effects. Phase II studies typically last several months to two years.
- **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. These randomized, controlled trials generate large amounts of data to support submission to the FDA for approval. Phase III studies typically last one to four years.
- **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.
- **Phase IV post-marketing studies**, which are conducted after a treatment is approved for use by the FDA, provide additional information including the treatment or drug's risks, benefits, and best use. Phase IV trials can vary significantly in terms of the duration of the study depending on the monitoring requirements.

  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—only one in eight or 12% of compounds entering a Phase I clinical trial will ultimately be approved.[3] Additionally, many more compounds are eliminated prior to human testing via laboratory and pre-clinical screening.

Estimating and Categorizing Industry-Sponsored Clinical Trials

This report provides estimates of the state-level economic impact associated with biopharmaceutical industry-sponsored clinical trials active for part or all of 2017. 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 summarized below and described in more detail in the Appendix.

ClinicalTrials.gov

The number of industry-sponsored clinical trials was tabulated directly from data available in ClinicalTrials.gov. ClinicalTrials.gov is a registry and resource maintained by the U.S. National Institutes of Health (National Library of Medicine), 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. The number of studies registered each year has increased markedly over time as more policies and laws requiring registration, most notably the FDA Amendments Act 2007 (FDAAA), have been enacted and as more sponsors and investigators voluntarily register their studies.[4] 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. Therefore, it is likely that ClinicalTrials.gov understates total industry-sponsored clinical trial activity and that the estimates reported here are correspondingly lower.

Active Clinical Trials – Number, Duration, and Locations

Using ClinicalTrials.gov, complete records were captured for all industry-sponsored (or co-sponsored) biopharmaceutical interventional studies (more commonly referred to as "clinical trials") active for at least one day of calendar year 2017.[5] For each trial record, a calculation was made to determine the number of days in 2017 that the trials were active – ranging from 1 day to 365 days, and the share of the trials' total expected duration.

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[3] DiMasi, et al, *Briefing: Cost of Developing a New Drug*, Tufts Center for the Study of Drug Development, November 18, 2014. Data point represents clinical (FDA) approval success rate of drugs entering Phase I trial. https://csdd.tufts.edu/csddnews/2018/3/9/march-2016-tufts-csdd-rd-cost-study.

[4] For more detailed information about ClinicalTrials.gov see: https://www.clinicaltrials.gov/ct2/about-site/background and https://clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime.

[5] Data were extracted for this analysis from ClinicalTrials.gov in August 2018.

Additionally, each trial record was tagged according to the number of unique trials and trial sites by state. For example, an active trial with two different locations in Los Angeles and one in San Francisco would be tagged as one California trial and three California sites. Estimates were generated for each trial representing the total number of sites. The geographic footprint of individual 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 in any estimates and subsequent analysis. 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.

According to data captured from the ClinicalTrials.gov web database, **4,516 interventional studies (more commonly referred to as "clinical trials") sponsored by one or more biopharmaceutical company were active in the U.S. at some point during 2017**—including trials that were completed in 2017, were initiated in 2017, or ran through the entire year.

Using the clinical trial record's total enrollment value, the average enrollment by global site was calculated and then applied to the number of sites for each trial in each state. Using this approach, TEConomy estimates that **these trials included more than 920,000 participants in the U.S.** (including the District of Columbia and Puerto Rico).

Active Clinical Trials – Phases and Disease Areas

As part of each trial record the active Phase of the trial is also reported by the trial sponsors. Table 1 provides the breakdown of the 4,516 trials and the estimated total U.S. enrollment by phase.

Table 1. Estimated Number of Industry-Sponsored Clinical Trials and Trial Participants by Phase, 2017

Phase	Number of Active Clinical Trials	Estimated Total U.S. Enrollment
Phase I	1,154	61,646
Phase II	1,844	173,900
Phase III	1,115	560,064
Phase IV	403	124,562
Total	**4,516**	**920,173**

Source: TEConomy estimates based on information from ClinicalTrials.gov.

