



P-hacking in clinical trials and how incentives shape the distribution of results across phases

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Clinical research should conform to high standards of ethical and scientific integrity, given that human lives are at stake. However, economic incentives can generate conflicts of interest for investigators, who may be inclined to withhold unfavorable results or even tamper with data in order to achieve desired outcomes. To shed light on the integrity of clinical trial results, this paper systematically analyzes the distribution of *P* values of primary outcomes for phase II and phase III drug trials reported to the ClinicalTrials.gov registry. First, we detect no bunching of results just above the classical 5% threshold for statistical significance. Second, a density-discontinuity test reveals an upward jump at the 5% threshold for phase III results by small industry sponsors. Third, we document a larger fraction of significant results in phase III compared to phase II. Linking trials across phases, we find that early favorable results increase the likelihood of continuing into the next phase. Once we take into account this selective continuation, we can explain almost completely the excess of significant results in phase III for trials conducted by large industry sponsors. For small industry sponsors, instead, part of the excess remains unexplained.

clinical trials | drug development | selective reporting | p-hacking | economic incentives in research

The evidence produced in clinical trials is susceptible to many kinds of bias (1–3). While some such biases can occur accidentally, even unbeknownst to the study investigators, other biases may result from strategic behavior of investigators and sponsors. In addition to the public value of improving medical treatments, the information obtained through clinical trials is privately valuable for the sponsoring pharmaceutical companies that aim to demonstrate the safety and efficacy of newly developed drugs—the prerequisite for marketing approval by authorities such as the US Food and Drug Administration (FDA). Given the sizeable research and development costs involved (4) and the lure of large potential profits, investigators can suffer from conflicts of interest (5–8) and pressure to withhold or “beautify” unfavorable results (9, 10) or even fabricate and falsify data (11).

In the 1990s and 2000s, many medical scholars began calling for more transparency in clinical research (12), following public outcry over alarming evidence of selective publication of trial results (13–15), cases of premature drug approvals (16), and allegations of data withholding (17). As a response to these concerns, policymakers established publicly accessible registries and result databases (18, 19), such as ClinicalTrials.gov (20, 21) (see *SI Appendix* for more details on the ClinicalTrials.gov registry and the legal requirements for reporting trial results).

ClinicalTrials.gov now contains sufficient data to allow for a systematic evaluation of the distribution of reported *P* values. Our analysis builds on and develops the methods proposed in the literature that investigates “p-hacking,” publication bias, and the “file-drawer problem” (22, 23) for academic journal publications in a number of fields, ranging from life sciences (24) to psychology (25, 26), political science (27, 28), and economics (29–31).

Given the escalation of stakes as research progresses through phases, clinical trials are particularly well suited to detect how economic incentives of sponsoring parties drive research activity (32–34) and reporting bias. Economic incentives in clinical trials may depend on the size of the sponsoring firm (32). Compared to larger companies, smaller firms may have more to gain by misreporting results—and less reputation to lose if they are exposed. In other contexts, such reputational concerns have been found to vary by firm size (35, 36) or by academic prominence (37).

While the previous literature focused mostly on scientific publications in academic journals for which prepublication research results are typically not observable, ClinicalTrials.gov allows us to observe results from clinical trials in earlier research phases. Thus, we are able to follow the evolution of research results over time and construct counterfactuals not available in previous work. By linking trials across different phases of clinical research, we are able to quantify the effect of the incentives to selectively continue experimental research depending on early stage results.

Methods and Results

Our focus is on preapproval interventional superiority studies on drugs carried out as phase II and phase III trials. Trials in phase II investigate drug safety and efficacy, typically with a small sample of experimental subjects. Phase III trials investigate

Significance

Statistical significance in clinical trials is a key prerequisite for marketing approval of new drugs. The large economic payoffs at stake might undermine investigators’ ethical obligations and incentivize manipulation of results. This study systematically evaluates the integrity of results reported to the largest registry of clinical trials, ClinicalTrials.gov. Contrary to what has been documented in previous studies of academic publications across a number of disciplines, our analysis does not detect evidence for widespread manipulation of results to clear the 5% threshold for statistical significance. However, we find that the increase in the share of significant results from phase II to phase III can be explained only partially by investigators’ incentives to selectively continue experimentation following favorable early results.

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The authors declare no competing interest.

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Data deposition: A complete replication package is available at the Harvard Dataverse (<https://doi.org/10.7910/DVN/NBLYSW>).

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efficacy, while monitoring adverse effects on a larger sample of individuals, and play a central role in obtaining approval to market the drug from regulators such as the FDA. To facilitate the analysis, we transformed the P values into test statistics, supposing that they would all originate from a two-sided Z test of a null hypothesis that the drug has the same effect as the comparison. This transformation allowed us to investigate both the overall shape of the distribution and the region around the thresholds for statistical significance more easily (see *Materials and Methods* and *SI Appendix* for further information on the data and the P - Z transformation).

The Distribution of Z Scores: Irregularity Tests. Fig. 1 displays density estimates of the constructed z statistics for tests performed for primary outcomes of phase II and phase III trials. We present results for all trials in Fig. 1A and subsequently provide the breakdown by affiliation of the lead sponsor: nonindustry (NIH, US federal agencies, universities, etc.) in Fig. 1B, top-10 industry (the 10 pharmaceutical companies in the sample with the largest revenues in 2018; *SI Appendix, Table S1*) in Fig. 1C, and small industry (the remaining smaller pharmaceutical companies) in Fig. 1D.

Next, we diagnosed three possible irregularities in the distribution of z statistics of trials, at or above the 5% significance threshold, corresponding to a z statistic of 1.96. Further technical details and robustness checks are gathered in *SI Appendix*.

Spike in the Density Function Just Above 1.96. First, we detected no spikes in the densities (or discontinuities in the distribution functions) just above 1.96, the salient significance threshold. Such spikes, indicating that results are inflated to clear the significance hurdle, have been documented in previous studies of z distributions for tests in academic publications across life sciences (24), as well as economics (31) and business studies (39). Thus, the more natural distribution of z scores from ClinicalTrials.gov displays more integrity compared to results reported for publications in scientific journals. This difference may partially be explained by the absence of the additional layer of editorial selection, which may be based also on the statistical significance

of presented results. This first finding suggests that registered results are not inflated at the margin just to clear the significance threshold.

Discontinuity of the Density Function at 1.96. Second, we investigated the presence of a discontinuity in the density of z statistics with a test that relies on a simple local polynomial density estimator (38). The densities for phase II trials were smooth and did not show a noteworthy upward shift at the 1.96 threshold in all cases. In contrast, the densities of z statistics for industry-sponsored (both small and top 10) phase III trials displayed a break at 1.96. The break was statistically significant only for phase III trials undertaken by small pharmaceutical companies (Fig. 1D), with a persistent upward shift to the right of the threshold, indicating an abnormal amount of significant results. This pattern is suggestive of “selective reporting” i.e., strategic concealment of some nonsignificant results.

The different patterns observed between large and small industry sponsors (Fig. 1C and D) were robust across a wide range of alternative ways to define “large” sponsors (*SI Appendix, Fig. S1*). Moreover, we found a similar discontinuity for phase III trials by small industry sponsors when transforming P values to test statistics of a one-sided instead of a two-sided test (*SI Appendix, Fig. S2*).

Excess of Significant Results in Phase III Compared to Phase II. Third, Fig. 1 indicates an excess of favorable results over the 1.96 threshold in phase III compared to phase II. More favorable results were more likely to be observed in phase III than in phase II. The phase III distribution of z statistics stochastically dominates the phase II distribution. Dominance is particularly strong for industry-sponsored trials (Fig. 1C and D). This pattern appears suspicious, but it is not as alarming as a spike at the significance threshold. While only 34.7% of phase II trial results by nonindustry sponsors fell above 1.96 (and 34.8%, respectively, for phase III, a difference that is not statistically significant), the fraction of significant results rose to 45.7% in phase II and 70.6% in phase III for industry-sponsored trials.

Recall that the analysis above considered only P values associated to primary outcomes of trials. These results constitute

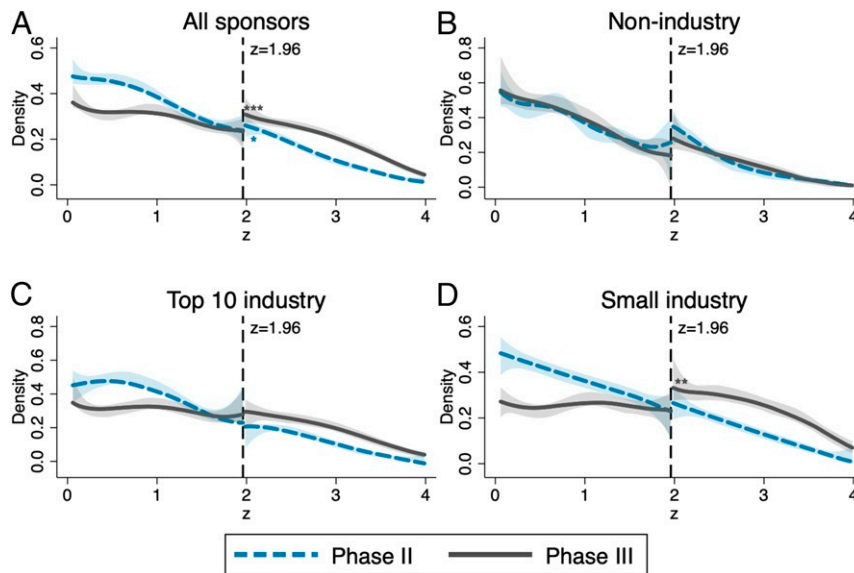


Fig. 1. Comparison of phase II and phase III densities of the z score and tests for discontinuity at $z = 1.96$, depending on the affiliation of the lead sponsor. Density estimates of the constructed z statistics for primary outcomes of phase II (dashed blue lines) and phase III (solid gray lines) trials are shown. The shaded areas are 95% confidence bands, and the vertical lines at 1.96 correspond to the threshold for statistical significance at the 0.05 level. Sample sizes: $n = 3,953$ (phase II), $n = 3,664$ (phase III) (A); $n = 1,171$ (phase II), $n = 720$ (phase III) (B); $n = 1,332$ (phase II), $n = 1,424$ (phase III) (C); and $n = 1,450$ (phase II), $n = 1,520$ (phase III) (D). Significance levels for discontinuity tests (38) are shown. $***P < 0.05$; $****P < 0.01$. Exact P values are reported in *SI Appendix, Table S2*.

the main measure for success of the treatment being trialed, for both the investigators themselves and the evaluating authorities. The densities of z scores from lower-stake secondary outcomes for all groups of sponsors and both phases did not display any meaningful discontinuity at the significance threshold (*SI Appendix, Fig. S3 and Table S5*). Moreover, for secondary outcomes, the excess of significant results from industry-sponsored trials in phase III relative to phase II was much smaller compared to the distribution for primary outcomes. We found irregularities only for higher-stake primary outcomes, suggesting that incentives of reporting parties play a role.

