

BMJ Open Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015–2017: a cross-sectional study

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ABSTRACT

Objectives Little is routinely disclosed about the costs of the pivotal clinical trials that provide the key scientific evidence of the treatment benefits of new therapeutic agents. We expand our earlier research to examine why the estimated costs may vary 100-fold.

Design A cross-sectional study of the estimated costs of the pivotal clinical trials supporting the approval of 101 new therapeutic agents approved by the US Food and Drug Administration from 2015 to 2017.

Methods We licensed a software tool used by the pharmaceutical industry to estimate the likely costs of clinical trials to be conducted by contract research organisations. For each trial we collected 52 study characteristics. Linear regression was used to assess the most important factors affecting costs.

Primary and secondary outcome measures The mean and 95% CI of 225 pivotal clinical trials using varying assumptions. We also assessed median estimated costs per patient, per clinic visit and per drug.

Results Measured as pivotal trials cost per approved drug, the 101 new molecular entities had an estimated median cost of US\$48 million (IQR US\$20 million–US\$102 million). The 225 individual clinical trials had a median estimate of US\$19 million (IQR US\$12 million–US\$33 million) per trial and US\$41 413 (IQR, US\$29 894–US\$75 047) per patient. The largest single factor driving cost was the number of patients required to establish the treatment effects and varied from 4 patients to 8442. Next was the number of trial clinic visits, which ranged from 2 to 166. Our statistical model showed trial costs rose exponentially with these two variables ($R^2=0.696$, $F=257.9$, $p<0.01$).

Conclusions The estimated costs are modest for measuring the benefits of new therapeutic agents but rise exponentially as more patients and clinic visits are required to establish a drug effect.

INTRODUCTION

The costs of conducting clinical drug trials are not among the extensive public disclosures now required by US federal law,¹ the International Committee of Medical Journal Editors² and other entities. When this project

Strengths and limitations of this study

- To ensure our selection of new drugs was representative, our sample included all new therapeutic drugs approved over a recent 3-year period.
- Our estimated costs were calculated using a software program that used extensive underlying actual trial site and protocol data.
- Our costs are estimated rather than actual and we used default assumptions for some trial characteristics that were not publicly available.
- The estimates assess a range of what a contract research organisation might charge to conduct the study and do not include sponsor costs for study design, contract monitoring or medication.
- These estimates do not reflect the total costs of developing a new drug, which include many other kinds of laboratory, animal and human studies.

began in 2017, a literature search revealed a single published study assessing the costs of conducting individual clinical trials.³ Nevertheless, this information is central to debates about whether requirements for testing a new drug to meet US Food and Drug Administration (FDA) or European Medicines Agency standards are too burdensome, or the trials are so expensive that they justify high drug prices. To provide a factual foundation for this debate, we licensed a pharmaceutical industry cost estimating tool and began systematically collecting data about recent pivotal trials that supported FDA approval. Pivotal trials are those studies in humans that provide under US law ‘substantial evidence’ of benefit to justify marketing approval.⁴ They are the largest and most expensive studies in the cycle of drug development testing and are conducted to verify the existence of or measure the extent of benefits in the patient population expected to be treated. Pivotal



trials also provide seminal information on safety, which is also assessed in phase I studies of pharmacokinetic effects and in specialised safety studies where needed.

We previously published initial reports on a subset of these trials.^{5,6} For this study we expanded our trial data by 40% and for the first time analysed cost per drug and focused on the reasons why costs of conducting clinical trials could vary by more than 100-fold.

METHODS

Study data

We identified all new therapeutic agents from the 2015–2017 annual reports on novel drugs published by the FDA's Center for Drug Evaluation and Research.^{7–9} We excluded agents for diagnostic, medical and surgical procedures because these short-term exposures require notably different clinical testing. The pivotal trials that provided substantial evidence of benefit were those specifically cited in the standard FDA approval document, the Summary Review or Cross Disciplinary Review.