Phase II trials constitute the largest number of trials at 1,844. Phase III trials involved the largest number of trial participants (560,064), accounting for more than 60 percent of all participants in industry-sponsored clinical trials in the data set. Phase III trials are the most lengthy and costly phase of the clinical trial process.

Trials were categorized into principal disease areas based on ClinicalTrial.gov records related to each trial's title, conditions, interventions, and outcomes.[6] Summary counts of trials and trial participants by selected disease area are shown in Table 2. Oncology accounted for the largest number of trials (1,577 trials, or 35 percent of industry-sponsored trials) while Cardiovascular/Circulatory accounted for the largest estimated number of trial participants (192,804, or 21 percent of participants). Large enrollment numbers were also seen in Oncology trials (178,804 participants) and Infectious Disease/ Virology trials

[6] Please see the Appendix for more details of this approach.

(96,375 participants). 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 disease and therapeutic areas beyond those listed here.

Table 2. Estimated Number of Industry-Sponsored Clinical Trials and Participants by Selected Disease Area, 2017

Disease/Therapeutic Area	Number of Active Clinical Trials	Estimated Total U.S. Enrollment
Oncology	1,577	178,258
Hematology	571	59,969
Cardiovascular/Circulatory	348	192,804
CNS/Brain	309	70,496
Infectious Disease/Virology	297	96,375
Endocrine/Metabolic/Diabetes	293	58,178
Dermatology	177	48,275
Respiratory	160	60,589
Ophthalmology	125	24,350
Pain/Anesthesia	114	35,186
Gastrointestinal	74	17,289
Other	471	78,404
Total	**4,516**	**920,173**

Source: TEConomy estimates based on information from ClinicalTrials.gov.

Estimating Clinical Trial Site Costs

The analysis includes data on the number of participants, the number and geographic diversity of trial site locations, and the disease or therapeutic area of the trial. However, to estimate the site-specific/state-specific economic impact of these trials, an estimate of the site-based expenditures associated with each trial must be developed.

To estimate these expenditures and ultimately, total industry clinical trial spending in each state, the data on the number of clinical trial participants summarized above was combined 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 data sources on the costs involved in initiating and operating a clinical trial. Some costs are specific to the trial sites where clinical trial participants are engaged, while other costs are related to more centralized functions, typically located at biopharmaceutical company 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 costs related to the clinical trial 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 and type 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 including:

- **Investigator, physician, and other site-specific labor costs:** including site-related overhead, investigator honoraria and fees, institutional review board, and ethics reviews
- **Participant enrollment:** Recruitment costs (advertising, travel stipend, etc.), screening, office visits (equipment, diagnostics, etc.), retention costs
- **Clinical procedures:** Initial exam, physical exam, vital signs, detailed medical history
- **Materials:** Drug supply, comparator drug, other equipment, shipping, etc.
- **Efficacy assessments:** Blood work, MRIs, CT scans, other diagnostic tests, etc.
- **Laboratory:** Local lab fees, storage, shipping of samples, etc.
- **Site-based IT/data management:** Trial master file, electronic data capture, source data verification, interactive voice/web response systems, etc.
- **Other site-specific expenses:** Monitoring, randomization, biostatistics, travel, meetings, etc.

To develop estimates of clinical trial site costs we used data developed by the Eastern Research Group, Inc. (ERG) for a project submitted to U.S. Department of Health and Human Services, Assistant Secretary of Planning and Evaluation (ASPE).[7,8] These data make use of a specialized database regarding clinical trial costs developed by Medidata Solutions to develop average clinical trial costs by phase and disease/therapeutic area. In total, the Medidata Solutions records used by ERG represented 7,000 distinct clinical trials with approximately 31,000 sites.