Linking Trials across Phases: Controlling for Selective Continuation.

The FDA focuses mainly on phase III results when deciding about marketing approval, a decision with major financial consequences for pharmaceutical companies. Given these incentives, the observed excess of significant results, particularly in the group of industry-sponsored phase III trials, could be interpreted as evidence of tampering (p-hacking) or nondisclosure of negative results (selective reporting). However, this conclusion would be premature without first carefully examining the dynamic incentives underlying clinical research, as we set out to do.

An alternative explanation for the excess of significant results in phase III relative to phase II is the selective continuation of drug testing to the next phase only when initial results are sufficiently encouraging. Selective continuation saves on costly clinical research and can thus even be socially desirable, as long as such economic considerations do not distort research activity away from important, but costly, projects (8). Also, from an ethical viewpoint, no further trials with volunteer patients should be conducted when a drug is highly unlikely to have a positive impact. Time and resources should be devoted to more promising projects instead. We outline a model of the sponsor's continuation decision in *Materials and Methods*.

To identify the impact of selective continuation, we developed a procedure to link phase II and phase III trials in our dataset based on the main intervention (i.e., the tested drug or combination of drugs), the medical condition to be treated, and the timing. This procedure is illustrated in Fig. 2. A given phase II trial may either 1) have no corresponding phase III trial with the same intervention and same condition; or 2) have one or multiple matches in phase III. In the latter case, we considered the phase II trial as continued into phase III. The resulting linked data, which we make available to the research community (40), is a key input in the methodology we developed to estimate a selection function capturing selective continuation for industry-sponsored trials.

Following our model of the firm's continuation decision, we estimated the selection function with a logistic regression of a dummy variable indicating if there is at least one match among the phase III trials in the database (regardless of whether phase III results are reported or not) on the phase II z score. We controlled for adjustment for multiple hypothesis testing, a flexible time trend, and other covariates that might influence the perceived persuasiveness of phase II results (square root of overall enrollment to each trial as proxy for power of the statistical tests and active comparator vs. placebo) or the economic incentives to undertake research (fixed effects for the treated condition) on top of the z score; see *Materials and Methods* for the exact specification. The predicted values of this selection function can be interpreted as the probability that a drug progresses to phase III, conditional on the information available at the end of phase II, consisting of the phase II z score and other covariates.

In most cases, very low P values are no longer reported precisely, but only as being below the thresholds 0.001 or 0.0001 (e.g., $P < 0.001$ instead of $P = 0.0008$). Therefore, we estimated the continuation probability separately for those two cases by including dummies for " $z > 3.29$ " (corresponding to the P value being reported as $P < 0.001$) and " $z > 3.89$ " (corresponding to $P < 0.0001$) in the specification of the selection function.

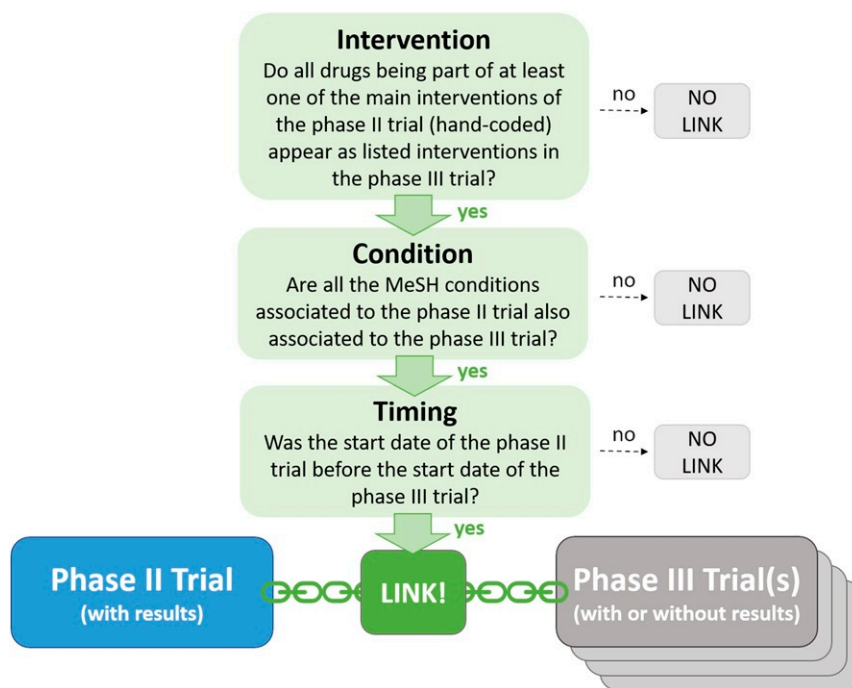


Fig. 2. Linking phase II and phase III trials. We considered a phase II trial as continued if we found at least one phase III trial registered in the database (regardless of whether associated results are reported or not) fulfilling all three criteria (intervention, condition, and timing). See *SI Appendix* for a more detailed description of the linking procedure.

Table 1 displays the estimated logit coefficients for all industry sponsors (column 1) and for small and top-10 industry sponsors separately (columns 2 and 3, respectively). Fig. 3 illustrates the estimated selection functions graphically. The solid green line shows the predicted continuation probability as function of the phase II z score. A higher z score in phase II significantly increases the probability of continuation to phase III. The lighter dotted and darker dashed lines show the predictions when considering only trials conducted by small sponsors or, respectively, the 10 largest industry sponsors. The estimated continuation probabilities suggest that larger companies continue research projects more selectively. The overall share of matched trials is lower for large industry sponsors, captured by the downward shift of the selection function.

In the context of our model of the firm's continuation decision, the continuation probability is negatively associated with the opportunity cost of continuing a specific project. On average, this cost can be expected to be greater for large sponsors with many alternative projects. This interpretation is in line with findings from previous studies arguing that managers of larger firms with multiple products in development have less private costs attached to terminating unpromising research projects and, thus, are more efficient (32).

In *SI Appendix, Table S6*, we report estimates of the same logistic model when considering the phase II z scores associated to secondary outcomes instead of primary outcomes. The coefficients related to the z score are much smaller in magnitude, and most of the coefficients are not statistically significant, notwithstanding the much larger sample size. This finding confirms that the evaluation of a trial's success, and therefore also selective continuation, is based predominantly on primary outcomes.

Decomposition of the Difference in Significant Results between Phase II and Phase III. Under the assumption that, conditional on our control variables, the expected z statistic in phase III equals the z of a similar phase II trial, we can construct a hypothetical phase III distribution for primary outcomes accounting for selective continuation. To do so, we estimated the kernel density of phase II statistics (for now, disregarding $z > 3.29$ and $z > 3.89$) reweighting each observation by the continuation probability predicted by our selection function, given the characteristics of the phase II trial. The resulting counterfactual density can be compared to the actual phase II and phase III densities, which we estimated using a standard unweighted kernel estimator.

Since the selection function is increasing in the phase II z score, the counterfactual z density rotates counter-clockwise, increasing the share of significant results (*SI Appendix, Fig. S4*). To calculate the overall share of significant results under the hypothetical regime, we combined the estimated densities with the number of $z > 3.29$ and $z > 3.89$ results predicted from the selection functions and renormalize to one.

Based on this construction, we decomposed the difference in the share of significant results in phase II and phase III into two parts: selective continuation and an unexplained residual. As illustrated in Fig. 4A and *SI Appendix, Table S7*, when we considered all industry-sponsored trials, selective continuation, i.e., economizing on the cost of trials that are not promising enough, accounted for more than half of the difference, leaving 48.5% of the difference unexplained.

Next, we repeated the estimation procedure separately for trials sponsored by large and small industry. The difference in the share of significant results between phase II and phase III was slightly larger for trials by small sponsors (21.9 percentage points for top-10 industry vs. 25.8 percentage points for small industry). For trials sponsored by the 10 largest companies, the difference between the actual share of significant phase III results and the share predicted by selective continuation from phase II shrank to 3.4 percentage points and was no longer statistically significant. Thus, for top-10 industry sponsors, our methodology suggests no indication of selective reporting or potential tampering: Selective continuation can explain almost the entire excess share of significant results in phase III trials compared to phase II trials.

A different picture emerged for small industry sponsors. According to the selection function estimated in Table 1 and displayed in Fig. 3, small sponsors were much more likely to proceed to phase III than large sponsors, especially following phase II trials with relatively low z statistics. Hence, for small sponsors, selective continuation was less pronounced and can only account for less than one-third of the excess share of significant results in phase III trials compared to phase II trials. Phase III results actually reported by small sponsors appeared to be much more favorable than predicted by the selection function; for these sponsors, we are left with a statistically significant unexplained residual of 18.4 percentage points, as displayed in Fig. 4A.

As illustrated by Fig. 4B and C, these different patterns between large and small industry sponsors are robust across a wide range of alternative ways to define "large" sponsors. For small sponsors (Fig. 4B), the share of the explained difference

Table 1. Estimates of logit selection function for selective continuation, based on primary outcomes

Sponsor	(1) All industry	(2) Small industry	(3) Top-10 industry
Phase II z score	0.331*** (0.0793)	0.266*** (0.100)	0.404*** (0.130)
Dummy for phase II z score reported as " $z > 3.29$ "	1.063*** (0.226)	0.756** (0.329)	1.750*** (0.373)
Dummy for phase II z score reported as " $z > 3.89$ "	1.232*** (0.255)	0.787*** (0.285)	1.643*** (0.446)
Mean dependent variable	0.296	0.344	0.246
P value Wald test (2) = (3)		0.00480	0.00480
Controls	Yes	Yes	Yes
MeSH condition fixed effects	Yes	Yes	Yes
Completion year fixed effects	Yes	Yes	Yes
Observations	3,925	2,017	1,908
No. of trials	1,167	674	493

Unit of observation: trial-outcome; included controls: square root of the overall enrollment, dummy for placebo comparator, and dummy for multiple hypothesis testing adjustment. See *Materials and Methods* for the exact specification. Categories for condition fixed effects are based on Medical Subject Headings (MeSH) terms associated to the trials (21); for more details, see *SI Appendix*. " P value Wald test (2) = (3)" reports the P value of a Wald test of the null hypothesis of joint equality of the coefficients in the first three rows and the constant between columns 2 and 3. SEs in parentheses are clustered at the MeSH condition level; significance levels (based on a two-sided t -test) are indicated. ** $P < 0.05$; *** $P < 0.01$.

