ESTIMATION OF CLINICAL TRIAL SUCCESS RATES AND RELATED PARAMETERS

by

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ABSTRACT

Previous estimates of drug development success rates rely on relatively small samples of pharmaceutical industry-curated databases, which are subject to potential sample selection biases. Using a sample of 185,994 unique entries of clinical-trial data for over 21,143 compounds from January 1st, 2000 to October 31st, 2015, we estimate aggregate success rates and durations of clinical trials. We also compute disaggregated estimates by stratifying across several features including: disease type, clinical phase, industry/academic sponsor, biomarker presence, lead indication status, and over time. In several cases, our results differ significantly from widely cited statistics. For example, oncology has a 3.4% success rate in our sample vs. 5.1% in prior studies. However, after declining to 1.7% in 2012, it has improved to 2.5% and 8.3% in 2014 and 2015 respectively. Also, trials with biomarkers have slightly lower success probabilities when all therapeutics groups are considered, but have much higher success probabilities in oncology and genitourinary diseases.

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Chapter 1 Introduction

The probability of success (POS) of a clinical trial is a critical input for scientific and economic decisions by clinical researchers and biopharma investors. Prudent resource-allocation decisions rely on accurate and timely assessments of risk—without up-to-date estimates of the POS, investors may misestimate the risk and value of drug development, leading to lost opportunities for both investors and patients.

One of the biggest challenges in estimating the success rates of clinical trials is access to accurate information on trial characteristics and outcomes. Gathering such data is expensive, time-consuming, and susceptible to errors. Previous studies of success rates have been constrained by the data in several respects. Abrantes-Metz et al. (2005) surveyed 2,328 drugs using 3,136 phase transitions (e.g., from Phase 1 to Phase 2 in the approval process) while DiMasi et al. (2010) studied 1,316 drugs from just 50 companies. The landmark study in this area, Hay et al. (2014), analyzed 7,372 development paths of 4,451 drugs using 5,820 phase transitions. In 2 recent papers, Smietana et al. (2016) computed statistics using 17,358 phase transitions for 9,200 compounds while Thomas et al. (2016) used 9,985 phase transitions for 7,455 clinical drug development programs. In contrast, ClinicalTrials.gov, the clinical trial repository maintained by the National Institutes of Health (NIH), contains over 217,000 clinical trial entries submitted by various organizations as of July 1st 2016, (see *www.clinicaltrials.gov*). It is estimated that trained analysts would require tens of thousands of man-hours to manually assimilate its full information to produce POS estimates.

Here, we construct estimates of POS and related risk characteristics of clinical trials using 185,994 unique entries of industry- and non-industry-sponsored trial data for over 21,143 compounds from Informa Pharma Intelligence's Trialtrove and Pharmaprojects database from January 1, 2000 to October 31, 2015. This is the largest investigation thus far into clinical trial success rates and their related parameters. To process this large amount of data, we develop an automated algorithm that computes these statistics in hours. We estimate aggregate success rates, completion rates, phase-transition probabilities, and trial durations, as well as more disaggregated measures across various dimensions such as clinical phase, disease, type of organization, and with and without biomarkers. Apart from the gains in efficiency, our algorithmic approach allows us to perform previously infeasible computations, such as generating time-series estimates of POS and related parameters.

Using this unique dataset, we find that the POS for all drug development programs across all indications is 13.8%, but when oncology trials are omitted, the POS becomes 20.9%. Consistent with previous studies,

oncology has the lowest POS among all disease groups, but our estimate of 3.4% is about two-third the value of the most recent prior estimate of 5.1% reported by Thomas et al. (2016). This lower estimate is driven largely by lower success rates across all phases which, in turn, is the result of the common practice of testing a single drug on multiple cancers simultaneously, leading to lower estimated success rates. Using only lead-indication trials, the estimated POS in oncology is 11.4%.

Computing the POS for all drug development programs over three-year rolling windows from 2005 to 2015 shows an initial declining trend from 11.2% in 2005 to 5.2% in 2013, after which the trend reverses to a POS of 6.7% and 13.8% in 2014 and 2015. The spike in approvals in 2015 may be due to incomplete data, as we shall explain later. Nonetheless, this recent rise in POS coincides with the fact that the FDA has approved more drugs between 2012 and 2015 (see Center for Drug Evaluation and Research. (2016, January)). The positive trend is observed in all therapeutic groups.

Our database contains additional information about each clinical trial which allows us to estimate conditional POSs. For example, we compute the POS conditioned on whether biomarkers are used and find a 0.8 percentage point decrease in POS (5.8% vs. 5.0%) with biomarkers, yielding the counter-intuitive implication that biomarkers do not seem to improve success rates. However, this is highly disease-specific—biomarkers are especially effective in the areas of oncology and genitourinary, where they increase overall POS by factors of 4.18 and 2.48, respectively. In addition, we estimate POS for rare diseases. Contrary to previous estimates, we find that these trials have lower POS (9.9%) when compared to the entire dataset (13.8%). The precipitous decline in POS is mainly caused by the very low POS of rare-disease oncology drug developments (1.9%), which includes the challenging subcategory of pediatric oncology. When these categories are excluded, the POS for rare diseases increases to 21.8% which is more consistent with common intuition.

This thesis also presents results for the statistical properties of clinical trial completion rates and duration, and compares the approval rate of industry-sponsored trials against jointly-sponsored drug developments. Three main points emerge: Firstly, we find differences in the completion rates and duration of trials between different phases and therapeutic areas. Secondly, oncology trials have lower completion rates and longer duration, signifying that it has greater risk in development. Thirdly, jointly-sponsored drug developments are more likely to succeed in bringing a drug to the market, and this suggests that everyone benefits when various parties share expertise in drug development. Before presenting these and other results, we begin by discussing our methodology and describing some features of our dataset.

Chapter 2 Modeling the Drug Development Process

In order to develop a drug, companies have to conduct clinical trials to demonstrate safety and efficacy of the drug in treating a particular medical condition, called an *indication*. Drug developments typically progress in stages, with Phase I being the safety test, Phase 2 a small test of efficacy for a given indication and Phase 3 a controlled test of efficacy using larger populations and against alternatives.

The POS for a given phase i, denoted by $POS_{i,i+1}$, is defined as the probability that the drug development advances to the next phase. The probability of getting a drug in Phase i through to approval is denoted by $POS_{i,APP}$. Hence the overall probability of success — moving a drug from Phase 1 to approval, which is called the likelihood of approval (LOA) in extant literature such as in Hay et al. (2014) — is $POS_{1,APP}$.