Using these clinical trial cost values, TEConomy developed an estimate of average per participant costs by using the average number of participants by phase and disease/therapeutic area in the 2017 active clinical trials data set (see Appendix for a description of the methodology used to derive these estimates). Because the estimates produced by ERG were published in 2014 making use of data obtained in 2012, TEConomy applied the Biomedical Research and Development Price Index (BRDPI) collaboratively developed by NIH and BEA to provide an inflationary adjustment to a 2017 value.[9]

The ERG study only provided average total costs by clinical trial and did not provide a total number of participants related to their data. To use these data to estimate industry clinical trial spending by state, a per-participant value was needed. This per-patient average was developed by taking the estimated 2017 costs by disease/therapeutic area and phase, multiplied by number of active 2017 trials in each, and dividing by the estimated total enrollment in these trials. Table 3 provides a summary of the per-participant site costs across all disease/therapeutic areas and phase. While Phase III (and at times Phase

[7] Eastern Research Group, Inc., *Examination of Clinical Trial Costs and Barriers for Drug Development*, Final Report to U.S. Department of Health and Human Services, Assistant Secretary of Planning and Evaluation (ASPE), July 25, 2014.

[8] A previous study performed by TEConomy principals used per-patient cost data obtained from Cutting Edge Information (CEI), a clinical trials data and operations consultancy. However, these data have not been updated since the prior study and were limited in their number of trial disease areas and sample size. Due to these limitations a new approach to estimating the per patient cost information was used for the current study.

[9] The Medidata information used by Eastern Research Group was in fact summary data representing trials that occurred from 2004 through 2012. Therefore, the costs used by TEConomy may therefore be underinflated to the extent trials from prior to 2012 are driving the costs reported by ERG.

IV) trials are typically the most expensive overall, the substantially larger total participant enrollment of Phase III trials often reduces the "per participant" costs of these trials as site-specific fixed costs are spread over a larger number of individual participants.

Table 3. Per Participant Site Cost of Industry-Sponsored Clinical Trials by Phase and Selected Disease Area, 2017

Disease/Therapeutic Area	Average Per Participant Trial Site Cost by Phase			
	Phase I	Phase II	Phase III	Phase IV
Cardiovascular/Circulatory	$42,808	$52,124	$12,102	$33,589
CNS/Brain	$81,566	$97,238	$43,516	$98,002
Dermatology	$10,572	$73,014	$22,135	$365,555
Endocrine/Metabolic/Diabetes	$23,206	$129,086	$35,013	$159,037
Gastrointestinal	$56,559	$138,059	$29,091	$209,691
Hematology	$37,505	$211,788	$49,982	$203,520
Infectious Disease/Virology	$56,396	$76,137	$31,825	$39,835
Oncology/Cancer	$65,327	$145,584	$42,956	$55,192
Ophthalmology	$74,087	$86,704	$82,087	$302,434
Pain/Anesthesia	$28,112	$108,170	$101,554	$353,856
Respiratory	$151,867	$83,684	$28,397	$208,267
Other (Average All Trials)	$58,667	$137,433	$46,060	$205,235

Source: TEConomy estimates.

Note: Disease/Therapeutic Areas are TEConomy nomenclature. Two areas from the ERG study, Genitourinary System and Immunomodulation where not used due to difficulty in assigning these categories to 2017 trials.

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

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

Economic Impact of Industry-Sponsored Clinical Research 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 **more than $15 billion spent by industry at clinical trial sites across the U.S. and Puerto Rico supported a total of more than $42 billion after including the economic ripple-effects created in the communities where trial sites are located (Table 4).** 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 4. Economic Impact of Industry-Sponsored Clinical Trial Activities at U.S. Trial Sites, 2017

Source of Impact	Economic Impact ($ Billions)
Direct – *Research activities at clinical trial sites around the country*	$15.2
Indirect and Induced – *Vendors and suppliers to trial sites; Consumer purchases by researchers and workers engaged in or supporting the clinical trial process*	$27.4
Total	**$42.6**

Source: TEConomy analysis.

Economic Impact of Industry-Sponsored Clinical Research Among the States

The state-level estimates provide a perspective on the distribution of industry-sponsored clinical trials across the country and provide an indication of what this industry clinical trial spending means for state economies. Using the developed clinical trials site-level dataset, the per-participant costs by disease/therapeutic area and phase are multiplied by the number of participants in such trials in each of the 50 states, the District of Columbia, and Puerto Rico (52 regions). The generated values are then summed across all trials to yield an estimate of the investment made in biopharmaceutical industry-related clinical trials in all 52 regions.