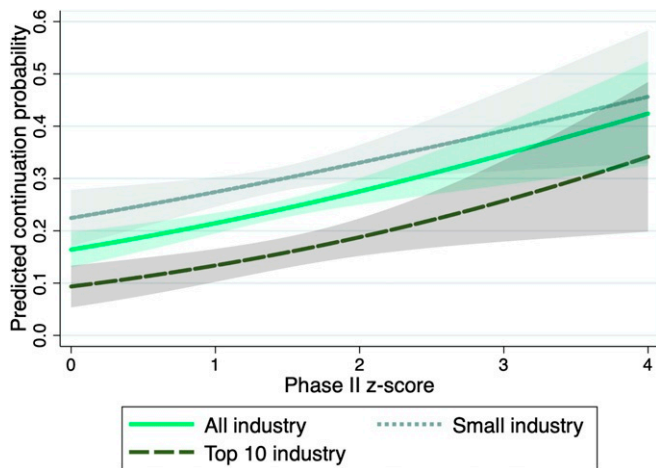


Fig. 3. Predicted continuation probability as function on the phase II z score, depending on affiliation of lead sponsor. Predictions are based on the estimated logit selection functions for selective continuation; see Table 1 for the estimated coefficients. All control variables are fixed at their mean values. The shaded areas are 95% confidence bands.

ranges between 19% and 44% with the majority of results being very close to the estimate in our main specification (29%). Also, for different definitions of large sponsors (Fig. 4C), the estimates are quite close to the result from our main specification (85%), ranging between 57% and 101%.

These findings are consistent with our earlier observation that small industry is the only group of sponsors for which the phase

III z density exhibits a statistically significant discontinuity at the 1.96 threshold. Along the same lines, a recent evaluation of compliance with FDA requirements for reporting of trial results to ClinicalTrials.gov finds that compliance improves with sponsor size (41).

Discussion and Conclusion

Overall, the distribution of z scores from ClinicalTrials.gov does not indicate widespread manipulation of results reported to the registry. Given the increasing adoption of randomized control trials across life and social sciences, our findings speak in favor of setting up repositories similar to ClinicalTrials.gov in these other domains to monitor results and improve the credibility of research.

As we show, to correctly interpret the distribution of research results, it is important to understand the sequential nature of research and its interplay with economic incentives. Although phase III trials appear to deliver too many positive results, we can explain a large part of this excess of favorable results by linking them to phase II outcomes and accounting for selective continuation.

However, we find that selective continuation cannot explain fully the high number of significant results in phase III trials sponsored by smaller firms. For the same group of trials, we also identified a discontinuity in the density at the classical significance threshold. These patterns suggest that enforcers of registration should pay particular attention to smaller industry sponsors, for which reputational concerns may be less consequential—a channel that should be investigated more thoroughly by future work.

In conclusion, our exploratory findings indicate that current levels of regulation and enforcement are not sufficient to fully

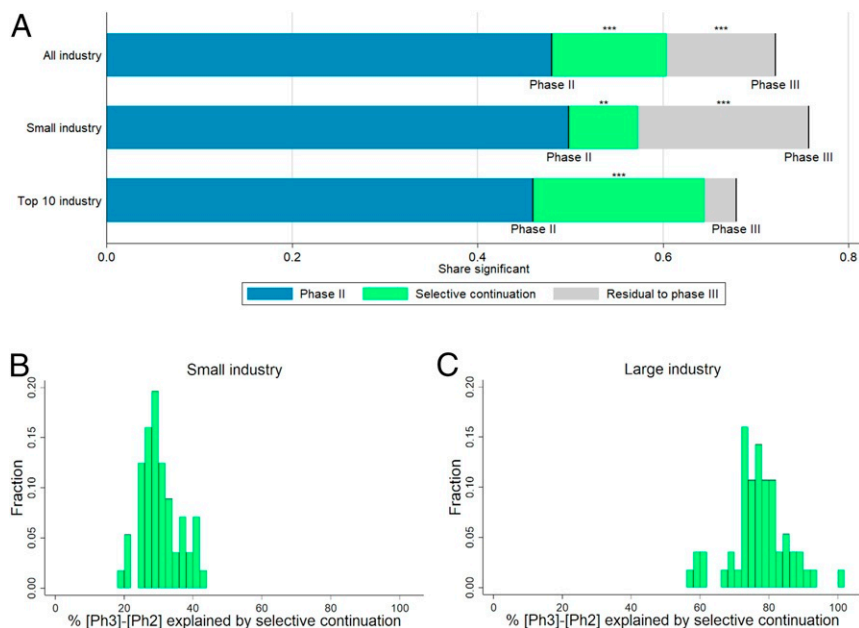


Fig. 4. (A) Selection-based decomposition of the difference in significant results from primary outcomes between phase II and phase III, depending on affiliation of lead sponsor (top-10 revenues criterion). Phase II and III lines represent the shares of trials with a P value below 5% (or, equivalently, a z score above 1.96). The green segments represent the parts of the differences explained by selective continuation, based on counterfactuals constructed from the phase II distribution. For precise numbers and sample sizes, see *SI Appendix, Table S7*. Significance levels for the differences (based on a two-sided t -test) are indicated. $**P < 0.05$; $***P < 0.01$. (B and C) Histograms of the percentage share of the difference in the share of significant results between phase III and phase II explained by selective continuation across different definitions for large vs. small industry sponsors. The shares correspond to the green area in A divided by the sum of the green and the gray areas. The sample of industry-sponsored trials is split according to 56 different definitions of large sponsors. These definitions are obtained by ranking sponsors by their 2018 revenues, volume of prescription drug sales in 2018, research and development spending in 2018, and the number of trials reported to the registry. For each of these four criteria, 14 different definitions of “large vs. small” were created: top seven vs. remainder, top eight vs. remainder, and so on, up to top 20 vs. remainder. Further details are provided in *SI Appendix*.

discipline reporting. To evaluate opportunities for reform, policymakers might want to weigh the ex post information benefits of mandatory registration against the reduced incentives of investigators to undertake clinical trials (42–46). An empirical quantification of this chilling effect could serve as an important input for a social cost–benefit analysis for tightening current rules.

Materials and Methods

Database for Aggregate Analysis of ClinicalTrials.gov. The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) was launched in September 2010 to allow for free bulk download of all of the data contained in the ClinicalTrials.gov registry (19–21). The project is administered by the Clinical Trials Transformation Initiative, a partnership of the FDA and Duke University with the aim of improving quality and efficiency of clinical trials. The database, which is updated daily and directly accessible in the cloud, contains over 40 subtables with information on timing, conditions, interventions, facilities, locations, sponsors, investigators, responsible authorities, eligible participants, outcome measures, adverse events, results, and descriptions of trials.

The trials in the database cover a wide range of different diseases, interventions, and study designs. Hence, also, the reported results are very diverse in nature. In contrast to a meta-analysis on a specific disease or treatment, which typically uses only a narrowly defined subgroup of the dataset, we analyzed the largest possible portion of the overall data. Given the aggregate level of our analysis, rather than using the estimated coefficients, we focused on P values, the only measure reported uniformly and comparably for many trials, independent of their characteristics and the statistical method used for the analysis.

This study is based on the AACT data available on August 15, 2019. Over the last 2 y, we obtained similar results in earlier drafts of this paper based on less data. We concentrated on phase II and phase III interventional (as opposed to observational) superiority (as opposed to noninferiority) studies on drugs (as opposed to medical devices and others) which report at least one proper P value for a statistical test on a primary outcome of the trial.

We dropped the trials of the sponsor Colgate Palmolive, which reported P values exactly equal to 0.05 for 137 out of its 150 results. We attributed these exact P values of 0.05 to a reporting mistake; clearly, these were intended to be reported as significant results with P value lower than or equal to 0.05. Leaving Colgate Palmolive's results in the sample would lead to a substantial spike at $z = 1.96$, which could be wrongly interpreted as evidence for p-hacking. Moreover, we dropped the trial with the identifier NCT02799472, as it reported 211 P values for primary outcomes and would therefore have much more impact than all other trials (average number of P values for primary outcomes per trial: 2.5; median: 1).

Altogether, we obtained a sample of 12,621 P values from tests performed on primary outcomes of 4,977 trials. These single P values constituted the units of observation for our analysis. As a consequence of the FDA Amendments Act, the largest part of our results data pertains to trials conducted after 2007.

P - z Transformation. We transformed the P values taken from the AACT database to corresponding z statistics by supposing that all P values would originate from a two-sided Z test of a null hypothesis that the drug has the same effect as the comparison. Given that under the null hypothesis, this statistic is normally distributed, we have the one-to-one correspondence $z = -\Phi^{-1}(\frac{p}{2})$, where z is the absolute value of the test statistic, and Φ^{-1} is the inverse of the standard normal cumulative distribution function. This transformation facilitates both the graphical analysis and the identification of discontinuities at the significance threshold, given that the z density is close to linear around the significance threshold, whereas the corresponding p density is highly nonlinear in this range.

Density Discontinuity Tests. We implemented tests of discontinuity in the z -score density at the $z = 1.96$ significance threshold based on the state-of-the-art procedure developed by Cattaneo et al. (38). This test builds on a local polynomial density-estimation technique that avoids prebinning of the data. More details on the testing procedure and supplementary results can be found in *SI Appendix*.

Linking Phase II and Phase III Trials. To analyze selective continuation from phase II to phase III, we linked phase II and phase III trials in our dataset, based on the main intervention, the medical condition to be treated, and the timing.