2.1 A model of drug development

In this paper, we consider an idealized process in which every drug development program passes through Phase 1, 2, and 3 trials, in this order. This is plausible since each of these stages involves distinct predefined tests, all of which are required by regulators in any new drug application (NDA). If we observe data for Phases 1 and 3 but not Phase 2 trials for a given drug-indication pair, our idealized process implies that there was at least one Phase 2 trial that occurred, but is missing from our dataset. Accordingly, we impute the successful completion of Phase 2 in these cases. There exists some cases where Phase 2 trials are skipped, as with the recent example of Aducanumab (BIIB037), Biogen's Alzheimer's candidate (see Root (2014)). Since skipping Phase 2 trials is motivated by compelling Phase 1 data, imputing the successful completion of Phase 2 trials in these cases to trace drug development paths may not be a bad approximation. In addition, we make the standard assumption that Phase 1/2 and Phase 2/3 trials are to be considered as Phase 2 and Phase 3 respectively.

Figure 1 shows the possible states as a drug progresses through a specific development pipeline. Drug developments in the state 'In-progress' have trials that are currently in progress. If a Phase i clinical trial concludes and its objectives are met, this trial is said to be completed. If it is terminated prematurely for any reason, the trial is categorized as failed. Conditioned on the trial being completed, the sponsor can choose to either pursue Phase i+1 trials or simply terminate development. If the company chooses the former option, the drug development program is categorized as advanced in Phase i, otherwise, it will be categorized as terminated in Phase i. A drug development may be terminated even if it shows great promise if the company faces financing

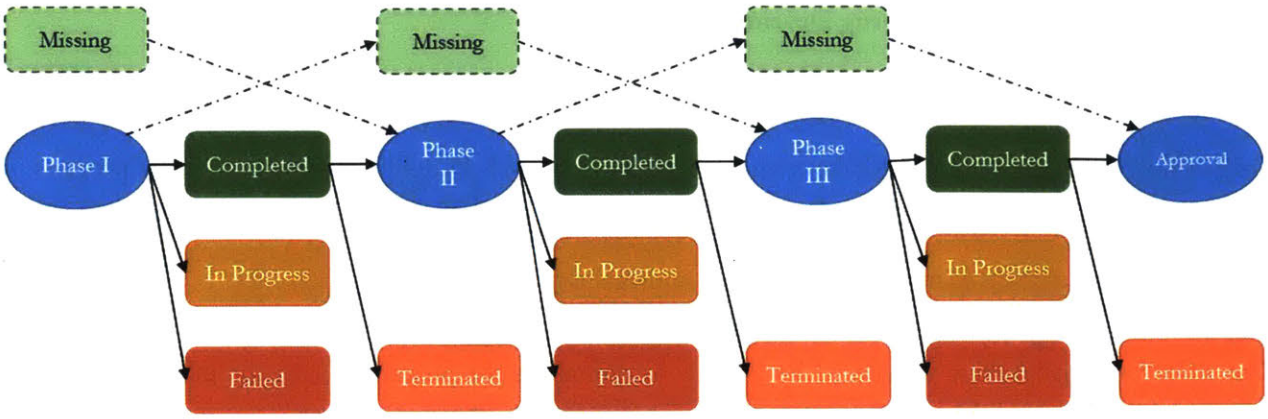


Figure 1. Observed and unobserved states in drug development, from Phase 1 to Approval

difficulties or wishes to pursue other business interests. Trials are considered "missing" if they have to be imputed.

As clinical trials are self-reported, there may be trials whose sponsors neglected to update their status. We hypothesize that such trials did not end favorably, since there is little incentive for any organization not to update a trial's favorable status; a successful completion of the trial would be a milestone that can boost a company's stock price or a research organization's prestige. Our database provider reviews the status of the trials annually and makes an effort to contact the sponsors to verify the current status of the trials. If there is no response from the sponsors, and if the time elapsed between the last update and current date is larger than a specified amount of time, the trial is automatically classified as 'suspended'. These are grouped under 'Failed' in our model.

With our assumptions, we model the drug development process as a directed graph, or more specifically, a directed tree where the nodes are the phases of a clinical trial for a specific indication and the edges are the transition between the phases. Thus, every path from the root to a leaf is a drug development path. Figure 2 shows an example of a graph with 4 unique drug development paths, even though all of them originate from a common node.

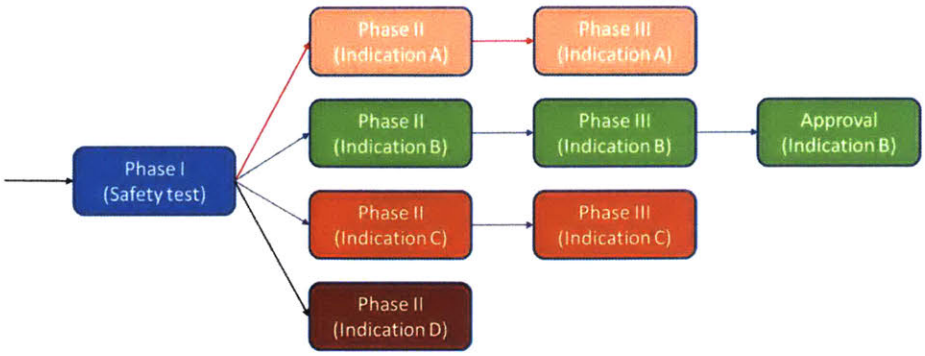


Figure 2. Examples of drug development paths

We formalize our simplified model of the drug development procedure as follows.

Let n^j be the number of drug development paths with observed Phase j trials and n_s^j be the number of drug development paths where we observe phase transitions of state s of Phase j:

$$s=\begin{cases} ip & \text{if all trials are in progress} \\ c & \text{if the trials have completed} \\ f & \text{if the trials have failed} \\ t & \text{if the trials have completed, but the program failed to proceed to phase } i+1 \text{ (i.e. terminated)} \\ m & \text{if the phase transition can be observed to be missing} \end{cases}$$

The following equations must hold:

$$n^j = n_{ip}^j + n_c^j + n_f^j \quad \forall j = 1,2,3,\text{App}$$

$$n_c^j = n_t^j + n^{j+1} - n_m^j \;\forall j = 1,2,3$$

The above two equations are conservation laws for the number of phase transitions. The first equation states that the number of drug development paths with observed Phase j trials must be the sum of all drug developments paths that have trials that are in progress, have been completed or have failed. The latter is the conservation law conditioned on a phase being successful.