Table 5 shows the 13 states with $1 billion or more in total economic impact from industry-sponsored clinical trials, and Figure 1 maps total economic impact for all 52 regions. Eleven states had more than 1,000 clinical trials underway at some point during 2017. The five states with the largest estimated clinical trial enrollment were California, Texas, Florida, New York, and North Carolina; each estimated to have 40,000 or more participants involved in industry-sponsored clinical trials.

Industry-sponsored clinical trial investments were found throughout the 50 states. It should be noted that because clinical trials occur "in the field" where doctors, trial centers, and volunteer participants are located, the list of key states include some states that may not typically be associated with a large biopharmaceutical industry presence, e.g., Ohio, Arizona, Tennessee, and Utah.

Table 6 provides estimates of clinical trial activity and the related economic impacts generated by industry-supported clinical trials for all 50 states, the District of Columbia and Puerto Rico. Only 6 states plus the Puerto Rico had fewer than 100 biopharmaceutical industry-sponsored clinical trials active in their states in 2017. Table 7 also provides details of the largest disease/therapeutic area for each of the 52 regions by total estimated enrollment. From an enrollment perspective, 26 states had the largest share of their enrollment in Oncology-related trials. Cardiovascular/Circulatory-related trials accounted for the largest share of enrollment in 20 additional states. Overall, the U.S. also had the largest share of enrollment in Cardiovascular/Circulatory-related trials.

Table 5. States with $1 Billion+ Total Industry-Sponsored Clinical Trial-related Economic Impacts, 2017

State	Number of Trials Active in State in 2017	Estimated Total Trial Enrollment	Estimated Total Site-Based Trial Investments ($ millions)	Total Economic Impact ($ millions)
California	2,152	102,669	$1,842.9	$5,384.7
Florida	1,735	93,375	$1,490.0	$4,654.2
Texas	1,989	91,696	$1,551.6	$4,611.2
New York	1,707	47,014	$917.2	$2,345.5
North Carolina	1,196	42,279	$648.6	$1,798.5
Ohio	1,297	35,343	$566.1	$1,611.1
Massachusetts	1,134	36,957	$584.6	$1,607.0
Pennsylvania	1,292	34,148	$532.0	$1,509.7
Arizona	900	24,984	$384.5	$1,155.9
Illinois	1,092	26,741	$387.1	$1,146.4
Georgia	1,024	23,479	$385.2	$1,116.9
Tennessee	1,016	24,089	$380.5	$1,042.5
Utah	572	15,666	$347.6	$1,007.3

Source: TEConomy analysis.

Figure 1. Estimate of Total Economic Impact of Industry-Sponsored Clinical Trials Activity Across the U.S., 2017