We read one by one the protocols for all of the phase II trials in the dataset for which at least one P value was reported. We considered only phase II trials that were completed before the end of December 2018 to allow for enough time such that a follow-up phase III trial could have been registered by August 2019. From the protocols, we determined the main experimental intervention(s), i.e., the main drug or combination of drugs whose efficacy and safety was to be established, for 1,773 phase II trials.

We considered a phase II trial as continued if we could link it to at least one phase III trial; that is, if we found at least one phase III trial registered in the database (regardless of whether associated results were reported or not) fulfilling all of the following criteria:

- 1) Intervention: All drugs being part of at least one of the determined main interventions of the phase II trial appear as listed interventions in the phase III trial. This is either with exactly the same name or with a synonym which the reporting party states to refer to the same drug.
- 2) Condition: All of the MeSH conditions (21) associated to the phase II trial are also associated to the phase III trial.
- 3) Timing: The start date of the phase II trial was before the start date of the phase III trial.

For more details on the linking procedure, see *SI Appendix*.

Selection Function. Denote by I_2 a vector collecting the relevant information pertaining to the clinical trial at the end of phase II. It contains the z score, z^{Ph2} , and other variables describing the circumstances of the trial (such as sample size to proxy for statistical power). If the sponsor firm decides to stop the development of the drug, it obtains a payoff of $\underline{V}(I_2) + \eta$. In case of continuation into phase III, the firm pays a development cost $c + \eta$. The idiosyncratic payoff and cost shocks η and η are only observable to the firm, but not to the econometrician. The future payoff is denoted V^{Ph3} and is increasing in the phase III z score, which is uncertain at the time of the decision to set up a phase III trial. The firm has an expectation on the distribution of the z score, based on the information available in I_2 . The decision of the firm is thus,

$$V^{Ph2}(I_2) = \max \left[\underline{V}(I_2) + \eta; -c - \eta + \delta E_{z_3|I_2} V^{Ph3}(z_3) \right],$$

where δ is the discount factor. Assuming that the idiosyncratic shocks η and η are both independent and identically extreme value distributed, the probability of undertaking a phase III trial is a logistic function (47).

$$\begin{aligned} \text{Prob}(\text{continuation}) &= \frac{\exp(-c + \delta E_{z_3|I_2} V^{Ph3}(z_3))}{\exp(\underline{V}(I_2)) + \exp(-c + \delta E_{z_3|I_2} V^{Ph3}(z_3))} \\ &= \text{logistic}(I_2). \end{aligned}$$

Following this model, we use a logistic regression to estimate a selection function that captures selective continuation for industry-sponsored trials. In the sample of phase II z scores, restricted as explained in the section above, we estimate the logistic model

$$\begin{aligned} \text{continuation}_i &= \text{logistic} \left[\alpha + \beta_0(1 - D1_i - D2_i)z_i^{Ph2} + \beta_1 D1_i \right. \\ &\quad \left. + \beta_2 D2_i + \mathbf{x}'_i \gamma + \phi_i + \tau_i + \varepsilon_i \right], \end{aligned}$$

where continuation_i is a dummy variable which results from our linking of trials across phases and equals one if there is at least one phase III trial matched to a phase II trial to which z -score i belongs (regardless of whether results are reported), and z_i^{Ph2} is the phase II z score associated to a primary outcome. $D1_i$ and $D2_i$ are dummy variables for a statistic to be reported as $z > 3.29$ or $z > 3.89$, respectively. As explained above, those cases are so frequent that we treat them separately.

Moreover, the vector \mathbf{x}_i gathers further control variables which might influence the perceived persuasiveness of phase II results or the economic incentives to carry on with the research on top of the z score. These include the square root of the overall enrollment to each trial (as proxy for the power of the tests), a dummy indicating whether there was a placebo involved in the trial (as opposed to an active comparator), and a dummy indicating whether the P value is explicitly declared as adjusted for multiple hypothesis testing. For the last variable, the baseline corresponds to no adjustment of the critical value of the testing procedure or no information provided. We codified this variable manually from the P -value descriptions; only 2.9% of the relevant observations are explicitly adjusted.

To account for potential systematic differences across drugs for the treatment of different kinds of conditions, we included condition fixed effects

ϕ_c . For this purpose, we assigned each trial in one of the 15 largest categories of conditions, based on the MeSH terms determined by the curators of the database (21). For more details, see *SI Appendix*.

As registration of trials and reporting of results occurs often with a substantial time lag, we also controlled for a flexible time trend by including completion year fixed effects τ_c .

Summing up, z^{ph2} , D_1 , D_2 , \mathbf{x} , and ϕ_c correspond to I_2 , the information relevant for the continuation decision at the end of phase II, in the model above. The predicted values $\widehat{continuation}_i$ can be interpreted as the probability of a drug moving to phase III conditional on the phase II z score (and other informative covariates observable at the end of phase II).

Kernel Density Estimation. Let Z_1, Z_2, \dots, Z_n be the sample of z scores in a given group of trials. To estimate the density, we use the standard weighted kernel estimator

$$\hat{f}(z) = \frac{1}{W} \sum_{i=1}^n \frac{w_i}{h} K\left(\frac{z - Z_i}{h}\right),$$

where $W = \sum_{i=1}^n w_i$, $K(\cdot)$ is the Epanechnikov kernel function, and h is the bandwidth which we choose with the Sheather–Jones plug-in estimator (48). To estimate the actual phase II and phase III densities, we set all weights w_i equal to one. To construct the hypothetical densities controlled for selective continuation, we estimated the kernel density of the phase II statistics, using the predicted probabilities from our selection function as weights, i.e.,

$w_i = \widehat{continuation}_i$. The resulting densities for precisely reported (i.e., not as inequality) test statistics by different groups of sponsors are plotted in *SI Appendix, Fig. S4*.

This procedure is similar in spirit to the weight-function approach used to test for publication bias in meta-analyses (49, 50), but it allows the weights to depend on more than one variable. The construction of counterfactual distributions by weighted kernel-density estimation has also been used in other strands of the economics literature, e.g., for the decomposition of the effects of institutional and labor-market factors on the distribution of wages (51).

Data Availability. A complete replication package of the econometric analysis presented in the paper, including all data files and our constructed linking of phase II and phase III trials, is deposited at the Harvard Dataverse at <https://doi.org/10.7910/DVN/NBLYSW>. The clinical trials data mainly analyzed in the paper are freely available for download at <http://aact.ctti-clinicaltrials.org/>.

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Supplementary Information for

P-hacking in clinical trials and how incentives shape the distribution of results across phases

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This PDF file includes:

- Supplementary text
- Figs. S1 to S4
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Supporting Information Text

p-z Transformation. Our analysis focuses on the reported p-values for the statistical evaluation of trial results. However, the p-density is not particularly well suited to perform discontinuity tests at the significance threshold because it is highly nonlinear in the relevant range. Neither is the p-density well suited for graphical representation, given that it is not possible to display both the region around the significant threshold and the overall distribution conveniently in the same graph.

To overcome these problems, we transform the p-values to corresponding z-statistics by supposing that all p-values would originate from a two-sided Z-test of a null hypothesis that the drug has the same effect as the comparison. Given that under the null hypothesis this statistic is normally distributed, we have the one-to-one correspondence $z = -\Phi^{-1}(\frac{p}{2})$, where z is the absolute value of the test-statistic and Φ^{-1} is the inverse of the standard normal cumulative distribution function. This transformation “stretches” the distribution from the $[0, 1]$ interval to the whole positive real axis with smaller p-values being stretched more. Hence, the region close to the significance threshold becomes more prominent without losing the other parts of the distribution. Moreover, in the range around the significance threshold the z-density is close to linear, making it easier to identify discontinuities (1, 2). A similar transformation has been applied in the literature on experimental biases across life sciences (3).

Note that the p-values in the dataset originate from diverse statistical procedures (e.g., ANCOVA, ANOVA, Chi-squared-test, mixed models analysis, linear regression, logistic regression, 1-sided t-test, 2-sided t-test, etc.), with test statistics that follow different distributions, some continuous, some discrete. Even though the sample size of the trials is sufficiently large that, according to the Central Limit Theorem, many of the resulting statistics are approximately normally distributed, in general the actual test-statistic of the trial and our calculated z do not coincide. Nevertheless, the p-z transformation allows us to conveniently compare the results of all trials.

To alleviate concerns that the discontinuity we find in the z-density for phase III trials by small industry sponsors (panel D of Figure 1 in the main text) may be driven by the specific transformation we choose, we provide density discontinuity tests for industry sponsored trials with p-values transformed to one-sided instead of two-sided test statistics. That is, $z_{1-sided} = -\Phi^{-1}(p)$. The results, displayed in Figure S2 and Table S4, resemble closely those relying on the transformation to two-sided z-scores. We still find a sizable and statistically significant upward shift at the classical significance threshold for phase III trials by small sponsors. Also, the densities for phase III top ten and phase II (both types of sponsors) are smooth.

The Missing Tail of the z-Distribution. Not all p-values in the registry are reported precisely, but some are only stated in comparison to a certain threshold, e.g. $p < 0.05$ or $p > 0.1$. Whereas for most parts of the distribution this is a minor issue and affects only a small number of observations, relative reporting becomes the rule for very low p-values, corresponding to high z-statistics. In particular, 30.8% of the p-values in our sample of tests for primary outcomes are reported as $p < 0.001$ (corresponding to $z > 3.29$) or $p < 0.0001$ (corresponding to $z > 3.89$). There are barely any p-values reported with equality below these thresholds. For the z-distribution, this implies that we know the size of the right tail (i.e., the mass above a certain threshold) but we do not have any information about the exact shape.

For our analysis of the share of significant results, we deal with this issue as following. As indicated in the regression equation, we include the dummies $D1$ for “ $z > 3.29$ ” and $D2$ for “ $z > 3.89$ ” into the estimation of the selection function, so that the probability of continuation is estimated separately for those two cases. Moreover, we include p-values which are reported as exactly zero (as a result of rounding) and hence cannot be transformed into a z-score in the group $D2$. For the few cases in which a z-score is reported as inequality with respect to a level \bar{z} other than 3.29 and 3.89, we replace the respective z with the mean of the precisely reported z-statistics conditional on being above or respectively below \bar{z} .