The probability of success from any one state to the next, $POS_{j,j+1}$, is thus the ratio of the number of drug development projects in Phase $j+1$, both observed and non-observed, to the number of drug development projects in Phase j, both observed and non-observed:

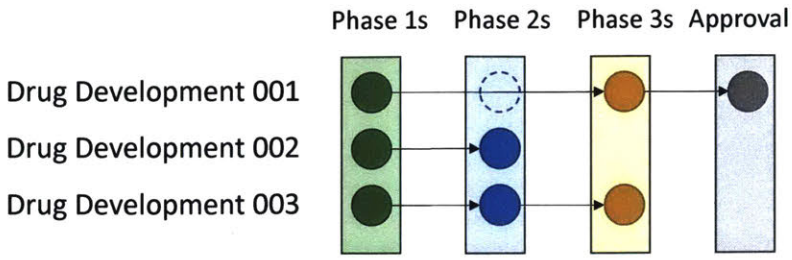


Figure 3. An example of how the "path-by-path" produces different result from the "phase-by-phase" method. In this example, we do not observe any Phase 2 trials for Drug Development 001. Our idealized model imputes the phase for the drug development and our "path-by-path" method computes $POS_{1,2}$, $POS_{2,3}$, $POS_{3,APP}$ and $POS_{1,APP}$ to be 1, ⅓, ½ and ⅓ respectively. In contrast, the "phase-by-phase" method does not impute the phase and will compute $POS_{1,2}$, $POS_{2,3}$, $POS_{3,APP}$ and $POS_{1,APP}$ to be 1, ½, ½ and ¼ respectively.

$$\mathrm{POS}_{j,j+1} = \frac{n^{j+1} + n_m^{j+1}}{n^j + n_m^j}$$

A drug candidate's $POS_{1,APP}$ is typically estimated by multiplying the empirical POS of Phases 1 , 2 and 3 trials. We call this the "phase-by-phase" probability of success. Mathematically,

$$\text{(Phase-by-phase) } \mathrm{POS}_{1,App} = \mathrm{POS}_{1,2} \cdot \mathrm{POS}_{2,3} \cdot \mathrm{POS}_{3,App}$$

In this paper, we take a different approach; since we are able to trace each drug development path from Phase *i* to approval, we can estimate of the overall probability of success simply by counting the proportion of drug developments that made it to approval. This method is referred to as the "path-by-path" probability of success.

$$\text{(Path-by-path) } \mathrm{POS}_{1,App} = \frac{n_c^{Approval}}{n^1 + n_m^1 - n_{ip}^1 - n_{ip}^2 - n_{ip}^3}$$

While the phase-by-phase approach has been shown to be unbiased if one only has random samples of the clinical trials and their transition status, they may suffer from systematic underestimation of the true POS. For clarity, we provide an example in Figure 3. This occurs due to the lack of information about how trials are related in a development path.

Algorithm 1 – Identifying trials in a drug development and computing the probability of success

```
Initialize count_12_succ = count_12_fail = count_23_succ = count_23_fail = count_3a_succ
= count_3a_fail = 0

for every pair {drug, indication}, do:

        Filter and populate a list of trials on indication using drug;

        if Drug is approved, then
                count_12_succ++;
                count_23_succ++;
                count_3a_succ++;
                continue;
        if there exists >=1 trial in Phase 3, then
                count_12_succ++;
                count_23_succ++;
                if latest end date of Phase 3 trials is < T - t3, then
                        count_3a_fail++;
                continue;
        if there exists >=1 trial in Phase 2 then
                count_12_succ++;
                if latest end date of Phase 2 trials is < T - t2, then
                        count_23_fail++;
                continue;
        if there exists >=1 trial in Phase 1 and if the latest end date is < T - t1, then
                count_12_fail++;
end
```

Figure 4. An algorithm for identifying trials in drug development and computing the probability of success.

2.2 An algorithm

Given our development-path framework, we can compute POSs using the algorithm presented in Figure 4. We recursively consider all possible drug-indication pairs and determine the maximum observed phase. Reaching Phase i would imply that all lower phases were completed. To determine if a drug development program has been terminated in the last observed phase or is still ongoing, we use a simple heuristic: if the time elapsed between the end date of the most recent Phase i and the end of our sample exceeds a certain threshold t_i, we conclude that the trial has terminated. Based on practical considerations, we set t_i, to be 360, 540 and 900 days for Phases 1, 2, and 3, respectively. For example, we assume that it takes approximately 6 months to prepare documents for an NDA filing after a Phase 3 trial has been completed. Since the FDA has a 6-month period to decide if it wishes to follow up on a filing, and an additional 18 months to deliver a verdict, this places the overall time between Phase 3 to approval to about 30 months, hence we set t_3 = 900 days.

2.3 Limitations of the Path-by-path Method

We caution that algorithm is based on the path-by-path approach, which is not suitable in analyzing instances where one does not have the full information about the drug development process, such as while performing a

Drug Development X

Phase	Start Date	End Date
1	Jan 2000	Jun 2000
2	Feb 2001	July 2003
3	Mar 2004	Dec 2007

Inference:

Time Window	Observed Phase(s)	Path-by-Path Inference	Phase-by-phase Inference
Jan 2000 to Dec 2002	1	1 completed	I completed
Jan 2001 to Dec 2003	2	1 & 2 completed	2 completed
Jan 2002 to Dec 2004	2	1 & 2 completed	2 completed
Jan 2003 to Dec 2005	2	1 & 2 completed	2 completed
Jan 2004 to Dec 2006	No observation	N.A.	N.A.
Jan 2005 to Dec 2007	3	1 & 2 & 3 completed	3 completed

Figure 5. An example that demonstrates that the path-by-path approach is inappropriate for analyzing trials over short time intervals.

rolling-window computation with the time window being much shorter than the complete drug development period (which is typically around a decade). This is because the path-by-path approach, to borrow the language of concurrency, 'linearizes' drug development at its endpoint. That is, progress in drug development appears to the algorithm to have occurred instantaneously at the conclusion of the last known trial. We give a fictitious example in Figure 5 to illustrate this point.

As can be seen, our algorithm inferred all completed trials for the drug development project given the latest information at that point in time. While the algorithm works accurately when one has a massive database across long time horizons, it is unable to provide an accurate assessment of changes in success rates over short time windows. In our example, the Phase 1 trial is repeatedly counted as a success across multiple time windows, and this inflates the true success rate of Phase 1 trials at any point in time. When this situation occurs, we modify Algorithm 1 to use the phase-by-phase approach.