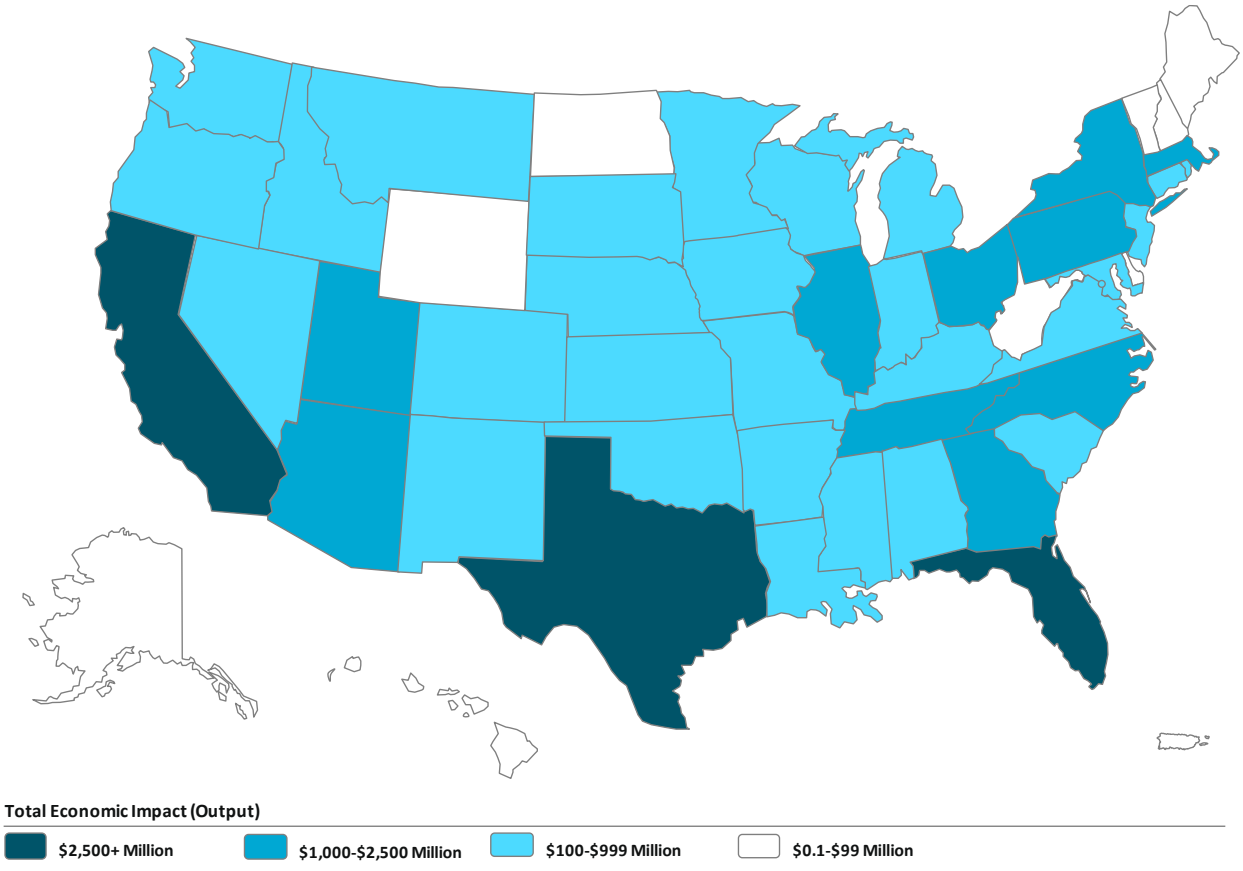

Table 6. Industry-Sponsored Clinical Trial Activity and Related Economic Impacts at Trial Sites by State, 2017