For each pivotal trial we collected 52 items of information from three public sources: clinicaltrials.gov, drugs@FDA and published peer-reviewed studies. One group of variables described basic clinical trial features, including the medical condition being treated, number of patients screened, number enrolled in the trial and duration of treatment. Another group of variables specified the varying kinds of treatment benefits being measured and the way they were measured. This included endpoint type (surrogate or biomarker, clinical scale, clinical benefit), and form of control or comparison group (uncontrolled, placebo, active drug). A third group of variables related to features that affect the conduct of the trial, including the number of patient personal visits to the study clinic, the geographic location and number of study sites, number of languages needed for study materials and length of time it took sites to complete the trial protocol. The variables, data sources and methods are described in greater detail in our previous study and supplement.⁵

Estimated trial cost study outcome

We derived the estimates for each trial using the IQVIA CostPro Mid-Level Tool,¹⁰ a clinical trial cost estimating programme used by pharmaceutical manufacturers. Its estimates were derived from actual data from 2000 final awarded trial proposals and integrates cost information from 200 000 trial sites in 60 countries. For each trial CostPro produced a low, median and high estimate based on industry benchmark data. The programme also provided default values derived from industry benchmarks for occasional missing values, such as number of patients screened. The medical condition treated and related therapeutic areas were defined in the IQVIA CostPro Mid-Level Tool based on a subset of the International Classification of Diseases Version 9. Our preliminary investigation revealed that some trial costs are driven by trial conduct features that are not publicly available.

This included the number of amendments to the trial protocol, the number of Institutional Review Boards, and how frequently sites were monitored. After consulting with experienced trialists, we computed two sets of estimates, one assuming more efficient trial conduct, and one less efficient. Our primary outcome variable was the mean (95% CI) of all six estimates, three from each efficiency assumption group. All costs were in current US dollars.

Statistical analysis

We report the median and IQR for most variables because they were not normally distributed. For assessing differences between categorical variables, we used a non-parametric test of significance, the Kruskal-Wallis rank sum tests. We used linear regression to model the relationship of trial cost with patients enrolled and patient visits but after log-transforming these variables to achieve a near-normal distribution. The R package for statistical computing, V.3.5.3, was used for all statistical analysis.

Review and verification

Prior to collecting the data for this study, we conducted sensitivity analysis of the input variables for the CostPro Mid-Level Tool to assess each major variable and whether default values were calculated on the basis of the underlying source data from clinical site contracts. Some variables, such as the countries where trial sites were located and the specific disease condition being treated, proved to have a marked effect on estimated costs. Next, we tested the CostPro tool to compare our estimating methods with some of the available published estimates and determined that they were similar. Finally, we reviewed our preliminary methods and results with experienced clinical trialists with hands-on experience working with trial cost estimates.

Patient and public involvement

No patient or public involvement.

RESULTS

Our data include 101 new drugs and 225 pivotal clinical trials that enrolled 156 140 patients who were studied for treatment effects in 2 241 401 clinic visits. Characteristics of the source trials data are shown in [table 1](#).

Overall, the estimated cost of trials supporting the approval of 101 approved drugs was a median of US\$48 million (IQR US\$20 million–US\$102 million). The estimated costs per drug and by therapeutic area are shown in [table 2](#). Each individual pivotal trial cost a median of US\$19 million (IQR US\$12 million–US\$33 million). The estimated cost per patient was US\$41 413 (IQR US\$29 894–US\$75 047), and each patient visit to the study clinic cost an estimated median of US\$3685 (IQR US\$2640–US\$5498).

Costs per drug varied substantially by the number of pivotal clinical trials conducted to support marketing

Table 1 Patients, trials and drug totals in pivotal trials

Total by approval year				
	2015	2016	2017	Total
Drugs	40	19	42	101
Trials	86	52	87	225
Patients	69 050	28 111	58 979	156 140
Total by trials per drug				
Trials per drug	Number of drugs	Total patients		
1	45	49 022		
2	29	32 157		
3–11	27	74 961		

approval. Costs were generally lowest when the requirement for replication was waived and a single trial accepted. Overall, 45/101 (45%) of drugs were approved with a single trial with a median cost of US\$28million (IQR US\$13million–US\$62million). As might be expected, the replication requirement for two trials nearly doubled the estimated cost per drug of 29 other drugs to a median US\$45million (IQR US\$28million–US\$69million). In addition, 27 drugs were approved with 3–11 clinical trials each at an estimated overall median cost of US\$91million (IQR US\$56million–US\$128million) per drug. The reason for three or more trials was because approval was sought for several closely related indications, often combination or adjuvant therapy.