To compute this, we first perform a scan through the entire database and increment the counts for phase transition i to j only if there exists a trial in phase i. This method does not attempt to infer missing information, and is thus able to reflect dynamic changes in the success rates. A subtle but important difference between the two computation methods is that, while the former measures the proportion of drug development projects that progress, the latter measures the proportion of phase transitions that progress. The two measures will produce the same results if there is no missing data point. However, these conditions do not hold true in real life clinical

trial databases. By applying the 'phase-by-phase' algorithm to the entire dataset, our evaluation is that it tends to underestimate the success rate. Nevertheless, the latter method is a strong enough proxy to estimate trends in drug development success rates.

2.4 All indications versus lead indications

The model and algorithm presented in the previous subsection considered each drug-indication pair as a unique development path. There are some who are interested in the lead indication for a given drug, the indication that has progressed furthest in the development pipeline. If there is more than one indication in the highest phase of the pipeline, the indication that reached the phase first will be considered the *lead indication. Indication B* in Figure 2 is the lead indication, as it is the only indication for which the drug is approved. We argue that using lead indications in financial analysis is problematic.

First, the definition of lead indication makes it confusing to analyze phase transition probabilities. Consider the following example: Suppose that a company at time *t* completes Phase 2 clinical trials for two indications, *IndA* and *IndB*. It then decides to conduct a Phase 3 trial for *IndA*, making *IndA* the lead indication for the drug at *t+1*. A short time later, at *t+2*, the company then reconsiders its priorities and decide to accelerate development of the drug for *IndB*. *IndB* makes it to the market earlier than *IndA* and is now the lead indication for the drug. Hence, depending on when one takes a snapshot of the data, one may end up with different lead indications and varying estimates of the indication-specific phase transition probabilities. As such, considering all indications in computing the phase transition probabilities is more robust and accurate.

Second, from a financial perspective, it may be more informative to use indication-specific drug development paths to compute the different metrics. Very often, a New Drug Application (NDA) specifies the indication and dosage that the drug is intended to treat, and a company would need to resubmit another application if they wish to market it for another disease or dosage. Since the patient segment determines the market size and thus the financial potential of the drug, it would be more appropriate to use indication-specific probabilities in the financial analysis of drug development endeavors.

Nonetheless, we present lead-indication computations in our analysis for completeness.

Chapter 3 Data

We use *Citeline* data provided by Informa Pharma Intelligence, which combines individual clinical trial information from *TrialTrove* and drug approval data from *Pharmaprojects*. *Citeline* is a superset of the most commonly data sources. In addition to incorporating multiple data streams—including nightly feeds from official sources such as ClinicalTrials.gov — *Citeline* contains data from primary sources such as institutional press releases, financial reports, study reports, and drug marketing label applications, and secondary sources such as analyst reports by consulting companies. Secondary sources are particularly important for reducing potential biases that can arise from the tendency of organizations to report only successful trials, especially prior to the FDA Amendments Act of 2007 requiring all clinical trials to be registered and tracked via ClinicalTrials.gov.

The trials range from January 1, 2000, to October 31, 2015, the latter being the date that we received the dataset. After deleting 46,524 entries with missing dates and unidentified sponsors, 1,818 entries that ended before January 1st 2000, 406,038 data points remain. Of these, 34.7% (141,086) are industry-sponsored and 65.3% (264,952) are non-industry sponsored. In our industry-sponsored analysis, we counted 41,040 development paths, or 67,752 phase transitions after imputation. Table 1 contains an illustrative sample of the dataset and Figure 6 provides some basic summary information.

Some trials are missing end-dates due to the failure of their sponsors to report this information. Since these dates are required by our algorithm, we estimate them by assuming that trials lasted the median duration of all other trials with similar features. Only 14.6% (59,208) of trials required the estimation of end-dates.

TrialID	Therapeutic Area	Drug Name	Phase	Disease Type	Start Date	End Date	Sponsor
48391	Autoimmune/ Inflammation	Loratadine	I/2	Allergic Rhinitis	NULL	2003-06-07	(Other Hospital/ Academic/ Medical Center)
70538	Autoimmune/ Inflammation	Loratadine	3	Allergic Rhinitis	NULL	2007-09-18	(Other Hospital/ Academic/ Medical Center)
100378	Autoimmune/ Inflammation	Loratadine	3	Asthma	NULL	2008-10-29	Merck & Co.
122164	Autoimmune/ Inflammation	Loratadine	4	Allergic Rhinitis	2010-01-01	2012-03-01	(Other Hospital/ Academic/ Medical Center)
151465	CNS	Loratadine	3	Pain (nociceptive)	2011-05-01	2014-05-14	Cancer and Leukemia Group B (CALGB)
153368	Autoimmune/ Inflammation	Loratadine	I	Asthma	NULL	2006-07-01	(Other Hospital/ Academic/ Medical Center)

Table 1. Sample of Citeline data entries. Our algorithm processes such data to identify drug developments and compute the various statistics