State	Number of Trials Active in State in 2017	Estimated Total Trial Enrollment	Estimated Total Site-Based Trial Investments in 2017 ($ millions)	Total Site-Based Economic Impact in 2017 ($ millions)	Largest Clinical Trial Disease Area by Total Estimated Enrollment
Alabama	664	14,062	$273.0	$672.8	Cardiovascular/Circulatory
Alaska	32	245	$2.8	$6.4	Oncology
Arizona	900	24,984	$384.5	$1,155.9	Cardiovascular/Circulatory
Arkansas	382	6,386	$109.0	$265.0	Oncology
California	2,152	102,669	$1,842.9	$5,384.7	Oncology
Colorado	847	14,947	$237.5	$706.9	Oncology
Connecticut	581	9,582	$145.2	$374.0	Oncology
Delaware	68	770	$7.3	$18.1	Cardiovascular/Circulatory
District of Columbia	294	4,433	$63.3	$106.9	Oncology
Florida	1,735	93,375	$1,490.0	$4,654.2	Oncology
Georgia	1,024	23,479	$385.2	$1,116.9	Cardiovascular/Circulatory
Hawaii	87	1,078	$13.7	$35.3	Oncology
Idaho	217	4,139	$58.7	$144.1	Infectious Disease/Virology
Illinois	1,092	26,741	$387.1	$1,146.4	Cardiovascular/Circulatory
Indiana	637	12,152	$183.5	$477.6	Cardiovascular/Circulatory
Iowa	293	5,650	$77.7	$187.1	Oncology
Kansas	535	13,255	$245.4	$628.4	Infectious Disease/Virology
Kentucky	501	9,866	$165.3	$406.5	Cardiovascular/Circulatory
Louisiana	516	12,591	$199.9	$502.6	Oncology
Maine	114	1,988	$24.5	$65.4	Cardiovascular/Circulatory
Maryland	872	19,317	$323.4	$845.7	Oncology
Massachusetts	1,134	36,957	$584.6	$1,607.0	Cardiovascular/Circulatory
Michigan	941	19,877	$288.0	$800.3	Oncology
Minnesota	653	13,942	$218.0	$629.8	Oncology
Mississippi	190	2,798	$51.9	$118.8	Cardiovascular/Circulatory
Missouri	970	18,953	$354.0	$981.1	Oncology
Montana	133	3,242	$61.6	$147.5	Infectious Disease/Virology
Nebraska	403	8,403	$153.2	$394.7	Infectious Disease/Virology
Nevada	418	8,189	$138.9	$357.1	Oncology
New Hampshire	151	2,144	$30.0	$79.4	Oncology
New Jersey	792	16,649	$320.4	$879.7	Oncology
New Mexico	232	3,536	$53.4	$126.0	Oncology
New York	1,707	47,014	$917.2	$2,345.5	Oncology
North Carolina	1,196	42,279	$648.6	$1,798.5	Cardiovascular/Circulatory
North Dakota	90	1,324	$16.4	$37.8	Cardiovascular/Circulatory
Ohio	1,297	35,343	$566.1	$1,611.1	Cardiovascular/Circulatory
Oklahoma	417	6,982	$113.1	$286.4	Cardiovascular/Circulatory
Oregon	577	8,675	$171.7	$450.2	Oncology
Pennsylvania	1,292	34,148	$532.0	$1,509.7	Oncology
Puerto Rico	15	53	$0.3	$0.5	Cardiovascular/Circulatory
Rhode Island	200	3,538	$53.1	$141.8	Oncology
South Carolina	708	18,475	$331.7	$829.4	Respiratory
South Dakota	144	2,338	$42.1	$101.8	Cardiovascular/Circulatory
Tennessee	1,016	24,089	$380.5	$1,042.5	Oncology
Texas	1,989	91,696	$1,551.6	$4,611.2	Oncology
Utah	572	15,666	$347.6	$1,007.3	Infectious Disease/Virology
Vermont	91	1,106	$12.2	$30.0	Cardiovascular/Circulatory
Virginia	759	17,685	$267.2	$695.7	Cardiovascular/Circulatory
Washington	847	25,267	$295.7	$783.5	Cardiovascular/Circulatory
West Virginia	118	1,276	$20.9	$46.5	Oncology
Wisconsin	409	6,811	$90.2	$237.4	Cardiovascular/Circulatory
Wyoming	4	8	$-*	$0.1	Oncology
U.S. Totals	**4,516**	**920,173**	**$15,231.9**	**$42,589.2**	**Cardiovascular/Circulatory**

Source: TEConomy analysis. Note: U.S. Totals for Number of Trials Active is non-duplicative so column will not sum.
*Wyoming value = $34 thousand.

Limitations of the Research

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 2017, because not all studies are required by law to be registered, especially a large number of Phase I trials. The estimates of the number of trials and spending by state for this early phase research are therefore likely to be conservatively low.

Second, data to estimate the share of a trial's participants in each state are limited. The data records within ClinicalTrials.gov provide target participation only at the trial level (actual participation is sometimes reported if recruitment is completed and the clinical trial record is updated). However, specific site or state level participation is not provided, so for estimation purposes participants are distributed equally across all trial sites provided.

However, evidence suggests that some sites over-enroll while others under-enroll. For example, the University of North Carolina at Chapel Hill found that[10]:

- 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 that the analysis relies on the use of average clinical trial costs by disease or therapeutic area to estimate total clinical trial spending, even though the cost of a clinical trial may vary significantly from trial to trial even within a therapeutic area. Drivers of variable and increased costs can include challenges of recruiting patients across multiple sites; certain therapeutic areas with unique recruitment and operational challenges, such as rare diseases; increasingly complex clinical trial protocol development; increased use of new technologies; and costs related to compliance regulations. This may be a particular concern for the 12 percent of trial records for which we lacked disease-specific average trial costs, and for which we therefore used the overall average cost across all disease areas. To the extent the actual cost per participant are above or below the average cost, total trial costs will be over or understated. However, we do not believe this introduce significant bias to the aggregate cost estimates.