For the discontinuity tests (Figure 1, Figures S1–S3, and Tables S2–S5) and plots of densities (Figure S4), we consider only p-values which are reported precisely (i.e., not as inequality).

The Definition of Large vs. Small Industry Sponsors. As our analysis relies on the estimation of densities, comparing trials by different groups of sponsors requires a discrete split of the sample. We focus on the impact of the size of the sponsoring corporations on their incentives. Therefore, we need a definition of “large vs. small” sponsors. In our main analysis, we compare the top ten sponsors in terms of 2018 revenues to the remaining smaller sponsors. These top ten are the ten companies in italics in the first column of Table S1. This particular definition is not only salient but also splits the sample of p-values roughly in half, maximizing statistical power in both subsamples. This is of particular importance for the density discontinuity tests, which require large sample sizes to be reliable.

To check robustness, we repeat our analysis for 56 alternative definitions of “large” and show that our main results hold across this wide range of alternatives for splitting the sample. As displayed in Table S1, we rank sponsors not only by their 2018 revenues (column 1), but also by the volume of prescription drug sales in 2018 (column 2), R&D spending in 2018, and the number of trials reported to the registry (column 4). It is not surprising that these four rankings are correlated. For each of the four criteria, we create fourteen different definitions of “large vs. small”: top seven vs. remainder, top eight vs. remainder, and so on up to top twenty vs. remainder. Hence, overall we have $14 \times 4 = 56$ different definitions, one of which is the top ten revenues definition we use for our main analysis.

Figure S1 shows histograms of the p-values of density discontinuity tests across these 56 different definitions. In panels A and B we can see that the phase II and phase III z-densities for large industry sponsor never exhibit significant breaks at the 1.96 threshold, no matter which definition we use. As shown in panel C, for a number of definitions we find a significant discontinuity for phase II small industry, but at the same time in many cases we have p-values far above 0.05. Phase III small

industry (panel D) is the only subgroup for which we find a significant break in our main specification. For the great majority of alternative definition, this finding is confirmed and the p-value never exceeds 0.146.

We also repeat the counterfactual exercise of predicting the share of significant phase III results based on *selective continuation* for each of the 56 different definitions. As discussed in the main text, the different patterns between large and small industry sponsors are robust across this wide range of alternative ways to define “large” sponsors (Figure 4, panels B and C).

Testing for Discontinuities of Distributions and Densities of z-scores. We provide a formal test of discontinuity in the z-score density at the $z = 1.96$ significance threshold. We implement manipulation tests based on a state-of-the-art procedure developed by Cattaneo, Jansson, and Ma (1, 2). This test builds on a local polynomial density estimation technique that avoids pre-binning of the data. Table S2 shows the p-values of the tests performed on the densities from primary outcomes, depending on the affiliation of the lead sponsors of the trials, as described in the main text. We do not find any evidence of manipulation for trials in phase II. For phase III, the p-values are lower, but when splitting the sample only significant for trials sponsored by small industry.

Figure 1 in the main text suggests that the breaks we find are not due to a spike, i.e., a concentration of mass right above 1.96 (leading to a discontinuity in both the density and the cumulative distribution function), but due to a persistent upward shift in the density with an increased frequency of results also further to the right of 1.96 (leading to a discontinuity only in the density but not in the cumulative distribution function). To reinforce this claim and distinguish the two cases, we perform further density discontinuity tests with cutoffs 0.05 and 0.5 above the significance threshold, corresponding to $z = 2.01$ and $z = 2.46$, for industry sponsored phase III trials, for which we found a break at 1.96.

With this method we can implicitly test for a discontinuity in the cumulative distribution function. If the discontinuity in the density was due to a spike at 1.96, we would expect our test to find a downward jump in the density at some point above. If there was manipulation and all inflated results were concentrated exactly at 1.96 (sharp discontinuity in the cumulative distribution function at 1.96), we should have a sharp downward discontinuity in the density right above the threshold (captured by the test at 2.01). Assuming more realistically that investigators want to push their results above the significance threshold but cannot perfectly target a p-value of 0.05, we would expect an excess mass above 1.96 that slowly vanishes (captured by the test at 2.46). Even in the absence of a sharp discontinuity, also in this case we would expect a downward tendency in the density.

The differences of the bias-corrected density estimates to the right and to the left of the respective cutoffs tabulated in Table S3 do not display such a downward tendency. To the contrary, for small industry sponsors, the differences at 2.01 and 2.46 have still a positive sign, the latter being even statistically significant. These findings confirm that there is a persistent upward shift in the density around the significance threshold, but there is no break in the cumulative distribution function with an excess mass concentrated only just above 1.96.

Similar discontinuity tests for the z-density from secondary outcomes do not display any noteworthy break at the significance threshold (Figure S3 and Table S5). Moreover, the excess mass of significant results from industry-sponsored trials in phase III relative to phase II is much smaller compared to the distribution for primary outcomes.

Linking Phase II and Phase III Trials. To analyze *selective continuation* from phase II to phase III, we link phase II and phase III trials in our dataset, based on the main intervention, the medical condition to be treated, and the timing. This is not such a straightforward exercise to implement for two reasons:

- The AACT dataset is a mere digitization of the reported trial protocols. Hence, most variables are not well codified and have non-generic entries. Even though the information on interventions and conditions of the trials for which results are reported is rather complete, the cells in the reporting forms are interpreted differently by different reporting parties. For instance, in the specification of a trial’s intervention, in many cases all the drugs involved in the trial are inserted in one cell, without specifying whether the drugs are given as a combination or separately to different arms of the trial. Often, it is not specified which drug constitutes the experimental treatment rather than the control. Hence, it is not possible to mechanically identify a trial’s main experimental intervention. As an additional complication, many drugs appear in the data with different names; some times the drugs are referred by the chemical composition, while other times by their commercial name.
- The process of drug development is not linear in the sense that we usually do not have one phase II trial followed by one phase III trial and then a request for FDA approval. In most cases, there is a number of phase II trials looking at similar but potentially slightly different interventions/conditions, such as different drug dosages, different characteristics of eligible patients, or different control interventions. These phase II trials are typically followed by an even larger number of phase III trials with similar interventions/conditions but slightly varying specifications.

We address these hurdles in the following way. We read one by one the protocols for all the phase II trials in the dataset for which at least one p-value is reported and which were completed before end of December 2018. With this restriction on the completion date, there could potentially be a follow-up phase III trial registered before August 2019. From the protocols, we determine the main experimental intervention(s), i.e., the main drug or combination of drugs whose efficacy and safety is to be established, for 1,773 phase II trials. As indication of the medical condition the trials address, we use the Medical Subject Headings (MeSH) terms determined by the curators for the purpose of making the *ClinicalTrials.gov* webpage searchable (4), disregarding overly generic categories such as simply “Disease”.

We consider a phase II trial as continued if we could link it to at least one phase III trial. That is, if we found at least one phase III trial registered in the database (regardless of whether associated results are reported or not) fulfilling all of the following criteria:

1. **Intervention:** All drugs being part of at least one of the determined main interventions of the phase II trial appear as listed interventions in the phase III trial. This is either with exactly the same name or with a synonym which the reporting party states to refer to the same drug.
2. **Condition:** All the MeSH-conditions associated to the phase II trial are also associated to the phase III trial.
3. **Timing:** The start date of the phase II trial was before the start date of the phase III trial.

This linking is not perfect, for instance because it disregards whether all the drugs in the phase III trial were part of one combination in one arm. Moreover, we do not take into consideration other details of the trials like the exact population of eligible patients. However, given the limitations of the data, this procedure appears reasonably accurate. We manage to link 33.3% of the industry-sponsored phase II trials in our restricted dataset to at least one phase III trial. These numbers are in line with the ones reported in previous studies (5) and on the FDA webpage (6). For non-industry sponsored trials, however, reporting in phase III is very meager and we can find phase III matches for only 18.0% of the phase II trials. Given this low number and the fact that there are no significant differences between the phase II and phase III distribution for non-industry sponsors to begin with, we investigate selection only for industry-sponsored trials.

Note that criterion 3 considers only the start dates of the trials. It might appear to be more intuitive to require the completion date of the phase II trial to be prior to the start date of the phase III trial. Indeed, most of our linked trials fulfill also this stronger condition. However, in some cases this condition is too strong. That is, some phase III trials start before the corresponding phase II trials are fully completed. For instance, some phase II results on long-run impacts might still be pending but the collected evidence is already strong enough for the investigators to start a phase III trial. Moreover, we consider the reported start dates to be more reliable. The responsible parties might have incentives to report a later completion date than the actual, in order to meet the requirements for timely reporting of results.

MeSH Condition Fixed Effects and Market Size Data. To account for potential systematic differences across drugs for the treatment of different kinds of conditions, we include condition fixed effects in the estimation of the selection functions for *selective continuation*. For this purpose, we assign each trial in one of the 15 largest categories of conditions (in terms of frequency in our data), based on the MeSH terms determined by the curators of the database (4). These categories are displayed in Table S8. Some strongly overlapping categories have been merged. Trials that could not be assigned to a specific group or belong to one of the smaller groups constitute the omitted category. In case a trial is associated with more than one category, we assign it to the one with the largest expected market size.

To obtain a proxy for the expected market size for a newly developed drug, we evaluate the Medicare D spending for existing drugs in 2011 according to information from the *Centers for Medicare & Medicaid Services* publicly available at <https://www.cms.gov/Research-Statistics-Data-and-Systems/Research-Statistics-Data-and-Systems.html>. *Part D Prescription Drug Event* (PDE) data is provided for a subset (~ 70%) of Medicare beneficiaries.

We classify manually 1,056 marketed drugs, among which the 420 with the highest Medicare D spending, into the MeSH categories for the treated conditions. Overall, these drugs make up for 90% of the expenditure on the drugs in the dataset. Table S8 shows also the total spending by category.

Background on *ClinicalTrials.gov*. *ClinicalTrials.gov* is an online registry of clinical research studies in human volunteers. The website is maintained by the *National Library of Medicine* (NLM) at the *National Institutes of Health* (NIH) in collaboration with the *U.S. Food and Drug Administration* (FDA). It was established in February 2000 with the aim to increase transparency in clinical research. Initially, the registry contained only trials to test the efficacy of new experimental drugs for serious or life-threatening diseases or conditions and registration was mainly voluntary. For more information on the history of the registry, related policies, and laws, see <https://clinicaltrials.gov/ct2/about-site/history> (accessed Jun 23, 2017).