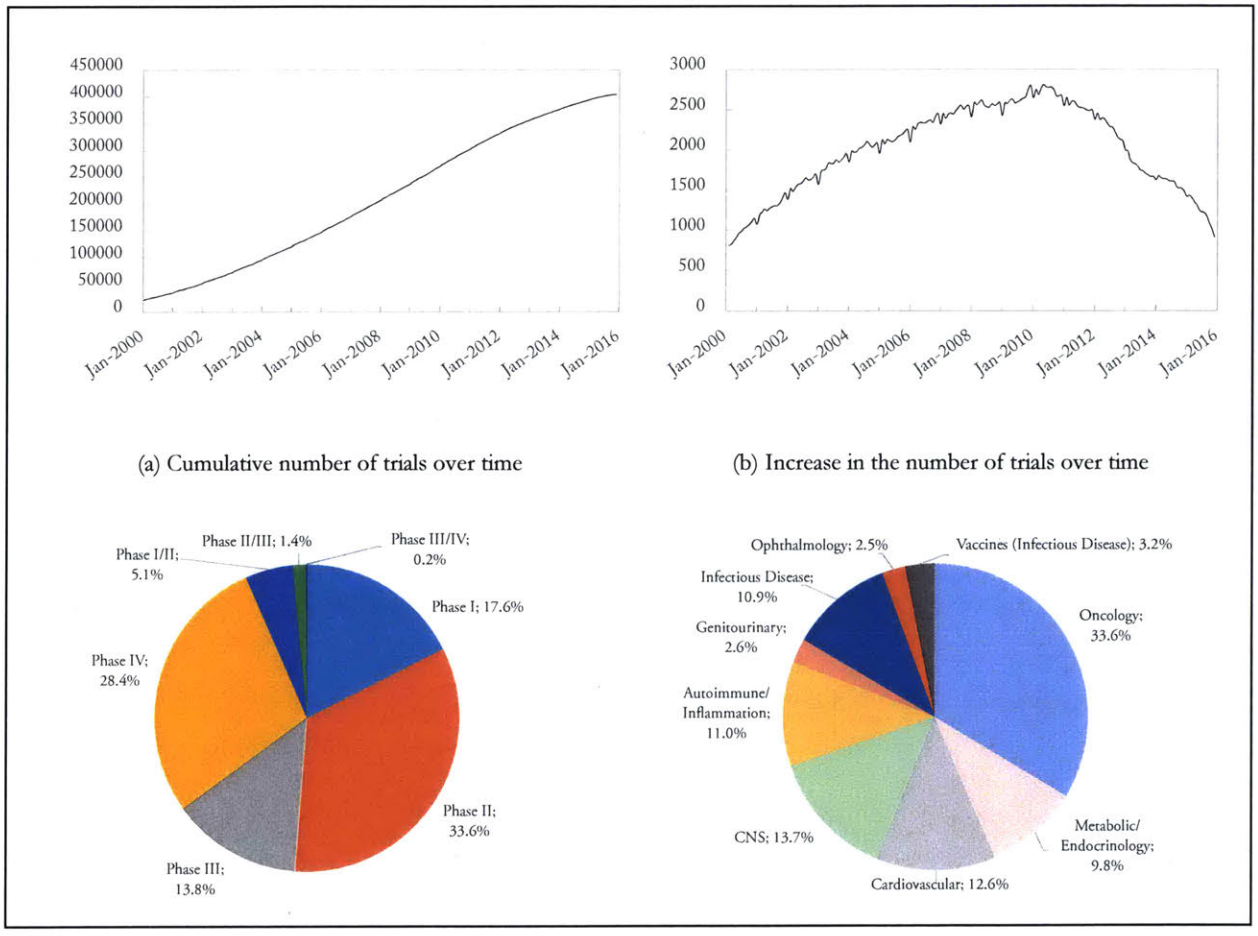


Figure 6. Summary of the entire dataset of 407,856 data points. Of these, 34.7% are industry-sponsored (n=141,436) and the remaining 65.3% are non-industry sponsored (n=266,420). The trials span from January 1, 2000 and October 31, 2015.

Chapter 4 Results for Industry Sponsored Trials

4.1 Probability of Success for the Entire Time Period

Table 2 contains our estimates of aggregate POSs for each clinical phase across all indications. Corresponding estimates from the prior literature are also included for comparison. We find that 13.8% of all drug development programs eventually lead to approval, which is higher than the 10.4% reported by Hay et al. (2014) and the 9.6% reported by Thomas et al. (2016). Our phase-specific POS estimates are higher in all the phases. The largest increase is seen in $POS_{2,3}$, where we obtained a value of 58.3% compared to 32.4% in Hay et al. (2014) and 30.7% in Thomas et al. (2016). These differences may be due to our method of imputing missing clinical trials.

	This study - All Indications (Industry)		**This study - Lead Indications (Industry)**		**Thomas et al. (2016) - All Indications**		**Hay et al. (2014) - All Indications**		**Hay et al. (2014) - Lead Indications**		**DiMasi et al. (2010) - Lead Indications**	
	$POS_{i,i+1}$	**$POS_{i,APP}$**	**$POS_{i,i+1}$**	**$POS_{i,APP}$**	**$POS_{i,i+1}$**	**$POS_{i,APP}$**	**$POS_{i,i+1}$**	**$POS_{i,APP}$**	**$POS_{i,i+1}$**	**$POS_{i,APP}$**	**$POS_{i,i+1}$**	**$POS_{i,APP}$**
Phase 1 to 2	66.4%	13.8%	75.8%	21.6%	63.2%	9.6%	64.5%	10.4%	66.5%	15.3%	71%	19.0%
Phase 2 to 3	58.3%	35.1%	55.9%	26.4%	30.7%	15.2%	32.4%	16.2%	39.5%	23.1%	45%	26.8%
Phase 3 to APP	59.0%	59.0%	70.0%	70.0%	49.6%	49.6%	50.0%	50.0%	58.4%	58.4%	60%	59.5%
Phase 1 to APP		13.8%		21.6%		9.6%		10.4%		15.3%		19.0%
Number of Drugs	15,102				?		5,820		4,736		1,316	
Years of source data (time-span)	2000- 2015 (15 years)				2006-2015 (9 years)		2003-2011 (9 years)				1993-2009 (17 years)	
Number of Companies	5,764				1,103		835				50	

Table 2. Comparison of the results of our paper with previous publications, using data from January 1st, 2000 to October 31st, 2015. We computed this using the algorithm shown in Figure 2, which traces drug development and calculates the proportion of drug developments that advance from one phase to another.

Table 3 contains phase and overall POS estimates by therapeutic group. POSs range from a minimum of 3.4% for oncology to a maximum of 33.4% for vaccines (infectious disease). The overall POS ($POS_{1,APP}$) for oncology drug development is about two thirds the previously reported estimates of 5.1% in Thomas et al. (2016) and 6.7% in Hay et al. (2014).