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

These limitations notwithstanding, the estimates in this report provide a useful snapshot of the economic impact of industry-sponsored clinical trials in the U.S. in 2017.

Conclusion

This report identifies and estimates the significant investments biopharmaceutical companies make every year in supporting clinical trial activities across the U.S. These investments are critical to bringing new medicines to patients that will improve their health and quality of life. Clinical trial activity also provides important benefits to state and local economies in terms of the economic impact generated through trial-related activities such as the development of clinical trial protocols; the selection of clinical trial sites; the implementation of trials including the recruitment of physicians and other health care providers and various vendors; costs related to regulatory compliance; the manufacture of small batches for testing; services to patients, including clinical procedures and lab tests and ongoing health monitoring; and the collection, management, 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, this analysis identified more than 4,500 industry-sponsored clinical trials involving more than 920,000 volunteer trial participants in 2017. Biopharmaceutical companies invested over $15 billion at these trial sites, with an economic impact of more than $42 billion across the communities where the trials were located. Clinical trial sites operated in all 50 states, the District of Columbia, and Puerto Rico, reflecting the broad reach of the biopharmaceutical industry as well as the substantial unmet medical needs that exist across the U.S. These estimates describe a thriving life sciences ecosystem, one that not only produces medical innovations that improve lives, but which also delivers significant benefits to state and local economies. Maintaining this ecosystem requires a long-term view, with policies and regulatory structures that are consistent, predictable, and focused on meeting the needs of patients.

APPENDIX: Methodological Approach and 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.

ClinicalTrials.gov does not contain all clinical studies conducted in the United States because not all Phase I studies are required by law to be registered. Therefore, it is reasonable to assume that the total number of trials and trial participants generated from ClinicalTrials.gov is a lower-bound estimate of actual biopharmaceutical industry clinical trial activities.

The number of trial participants in each state was estimated based on total reported enrollment per trial, apportioned by state based upon the number of sites in each state listed within the ClinicalTrials.gov record, and with each site assigned the same number of participants. Total site-based trial costs were estimated by applying derived estimates of average per-participant costs by phase and disease or therapeutic area to the state-level enrollment estimates. Total state-level economic impacts were then estimated using standard input-output analysis, reflecting the economic multiplier effect in the states in which the clinical trials were located. The sections below describe these steps and the data used in more detail.

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 and include information on funding sources, trial sites, and numbers of enrolled participants. Using the ClinicalTrials.gov website search interface to access trial records, a query was used to identify the records of all interventional clinical trials sponsored by biopharmaceutical-related industry sources.

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

- Title, description, and design of the study
- Sponsors and collaborators in the study
- Recruitment status and total planned or actual enrollment
- Phase
- Disease or condition
- Intervention (for example, the medical product, behavior, or procedure being studied).
- Requirements for participation (eligibility criteria) and description of study participants (number starting and completing the study and their demographic data)
- Key trial and administrative dates – start date; primary completion date; completion date; and date of latest record update

Each clinical trial record also contains structured text field information containing additional trial protocol details. These records are available for large batch downloading in the form of Extensible Markup Language, also known as XML files. These files contain 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 records that correspond to non-fielded information including the locations of trial sites.

Records for all biopharmaceutical-related industry clinical trials (one XML file for each trial) active for at least one day in 2017 were downloaded in August 2018. 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.

Mapping Clinical Trials to Key Disease Areas

Using textual information found within the ClinialTrials.gov records as well as additional keywords generated by TEConomy, a broad list of keywords were developed to classify each clinical trial into one or more of the eleven specific disease/therapeutic areas or "other" (used when a trial did not map to one of the eleven areas). These keywords were often truncated textual roots (e.g., searching using "neuro" to capture neuroscience, neurodegenerative, neuropathy).