In 2007 the requirements for registration of trials were extended substantially through the *FDA Amendments Act* (FDAAA) (7). Even though in January 2017 those rules have been redefined more precisely (8), in the following we will refer to the regulation of Section 801 of the FDAAA which was the legislation in force at the time when the great majority of the data in our analysis was generated. According to <https://clinicaltrials.gov/ct2/manage-recs/fdaaa> (accessed Jun 23, 2017), the main criteria a trial must meet to be affected by this regulation are the following:

- initiated after September 27, 2007, or initiated on or before that date and still ongoing as of December 26, 2007;
- controlled clinical investigation of drugs, biologics or medical devices other than phase I trials and small feasibility studies;
- the trial has one or more sites in the United States or it involves drugs, biologics or medical devices manufactured in the United States.

If these criteria apply, the responsible party (i.e., the sponsor or the principal investigator of the trial) must register the trial and provide the required information no later than 21 days after enrollment of the first participant. In case the investigated

drug, biologic, or device is approved, licensed, or cleared by FDA, moreover, the responsible party must submit some basic summary results of the trial no later than twelve months after the completion date. Since September 2008, these submitted results are publicly accessible in the *ClinicalTrials.gov* results database so as to reach an even higher level of transparency. However, there are some loopholes in the legislation (9); for instance, the required level of details of the results is not clearly defined and phase I trials and trials of not-approved products are exempt. In all the other cases that do not meet the stated criteria, registering and reporting of results is voluntary.

The FDAAA establishes penalties for non-compliance of up to \$10,000 per day. However, no enforcement has yet occurred (10–13). Assessing compliance rates is not easy because the aforementioned exemptions and imprecisions in the FDAAA legislation complicate identifying which trials are applicable. An early algorithm-based study (10) shows that only 13.4% of applicable clinical trials registered on *ClinicalTrials.gov* between 2008 and 2012 reported results in a timely fashion and only 38.3% reported results at any time at all. However, in a manual review of a subsample of trials the same authors (10) found that their methodology based on assumptions about the approval status of the drug tended to underestimate reporting rates. Later studies document for a sample of 329 industry-sponsored phase II-IV US trials completed or terminated 2007-2009 a result reporting rate to *ClinicalTrials.gov* of 58% by December 2014 (14) and an increase of the overall reporting rate for applicable trials from 58% to 72% in the two years before September 2017, driven not by fear of sanctions but by public pressure on the responsible parties (11).

Since January 2017 the improved “Final Rule” is in place (hence, it does not affect the great majority of the trials we analyze), addressing many loopholes and broadening the scope of the 2007 legislation (8). However, the FDA’s efforts to police compliance are still very limited (11–13). Beyond the disclosure mandate, the FDAAA raised public awareness about the importance of transparency in clinical research and led many large pharmaceutical companies and research institutions to develop internal disclosure policies (10, 11, 13).

The most recent and complete evaluation of compliance with the FDAAA Final Rule finds 64.5% of industry-sponsored trials to report any results and 50.3% to be fully compliant with the rules; that is, to report results within one year of the primary completion date (12).

Considering the missing enforcement of the FDAAA regulations, lack of reporting does not necessarily mean that the responsible parties intend to hide their results, but rather that they just do not take the time to go through the lengthy reporting process. In this light, notwithstanding the legal requirements, for the purpose of our analysis reporting of results should be seen as mostly voluntary.

Several studies in the medical literature assess the quality of the data reported to the registry and the results database along different dimension, e.g., information about scientific leadership (15), consistency of reported primary outcomes (16, 17), comparisons to results published in academic journals (14, 18), and the provision of Individual Participant Data (IPD) (19). All these studies, as well as overall assessments by the curators of the database (20, 21), find ambiguous results and see scope for improvement (22).

The biggest challenge when working with the AACT data is that, as a mere digitization of the trial protocols, most variables have non-generic entries and many of them contain large bodies of text. Moreover, reporting parties do not always interpret the different cells in the reporting form in the same way. For instance, when reporting the intervention of a trial, in many cases all the drugs involved in a trial are inserted in one cell without specifying whether they are given as a combination or separately to different arms of the trial. Furthermore, reporting parties indicate differently which drug constitutes the experimental treatment and which one is the control. Often, one can find a clarification in other parts of the protocol. Similar issues arise with many of the self-reported variables. Even though for most trials the reported content is complete and the whole study protocol embedded in the context gives a clear picture, different parties often report the same information in different cells. This non-uniformity prevents the mechanical evaluation of large parts of the data, even with natural language processing algorithms.

Consequently, we are forced to either codify the data by hand (like the main intervention of phase II trials which we use for our linking of trials across phases) or restrict attention to characteristics that are codified uniformly among all the trials in the database. The latter are numerical entries or entries that allow only for a finite, prespecified number of answers (e.g., binary variables).

We classify trials and link them across phases based on the MeSH terms associated to the treated conditions. The MeSH thesaurus is a controlled list of vocabulary produced by the *National Library of Medicine* and used for indexing, cataloging, and searching biomedical and health-related information. The MeSH classification is provided by *ClinicalTrials.gov* administrators based on natural language processing algorithms.

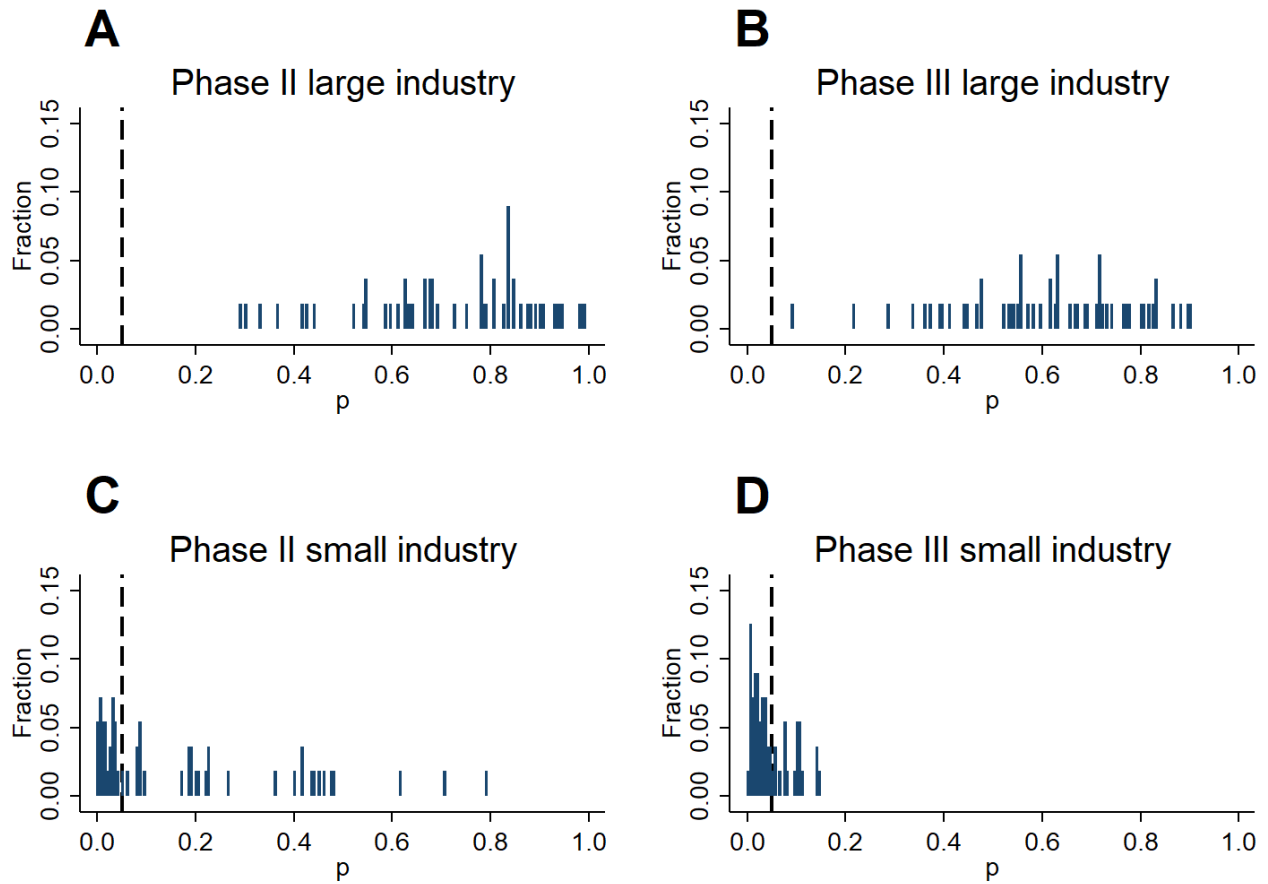


Fig. S1. Robustness check: histograms of p-values from density discontinuity tests at $z = 1.96$ across 56 different definitions for large vs. small industry sponsors. The p-values result from discontinuity tests (1) at $z = 1.96$ in the densities of constructed z-statistics for primary outcomes. The dashed vertical lines indicate $p = 0.05$. The sample of industry sponsored trials is split according to 56 different definitions of large sponsors. These definitions are obtained by ranking sponsors by their 2018 revenue, volume of prescription drug sales in 2018, R&D spending in 2018, and the number of trials reported to the registry. For each of these four criteria, 14 different definitions of “large vs. small” are created: top seven vs. remainder, top eight vs. remainder, and so on up to top twenty vs. remainder. Further details are provided in the [supplementary text](#).