A significantly different pattern emerges when we consider the phase POSs for lead indications. The overall POS ($POS_{1,APP}$) increases when considering only lead indications, which is in line with the findings by Hay et

All indications (Industry)								
	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic Groups	Total	$POS_{1,2}$, % (SE, %)	Total	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	17,368	57.6 (0.4)	6,533	32.7 (0.6)	6.7 (0.3)	1,236	35.5 (1.4)	3.4 (0.2)
Metabolic/ Endocrinology	3,589	76.2 (0.7)	2,357	59.7 (1.0)	24.1 (0.9)	1,101	51.6 (1.5)	19.6 (0.7)
Cardiovascular	2,810	73.3 (0.8)	1,858	65.7 (1.1)	32.3 (1.1)	964	62.2 (1.6)	25.5 (0.9)
CNS	4,924	73.2 (0.6)	3,037	51.9 (0.9)	19.5 (0.7)	1,156	51.1 (1.5)	15.0 (0.6)
Autoimmune/	5,086	69.8 (0.6)	2,910	45.7 (0.9)	21.2 (0.8)	969	63.7 (1.5)	15.1 (0.6)
Genitourinary	757	68.7 (1.7)	475	57.1 (2.3)	29.7 (2.1)	212	66.5 (3.2)	21.6 (1.6)
Infectious Disease	3,963	70.1 (0.7)	2,314	58.3 (1.0)	35.1 (1.0)	1,078	75.3 (1.3)	25.2 (0.8)
Ophthalmology	674	87.1 (1.3)	461	60.7 (2.3)	33.6 (2.2)	207	74.9 (3.0)	32.6 (2.2)
Vaccines (Infectious	1,869	76.8 (1.0)	1,235	58.2 (1.4)	42.1 (1.4)	609	85.4 (1.4)	33.4 (1.2)
Overall	41,040	66.4 (0.2)	21,180	58.3 (2.3)	35.1 (2.2)	7,532	59.0 (0.6)	13.8 (0.2)
All without oncology	23,672	73.0 (0.3)	14,647	27.3 (0.4)	27.3 (0.4)	6,296	63.6 (0.6)	20.9 (0.3)
Lead indications (Industry)								
	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic Groups	Total	$POS_{1,2}$, % (SE, %)	Total	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	3,107	78.7 (0.7)	1,601	53.9 (1.2)	13.1 (0.8)	431	48.5 (2.4)	11.4 (0.7)
Metabolic/ Endocrinology	2,012	75.2 (1.0)	1,273	57.0 (1.4)	26.4 (1.2)	535	62.8 (2.1)	21.3 (1.0)
Cardiovascular	1,599	71.1 (1.1)	1,002	64.9 (1.5)	34.1 (1.5)	473	72.3 (2.1)	26.6 (1.2)
CNS	2,777	75.0 (0.8)	1,695	54.5 (1.2)	24.1 (1.0)	648	63.0 (1.9)	19.3 (0.9)
Autoimmune/	2,900	78.9 (0.8)	1,862	48.7 (1.2)	24.3 (1.0)	659	68.6 (1.8)	20.3 (0.9)
Genitourinary	568	73.4 (1.9)	382	59.2 (2.5)	31.9 (2.4)	176	69.3 (3.5)	25.3 (2.0)
Infectious Disease	2,186	74.6 (0.9)	1,326	58.0 (1.4)	34.3 (1.3)	594	76.6 (1.7)	26.7 (1.1)
Ophthalmology	437	89.0 (1.5)	302	57.6 (2.8)	30.5 (2.6)	124	74.2 (3.9)	30.7 (2.7)
Vaccines (Infectious	881	75.8 (1.4)	567	57.1 (2.1)	40.4 (2.1)	269	85.1 (2.2)	31.6 (1.7)
Overall	16,467	75.8 (0.3)	10,010	55.9 (0.5)	26.4 (0.4)	3,478	70.0 (0.8)	21.6 (0.4)
All without oncology	13,360	75.8 (0.4)	8,409	29.0 (0.5)	29.0 (0.5)	3,478	70.0 (0.8)	23.4 (0.4)

Table 3. The probability of success by therapeutic groups, using data from January 1st, 2000 to October 31st, 2015. We computed this using the algorithm shown in Figure 2, which traces drug development and calculates the proportion of drug developments that advance from one phase to another.

al. (2014). However, we find an increase in the POSs for Phase 1 ($POS_{1,3}$) and Phase 3 ($POS_{2,3}$) but a decrease in the POS for Phase 2 ($POS_{2,3}$) when one looks only at lead indications. The POS for lead indications may be lower than the POS for all indications if a company initiates clinical trials for many indications, and most of them move on to the next phase. Conversely, the POS for lead indications is higher if many of the initiated clinical trials for the same drug fail. This practice of initiating multiple clinical trials for indications using the same drug is prevalent in the industry, as documented in Table 4. The relative performance of the various therapeutic groups remain the same, with oncology still being the lowest performing group at 11.4% for $POS_{1,APP}$. The lead indication overall POSs for the individual therapeutic groups show mixed directions when compared to the respective indication-specific overall POSs.

Average Number of Indications Per Drug					
	Mean	*Std Dev*		*Mean*	*Std Dev*
Oncology	2.61	3.24	Genitourinary	1.06	0.25
Metabolic/Endocrinology	1.38	0.71	Infectious Disease	1.5	0.72
Cardiovascular	1.3	0.65	Ophthalmology	1.25	0.48
CNS	1.26	0.60	Vaccines (Infectious Disease)	1.91	0.48
Autoimmune/Inflammation	1.34	0.81	**Overall**	**1.74**	**1.95**

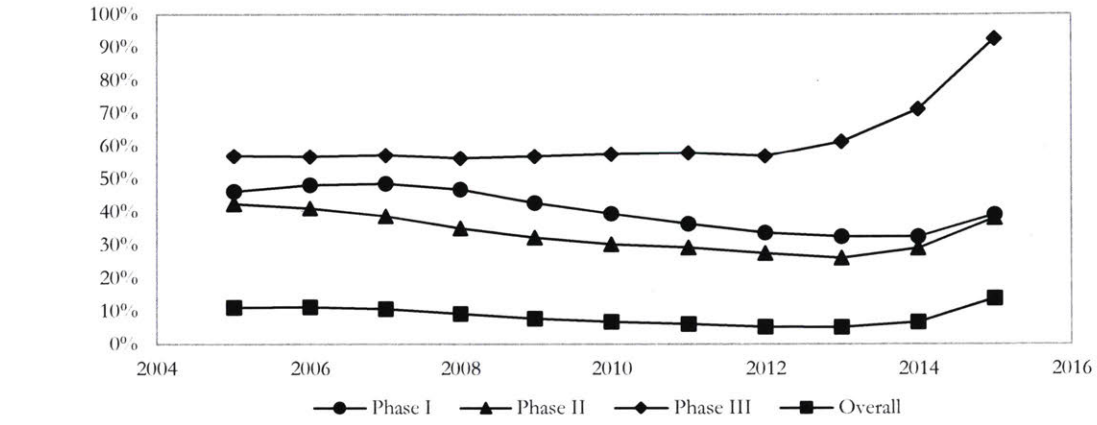
Table 4. Average number of indications per drug, computed using the entire dataset from January 1, 2000 to Oct 31, 2015.