From an individual clinical trial perspective, the largest single influence on estimated cost was the number of patients needed to establish the treatment effects. Although the trials enrolled a median of 495 patients there was wide variation, ranging from 4 patients to 8446

Table 2 Estimated cost of trials per drug by therapeutic area

Therapeutic area	Drugs	Median (IQR), US\$ in millions
Blood	2	6(4–8)
Cardiovascular	6	141(74–183)
Central nervous system	14	42(16–85)
Dermatology	9	50(31–77)
Endocrine/metabolism	12	72(14–144)
Genitourinary	4	23(12–37)
Gastrointestinal	7	31(15–63)
Infectious	9	54(26–102)
Musculoskeletal	2	68(48–87)
Oncology	30	45(29–72)
Ophthalmological	3	36(34–44)
Respiratory	3	91(73–110)
Overall	101	48(20–102)

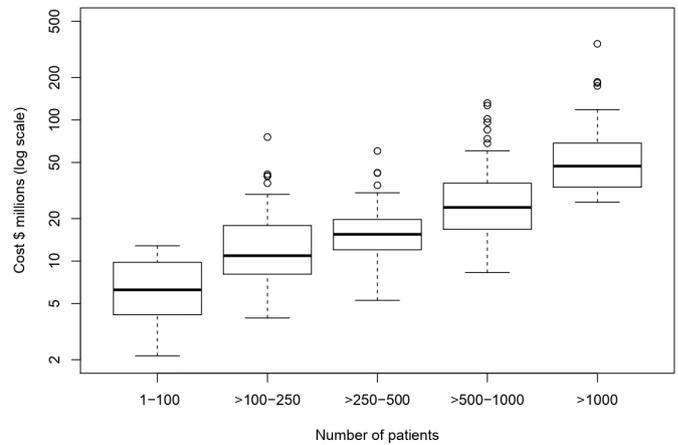


Figure 1 Patient enrolment and estimated cost of pivotal trials. Kruskal-Wallis $\chi^2=110.1$, $df=4$, p value <0.01 .

patients. The differences and variability within patient enrolment categories are shown in the boxplots in figure 1. It also shows that there were often outliers to the median estimates even after plotting the data on a log scale.

One factor requiring more patient enrolment was when already approved drugs were known to be effective for the indication sought. One measure of the availability of other effective drugs was the need for an active drug comparison group rather than an inactive placebo. The 62 trials with an active drug control group enrolled a median of 653 patients, compared with 547 patients for placebo control, and 145 patients in uncontrolled trials.

While the number of patients required was the most important cost driver, we also observed variation in the trial cost per patient. Treatments varied in intensity from eye drops and skin creams to infusions of multiple oncology drugs. Table 3 shows how cost per patient varied by therapeutic area.

Table 3 Per patient estimated pivotal trial costs by therapeutic area

Therapeutic area	Trials	Median (IQR), US\$
Blood	2	310 975(200 213–421 738)
Cardiovascular	6	34 857(22 922–50 540)
Central nervous system	33	39 467(31 825–67 988)
Dermatology	21	24 861(19 523–30 573)
Endocrine/metabolism	52	40 612(34 874–63 420)
Genitourinary	7	39 640(23 179–47 100)
Gastrointestinal	12	27 887(25 633–55 687)
Infectious	31	37 175(31 497–49 283)
Musculoskeletal	3	58 212(34 811–63 447)
Oncology	39	100 271(80 880–155 714)
Ophthalmological	9	23 893(16 990–29 894)
Respiratory	10	53 590(39 062–59 814)
Overall	225	41 413(29 894–75 047)