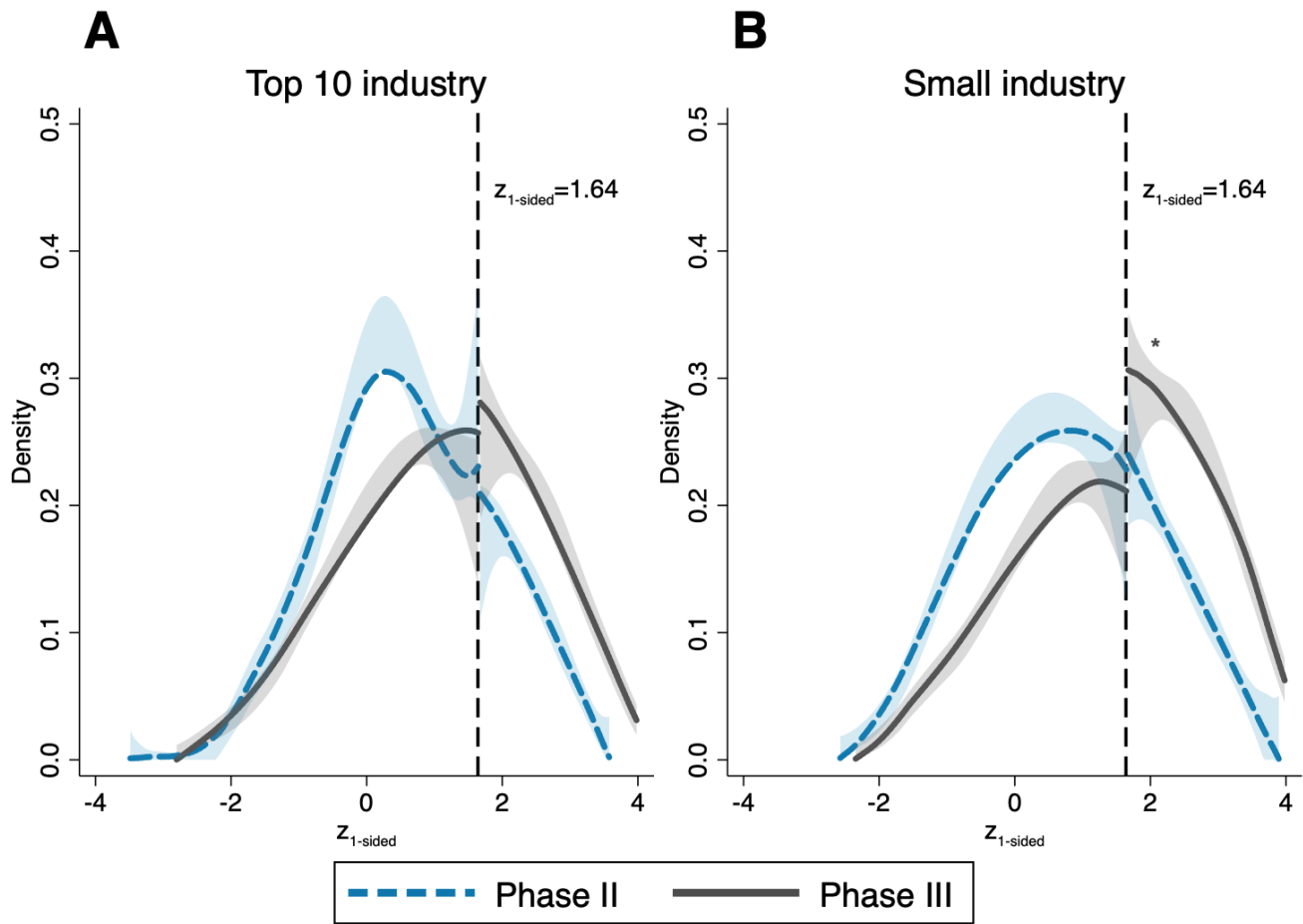


Fig. S2. Robustness check: density discontinuity tests for large and small industry sponsored trials with transformation to *one-sided* test scores. Density estimates of constructed one-sided z-statistics for primary outcomes of phase II (dashed blue lines) and phase III (solid grey lines) trials. The shaded areas are 95%-confidence bands and the vertical lines at 1.64 correspond to the threshold for statistical significance at 0.05 level. Sample sizes: A: $n = 1,332$ (phase II), $n = 1,424$ (phase III); B: $n = 1,450$ (phase II), $n = 1,520$ (phase III). Significance levels for discontinuity tests (†): * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$; exact p-values reported in [Table S4](#).

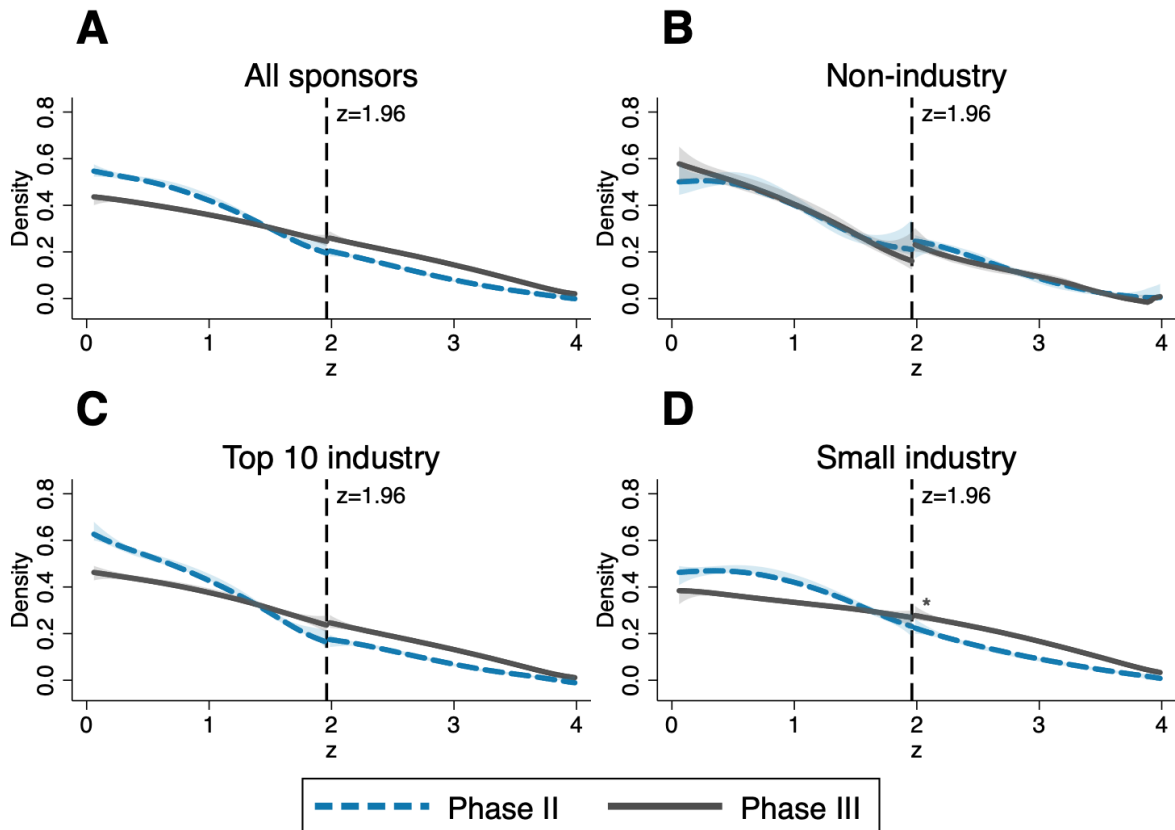


Fig. S3. Comparison of phase II and phase III z-score distributions and test for a discontinuity at $z = 1.96$ for *secondary outcomes*, depending on affiliation of lead sponsor. Density estimates of the constructed z-statistics for tests on secondary outcomes of phase II (dashed blue lines) and phase III (solid grey lines) trials. The shaded areas are 95%-confidence bands and the vertical lines at 1.96 correspond to the threshold for statistical significance at 0.05 level. Sample sizes: A: $n = 17,840$ (phase II), $n = 25,050$ (phase III); B: $n = 2,553$ (phase II), $n = 2,102$ (phase III); C: $n = 8,579$ (phase II), $n = 11,480$ (phase III); D: $n = 6,672$ (phase II), $n = 11,486$ (phase III). Significance levels for discontinuity tests (1): * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$; exact p-values reported in [Table S5](#).

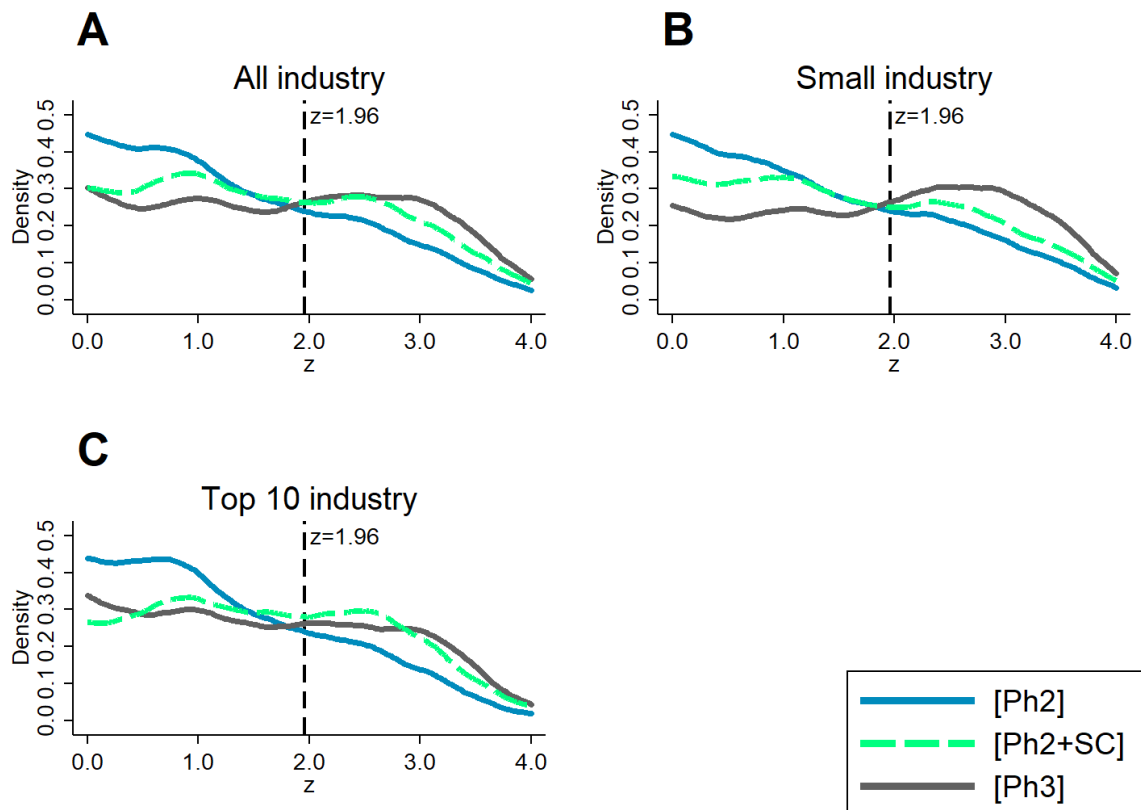


Fig. S4. Kernel density estimates for phase II and phase III z-scores and constructed counterfactuals accounting for *selective continuation*, depending on affiliation of lead sponsor. Estimated densities based only on p-values which are reported precisely (i.e. not as inequality). Shorthand notation: Ph2=phase II, Ph3=phase III, and SC=*selective continuation*. Sample sizes: A: $n = 4, 135$ (phase II), $n = 5, 957$ (phase III); B: $n = 2, 181$ (phase II), $n = 3, 209$ (phase III); C: $n = 1, 954$ (phase II), $n = 2, 748$ (phase III).