4.2 Probability of Success over Time

Many observers in both the industry and academia believe that the success rates of clinical drug development have fallen over the past decade. We attempt to evaluate this intuition quantitatively by computing the sample phase success rates for the years between 2005 and 2015 using 3-year rolling windows to capture time variation while smoothing estimation errors. We define the 3-years window to be January 1st in year t–2 to December 31st in year t, with the exception of the last window, which terminates on October 31st 2015, the day of the snapshot of the data. Caution must be exercised in interpreting the results for 2015, which very likely overestimate the true success rates due to boundary effects. As insufficient time has passed to allow our algorithm to conclude that a trial has failed, we obtain a smaller denominator in our computation of probabilities, translating to upward-biased success rates for this last year.

The overall success rate for all drug development did decrease between 2005 (11.2%) and 2013 (5.2%), as anecdotal reports suggest. However, this decline reversed after 2013 (see Figure 7). The overall success rate is

	Phase I to Phase II			Phase II to Phase III			Phase III to Approval			Overall	
Year	Total Trials	$POS_{1,2}$, %	(SE, %)	Total Trials	$POS_{2,3}$, %	(SE, %)	Total Trials	$POS_{3,APP}$, %	(SE, %)	POS, %	(SE, %)
2005	3605	46.2	(0.8)	3518	42.4	(0.8)	1988	56.9	(1.1)	11.2	(0.6)
2006	4218	48.1	(0.8)	3962	41.0	(0.8)	2246	56.7	(1.0)	11.2	(0.6)
2007	4707	48.5	(0.7)	4201	38.6	(0.8)	2501	57.1	(1.0)	10.7	(0.6)
2008	5187	46.8	(0.7)	4538	35.0	(0.7)	2717	56.2	(1.0)	9.2	(0.5)
2009	5988	42.7	(0.6)	4817	32.2	(0.7)	2854	56.8	(0.9)	7.8	(0.4)
2010	6753	39.4	(0.6)	5240	30.1	(0.6)	2873	57.5	(0.9)	6.8	(0.4)
2011	7414	36.3	(0.6)	5355	29.2	(0.6)	2654	57.9	(1.0)	6.1	(0.3)
2012	7885	33.6	(0.5)	5510	27.5	(0.6)	2671	56.9	(1.0)	5.3	(0.3)
2013	7872	32.5	(0.5)	5272	26.0	(0.6)	2375	61.3	(1.0)	5.2	(0.3)
2014	7491	32.4	(0.5)	4384	29.0	(0.7)	2116	71.2	(1.0)	6.7	(0.4)
2015	5315	39.2	(0.7)	2856	38.1	(0.9)	1424	92.6	(0.7)	13.8	(0.7)



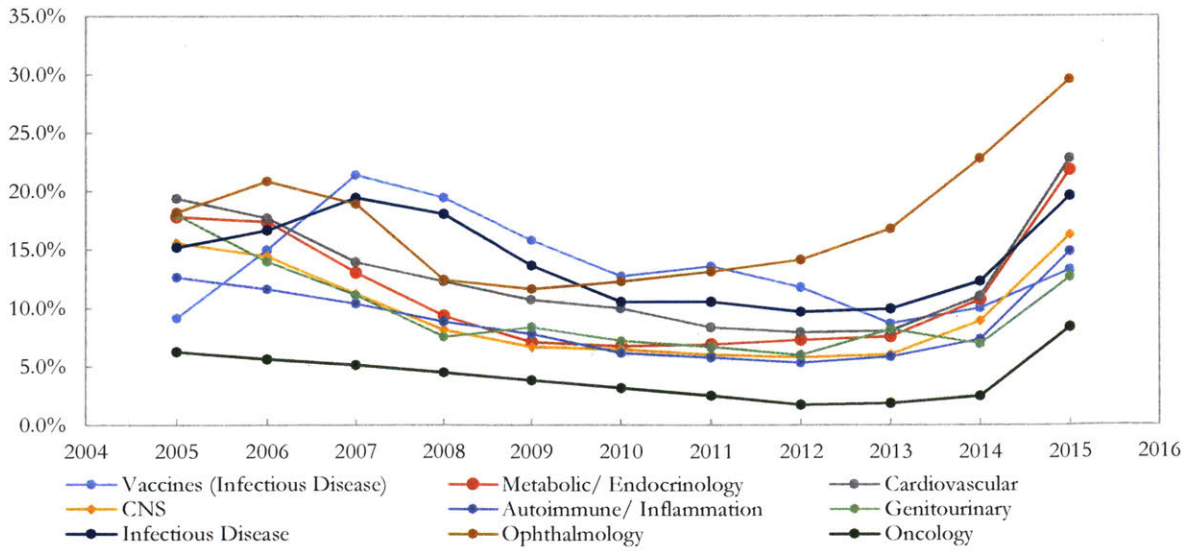


Figure 7. The probability of success over the period of Jan 1, 2005 to Oct 31, 2015 computed using a 3-years rolling window from Jan 1 in year t-2 to Dec 31 in year t, with the exception of the last window, which terminates on Oct 31, 2015. This probability of success is computed using the phase-by-phase method, our adaptation of Hay et al.'s methodology, which reports the proportion of phase transitions that advances to the next phase. The algorithm from Figure 2 is not used as it would overestimate the phase success if applied on a short window. The result for 2015 has to be treated with caution as boundary effects increases the success rates artificially.

mainly driven by the changes in $POS_{1,2}$ and $POS_{2,3}$. The timing of the upward trend coincides with the time period where FDA has been approving more novel drugs, compared to the historical mean (see Center for Drug Evaluation and Research. (2016, January)). Our results are not directly comparable with Smietana et al. (2016) because they used a different aggregation method and studied only lead indications.

The overall POS across the different therapeutic groups move in tandem across time. There are some minor deviations, such as when the POS of drugs and vaccines for infectious diseases increased between 2005 and 2007. Nonetheless, these results suggest that there is a systemic factor driving the trends over time. Numerical results of our analysis are provided in Appendix A.

4.3 Probability of Success for Biomarkers

The use of biomarkers to select patients, enhance safety, and serve as surrogate clinical endpoints has become more common, and it has been hypothesized that trials using biomarkers are more likely to succeed. We test this hypothesis by comparing the POSs of drugs with and without biomarkers.