These keywords were searched against the textual information about the clinical trials (including title, conditions, interventions, and outcome measures) obtained from the ClinicalTrial.gov record. For those trials with keywords reflecting more than one disease area, TEConomy made a judgment call regarding which category to assign the clinical trial by examining the title and specific information about 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.

Finally, all Early Phase I trials were treated as Phase I trials for calculation purposes.

Estimating the Number of Industry-Sponsored Clinical Trials by State

Beyond the core information regarding each clinical trial's purpose, 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, Phase I trials listing only one site to large multinational Phase III and IV 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 calendar year 2017.

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, with trials increasingly likely to report actual enrollment numbers once trial recruitment is finished. For some trials providing estimated enrollment values, the final number of enrollees does not reach this level, while other trials exceed it. For the purposes of this estimation study, TEConomy used the estimated enrollment values as representative of overall clinical trial enrollment activity. Using the site and location information parsed out of the ClinicalTrials.gov records, TEConomy 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 global 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-state pair, 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 expected enrollment of 1,000 participants and includes 5 sites in Canada, 3 sites in Massachusetts, and 2 sites in North Carolina, the trial-specific state records would include one record with 300 enrollees for Massachusetts and one record with 200 enrollees for North Carolina and the remaining 500 enrollees assigned to Canada would be removed from subsequent data and calculations of U.S. activities.

Estimating Inflationary Increases in Clinical Trial Spending

The estimates developed from the ERG/Medidata Solutions information allowed for the development of phase-specific per-patient cost estimates for eleven disease/therapeutic areas and a twelfth "other" category for trials not related to one of the disease areas. These values were then expressed in 2017 dollars using the Biomedical Research and Development Price Index (BRDPI). (Table A-1).

Table A-1. Biomedical Research and Development Price Index, 2013-2017

Year	Inflationary Adjustment Over Previous Year
2013	1.9%
2014	2.1%
2015	2.0%
2016	2.2%
2017	2.5%

Source: NIH Office of Budget; https://officeofbudget.od.nih.gov/gbipriceindexes.html

The annual change in the BRDPI indicates how much the NIH budget must change to maintain purchasing power. The BRDPI was developed and is updated annually by the Bureau of Economic Analysis (BEA), Department of Commerce under an interagency agreement with the NIH. While the focus of NIH's work is largely basic and preclinical research, use of this inflationary factor is deemed more relevant than other available price indexes to the mix of inputs, supplies, and costs related to clinical trial research.

Estimating "Annual" Trial Duration

Most records within ClinicalTrials.gov have a sponsor provided "start date" and "primary completion date" indicating 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 six months to recruit a suitable participant group, these six 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; For this study's purposes 2017 is used. This 2017 filter was applied to the timeframe established by each trial's start and completion dates. Only trials that were active for at least one day in 2017 are included in the analysis. The number of active days in 2017 is then applied to the total number of days covered from Start Date to Primary Completion Date, to estimate what share of the trial's timeframe occurred within 2017. Of the 4,516 the 2017 "trial share" ranges from 0.04% to 100.00% (typically a Phase I trial that begins and ends all in 2017).

For example, if a Phase I trial started October 1, 2017 and was completed on December 31, 2017, all three months of this trial falls within the window, and hence, 100% of the trial's impact is captured as part of the analysis. If a Phase III started on October 1, 2016 and will complete on September 30, 2020, only 12 months of the total 48 months of the trial fall within the window, and hence, 25% of the trial's total impacts are captured as part of the analysis.

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

Economic impact broadly consist of three types of effects: ***direct effects*** (the impact of the actual "first round" spending by the biopharmaceutical companies for clinical trial service providers to conduct trials at each site), ***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 effects 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 I/O models for the U.S. and each state for 2016, the most recent models available. Economic values for 2017 activities were entered into the model as current dollars.

Because the overwhelming majority of state-level clinical trial activity (e.g., patient interactions and clinical trial costs) occur in "doctor's office" type settings, the model incorporates employment and other details of the economic sector Offices of Physicians (IMPLAN Sector 475).

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 economy, leading to a total economic impact metric (i.e., total output impacts) for the U.S., each state, the District of Columbia, and Puerto Rico.