Table S1. Ranking of Industry Sponsors by Different Criteria.

Rank	Revenues 2018	Rx Sales 2018	R&D Spending 2018	No. Trials Reported
1	<i>Johnson & Johnson</i>	Pfizer	Roche	GlaxoSmithKline
2	<i>Roche</i>	Roche	Johnson & Johnson	Pfizer
3	<i>AbbVie/Abbott Laboratories</i>	Novartis	Novartis	Merck Sharp & Dohme Corp.
4	<i>Pfizer</i>	Johnson & Johnson	Pfizer	Eli Lilly & Co
5	<i>Novartis</i>	Merck Sharp & Dohme Corp.	Merck Sharp & Dohme Corp.	Boehringer Ingelheim
6	<i>Bayer</i>	AbbVie/Abbott Laboratories	Sanofi	AstraZeneca
7	<i>GlaxoSmithKline</i>	Sanofi	AbbVie/Abbott Laboratories	Roche
8	<i>Merck Sharp & Dohme Corp.</i>	GlaxoSmithKline	AstraZeneca	Novartis
9	<i>Sanofi</i>	Amgen	Bristol-Myers Squibb	Takeda Pharmaceutical
10	<i>Eli Lilly & Co</i>	Gilead Sciences	Eli Lilly & Co	Shire
11	Amgen	Bristol-Myers Squibb	GlaxoSmithKline	Amgen
12	Bristol-Myers Squibb	AstraZeneca	Celegne	Bayer
13	Gilead Sciences	Eli Lilly & Co	Gilead Sciences	Sanofi
14	AstraZeneca	Bayer	Amgen	Johnson & Johnson
15	Danaher Corporation	Novo Nordisk	Bayer	Gilead Sciences
16	Boehringer Ingelheim	Takeda Pharmaceutical	Boehringer Ingelheim	Bristol-Myers Squibb
17	Takeda Pharmaceutical	Celegne	Takeda Pharmaceutical	Otsuka Holdings
18	Teva Pharmaceutical Industries	Shire	Biogen	AbbVie/Abbott Laboratories
19	Novo Nordisk	Boehringer Ingelheim	Novo Nordisk	Novo Nordisk
20	Merck KGaA	Allergan	Regeneron Pharmaceuticals	Merck KGaA

Notes: The companies in italics are defined as the top ten industry sponsors in our main analysis. Known large-scle subsidiaries are grouped with their mother corporation (e.g. Janssen Research & Development as part of Johnson & Johnson). Small companies that may have alliances with (or are later acquired by) larger companies are coded as separate sponsors. Shire was acquired by Takeda Pharmaceutical in early 2019 but we treat the two companies separately, as this acquisition happened at the very end of our sample period. Sources: Revenues 2018:

https://en.wikipedia.org/wiki/List_of_largest_biomedical_companies_by_revenue (revenues data collected from financial statements on company websites, accessed Oct 23, 2019); Rx (i.e. prescription drugs) Sales 2018 and R&D Spending 2018: (23) (based on data from EvaluatePharma®);

No. Trials Reported: own calculations based on *ClinicalTrials.gov* data.

Table S2. P-values for tests of density discontinuity at the $z = 1.96$ threshold.

Sponsor	(1)	(2)
	Phase II	Phase III
All	0.09* (3,953)	0.00*** (3,664)
Non-industry	0.23 (1,171)	0.35 (720)
All industry	0.30 (2,782)	0.52 (2,944)
Small industry	0.20 (1,450)	0.032** (1,520)
Top 10 industry	0.91 (1,332)	0.67 (1,424)

Notes: P-values result from the density discontinuity test (1), described in detail in the [supplementary text](#), for primary outcomes; significance levels: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$. Sample sizes in parentheses.

Table S3. Size of discontinuities in the z-density at the significance threshold, as well as at $z = 2.01$ and $z = 2.46$, for industry-sponsored phase III trials.

Sponsor \ Cutoff value	(1)	(2)	(3)
	z=1.96	z=2.01	z=2.46
All industry	0.031	0.087**	0.11*
Small industry	0.166**	0.056	0.177**
Top 10 industry	0.029	0.075	0.015

Notes: Differences of the bias-corrected density estimates to the right and to the left of the respective cutoff, resulting from the density discontinuity test (1), described in detail in the [supplementary text](#), for primary outcomes. Sample sizes: All industry $n = 2,944$, Small industry $n = 1,520$, Top 10 industry $n = 1,424$. Significance levels: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.

Table S4. Robustness check – transformation to *one-sided* test scores: P-values for tests of density discontinuity at the $z_{1-sided} = 1.64$ threshold.

Sponsor	(1)	(2)
	Phase II	Phase III
Small industry	0.20 (1,450)	0.076* (1,520)
Top 10 industry	0.31 (1,332)	0.74 (1,424)

Notes: P-values result from the density discontinuity test (1), described in detail in the [supplementary text](#), for primary outcomes; significance levels: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$. Sample sizes in parentheses.

Table S5. P-values for tests of density discontinuity at the $z=1.96$ threshold – secondary outcomes.

Sponsor	(1)	(2)
	Phase II	Phase III
All	0.54 (17,804)	0.21 (25,050)
Non-industry	0.34 (2,553)	0.35 (2,102)
All industry	0.34 (15,251)	0.07*
Small industry	0.87 (6,672)	0.06*
Top 10 industry	0.44 (8,579)	0.36 (11,480)

Notes: P-values result from the density discontinuity test (1), described in detail in the [supplementary text](#), for secondary outcomes; significance levels: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$. Sample sizes in parentheses.

Table S6. Estimates of logit selection function for *selective continuation*, based on *secondary outcomes*.

Sponsor	(1) All industry	(2) Small industry	(3) Top 10 industry
Phase II z-score	0.109* (0.0557)	0.197** (0.0839)	-0.0612 (0.0674)
Dummy for phase II z-score reported as “z > 3.29”	0.465 (0.416)	0.600 (0.628)	0.0737 (0.461)
Dummy for phase II z-score reported as “z > 3.89”	0.512 (0.353)	0.279 (0.395)	0.779** (0.351)
Mean dependent variable	0.353	0.360	0.347
Controls	yes	yes	yes
MeSH condition fixed effects	yes	yes	yes
Completion year fixed effects	yes	yes	yes
Observations	17,724	7,502	10,222
No. of trials	720	402	318

Notes: Unit of observation: trial-outcome; included controls: square root of the overall enrollment and dummy for placebo comparator. Categories for condition fixed effects are based on Medical Subject Headings (MeSH) terms associated to the trials (4); for more details, see [supplementary text](#). Standard errors in parentheses are clustered at the MeSH condition level; significance levels (based on a two-sided t-test): * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.

Table S7. Selection-based decomposition of the difference in significant results from primary outcomes between phase II and phase III, depending on affiliation of lead sponsor.

Share of significant results			
Sponsor	(1) All industry	(2) Small industry	(3) Top 10 industry
[Ph2]	0.481 (0.0205)	0.499 (0.0226)	0.460 (0.0319)
[Ph3]	0.721 (0.0149)	0.757 (0.0136)	0.679 (0.0245)
[Ph2+SC]	0.604 (0.0316)	0.573 (0.0406)	0.645 (0.0458)
Differences			
Sponsor	(4) All industry	(5) Small industry	(6) Top 10 industry
[Ph3]-[Ph2]	0.241*** (0.0259)	0.258*** (0.0256)	0.219*** (0.0422)
[Ph3]-[Ph2+SC]	0.117*** (0.0354)	0.184*** (0.0426)	0.0339 (0.0529)
[Ph2+SC]-[Ph2]	0.123*** (0.0260)	0.0746** (0.0347)	0.185*** (0.0410)
Observations	10,092	5,390	4,702
Observations Ph2	4,135	2,181	1,954
Observations Ph3	5,957	3,209	2,748
No. of trials Ph2	1,244	732	512
No. of trials Ph3	2,655	1,544	1,111

Notes: Columns 1-3 display the share of significant results based on kernel density estimates and adjustment for selection, with shorthand notation Ph2=phase II, Ph3=phase III, and SC=*selective continuation*. Columns 4-6 display the differences in these shares. The standard errors in parentheses are obtained by bootstrapping the whole estimation procedure (500 repetitions, clustered at the trial level); significance levels (based on a two-sided t-test): * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.

Table S8. Categories for MeSH condition fixed effects with market size determined from total Medicare D spending.

MeSH code	Category	Total Medicare D Spending in 2011 in bn US\$
C14	Cardiovascular Diseases	13.215
F03	Mental Disorders	12.336
C18	Nutritional and Metabolic Diseases	8.957
C19	Endocrine System Diseases	8.45
C10	Nervous System Diseases	5.956
C08/C09	Respiratory Tract Diseases/Otorhinolaryngologic Disease	5.945
C06	Digestive System Diseases	4.377
C05	Musculoskeletal Diseases	2.888
C04	Neoplasms	2.64
C12/C13	Male Urogenital Diseases/ Female Urogenital Diseases and Pregnancy Complications	2.262
C20	Immune System Diseases	1.355
C23	Pathological Conditions, Signs and Symptoms	0.812
C17	Skin and Connective Tissue Diseases	0.683
C25	Chemically-Induced Disorders	0.17
C16	Congenital, Hereditary, and Neonatal Diseases and Abnormalities	0.101

Notes: Details of the calculations provided in the [supplementary text](#).

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