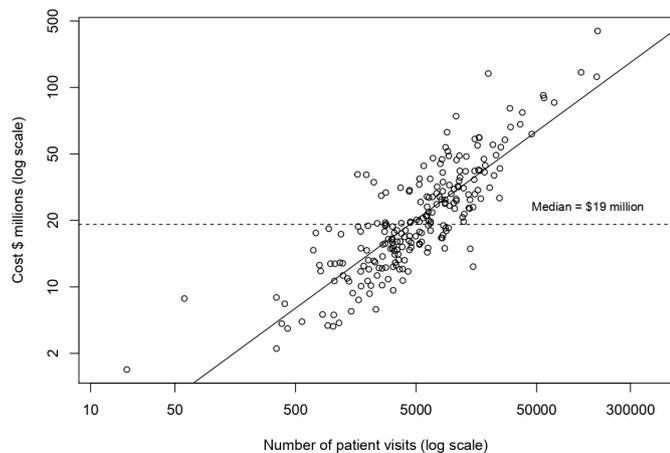


Figure 2 Patient visits versus estimated costs for pivotal trials. Adjusted $R^2=0.696$, $F=257.9$ on 2 and 222 df, $p<0.01$. Variables log transformed.

The second-ranked influence on the estimated cost of the pivotal trials was the number of clinic visits required for screening, baseline randomisation, treatment and benefit assessment. The pivotal trials had a median 11 trial visits (IQR 8–17) and ranged from 2 to 166 visits. Each additional trial visit added a median of US\$2 million (IQR US\$1 million–US\$3 million) to the overall estimated trial cost. More trials visits could reflect greater intensity of treatment as well as longer duration of treatment or observation.

The results of linear regression predicting estimated trial costs based on the number of enrolled patients and the number of trial visits are shown in figure 2. This combination of just these two variables into individual patient clinic visits explained 69% of the variation (R^2) in estimated costs of pivotal trials. Both dependent and independent variables were log transformed to normalise the distribution. Analysis of variance showed the number of patients explained more than three times as much variation as the number of visits. Additional regression details are shown in figure 2.

DISCUSSION

Our study shows that the cost burden of conducting pivotal trials is driven by two central questions: (1) How many patients are needed to show a drug benefit? (2) How many times do they need to be seen? Our model reveals an exponential growth in estimated costs as the numbers of patients and clinic visits increase. Furthermore, both the number of patients enrolled and the number of clinic visits varied widely even among new molecular entities receiving their initial approval. From the perspective of total pivotal trial costs for new drug approval, estimated costs also increased with the number of trials required.

Overall, the estimated costs are modest for establishing the benefits that will guide the treatment of thousands to millions of future patients. We estimated a median of US\$48 million per drug and US\$41 413 per patient enrolled. Note that these costs-per-patient for these trials

are sometimes similar to what pharmaceutical companies charge for these same drugs to treat a single patient or a handful of patients after marketing approval.

Our study has limitations. Our pivotal trial costs are credible estimates and not actual trial costs—which could have been lower or higher. For some trial features that were not publicly available we used default values derived from other studies, or a range of assumptions. The study did not include sponsor costs for trial design, contract monitoring and the medication. While our selection of recent trials was large and varied, it includes only a recent 3-year period. These estimates are intended to characterise the costs of obtaining the most important scientific evidence of benefit of a new molecular entity and do not reflect the overall costs of drug development.

CONCLUSIONS

At a median cost of US\$41 413 per patient enrolled, the costs of obtaining this key scientific evidence are modest. Estimated costs were higher for drugs that required a comparison with an already approved and effective drug. They were lowest when the FDA waived the requirements for a control group and replication of the trial evidence.

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Competing interests GCA is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; serves as a paid advisor to IQVIA; is a paid consultant and holds equity in Monument Analytics, a healthcare consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation and is a member of OptumRx's National P&T Committee. This arrangement has been

reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Declared exempt from review by the Johns Hopkins School of Public Health Institutional Review Board because the source data did not contain identifiable human data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The cost estimates for this study were obtained under license and are not available for sharing.

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