In contrast to Thomas et al. (2016), who investigated the use of biomarkers only for patient selection, we code a trial as involving biomarkers if it includes an objective of evaluating or identifying the use of any novel biomarkers as indicators of therapeutic efficacy or toxicity, or to use biomarkers in the selection of patients.

In our database, only 7.1% of all drug development paths that use biomarkers use them in all stages of development. As such, we adopt the phase-by-phase approach instead of using the path-by-path approach. This is done by modifying Algorithm 1 (Figure 4) to increment counts only if there exists a biomarker trial in that phase. Furthermore, as 92.3% of the trials using biomarkers in our database are observed only on or after January 1, 2005, we do not include trials before this date to ensure a fair comparison of POS between trials that and do not use biomarkers.

Table 5 shows that there is substantial variation in the use of biomarkers across therapeutic areas. Biomarkers are seldom used in vaccines for infectious diseases, ophthalmology, and genitourinary conditions. Trials using biomarkers exhibit an overall POS ($POS_{1,APP}$) of 5.0%, compared to 5.8% for trials without biomarkers, implying that biomarkers have little impact on POS. However, this observation must be tempered by the fact that for genitourinary diseases and oncology, the use of biomarkers raises the POSs from 6.3% to 26.3% and

Therapeutic Groups		Phase 1 to Phase 2			Phase 2 to Phase 3			Phase 3 to Approval			Overall	
		Total Phase Transitions	$POS_{1,2}$, %	(SE, %)	Total Phase Transitions	$POS_{2,3}$, %	(SE, %)	Total Phase Transitions	$POS_{3,APP}$, %	(SE, %)	POS, %	(SE, %)
Oncology	No Biomarker	5,499	26.3	(0.6)	3,190	16.2	(0.7)	903	33.6	(1.6)	1.4	(0.2)
	With Biomarker	4,986	33.5	(0.7)	2,325	25.8	(0.9)	333	40.8	(2.7)	3.5	(0.4)
	All	10,485	29.7	(0.4)	5,515	20.3	(0.5)	1,236	35.5	(1.4)	2.1	(0.2)
Metabolic/ Endocrinology	No Biomarker	1,424	45.5	(1.3)	1,214	34.5	(1.4)	865	54.1	(1.7)	8.5	(0.9)
	With Biomarker	115	33.0	(4.4)	226	31.0	(3.1)	236	42.4	(3.2)	4.3	(1.5)
	All	1,539	44.6	(1.3)	1,440	34.0	(1.2)	1,101	51.6	(1.5)	7.8	(0.8)
Cardiovascular	No Biomarker	1,117	38.1	(1.5)	711	36.8	(1.8)	673	67.5	(1.8)	9.5	(1.1)
	With Biomarker	131	55.0	(4.3)	321	41.1	(2.7)	291	50.2	(2.9)	11.3	(2.5)
	All	1,248	39.9	(1.4)	1,032	38.2	(1.5)	964	62.2	(1.6)	9.5	(1.0)
CNS	No Biomarker	2,011	40.3	(1.1)	1,858	29.9	(1.1)	1,049	51.2	(1.5)	6.2	(0.6)
	With Biomarker	212	43.9	(3.4)	234	32.5	(3.1)	107	50.5	(4.8)	7.2	(2.1)
	All	2,223	40.7	(1.0)	2,092	30.2	(1.0)	1,156	51.1	(1.5)	6.3	(0.6)
Autoimmune/ Inflammation	No Biomarker	2,227	37.7	(1.0)	1,765	24.9	(1.0)	867	64.0	(1.6)	6.0	(0.6)
	With Biomarker	288	49.0	(2.9)	355	28.5	(2.4)	102	60.8	(4.8)	8.5	(2.0)
	All	2,515	39.0	(1.0)	2,120	25.5	(0.9)	969	63.7	(1.5)	6.3	(0.6)
Genitourinary	No Biomarker	354	33.9	(2.5)	271	28.4	(2.7)	204	65.2	(3.3)	6.3	(1.5)
	With Biomarker	10	70.0	(14.5)	16	37.5	(12.1)	8	100.0	(0.0)	26.3	(15.7)
	All	364	34.9	(2.5)	287	28.9	(2.7)	212	66.5	(3.2)	6.7	(1.5)
Infectious Disease	No Biomarker	1,888	40.1	(1.1)	1,372	34.1	(1.3)	1,007	75.1	(1.4)	10.3	(0.9)
	With Biomarker	79	32.9	(5.3)	108	44.4	(4.8)	71	78.9	(4.8)	11.5	(4.2)
	All	1,967	39.8	(1.1)	1,480	34.9	(1.2)	1,078	75.3	(1.3)	10.5	(0.9)
Ophthalmology	No Biomarker	172	54.7	(3.8)	256	35.2	(3.0)	186	72.0	(3.3)	13.8	(3.0)
	With Biomarker	9	0.0	(0.0)	21	28.6	(9.9)	21	100.0	(0.0)	0.0	(0.0)
	All	181	51.9	(3.7)	277	34.7	(2.9)	207	74.9	(3.0)	13.5	(2.8)
Vaccines (Infectious Disease)	No Biomarker	718	41.4	(1.8)	748	33.2	(1.7)	597	85.8	(1.4)	11.8	(1.4)
	With Biomarker	15	13.3	(8.8)	18	11.1	(7.4)	12	66.7	(13.6)	1.0	(2.3)
	All	733	40.8	(1.8)	766	32.6	(1.7)	609	85.4	(1.4)	11.4	(1.3)
Overall	No Biomarker	15,410	35.3	(0.4)	11,385	27.0	(0.4)	6,351	60.7	(0.6)	5.8	(0.2)
	With Biomarker	5,845	35.0	(0.6)	3,624	28.8	(0.8)	1,181	50.0	(1.5)	5.0	(0.4)
	All	21,255	35.2	(0.3)	15,009	27.4	(0.4)	7,532	59.0	(0.6)	5.7	(0.2)

Table 5. Probability of success with and without biomarkers, using data from January 1, 2005 to October 31, 2015. We computed the results using the algorithm shown in Figure 4, which traces drug development and calculates the proportion of drug developments that advance from one phase to another. Since the statuses of the majority (92.3%) of the trials using biomarkers are observed only on or after January 1, 2005, the choice of the time period is to ensure a fair comparison between trials using biomarkers and without using biomarkers.

from 1.4% to 3.5%, respectively. On the other hand, they are not particularly helpful in ophthalmology and vaccines for infectious diseases.

Our findings differ from those of previous studies such as Thomas et al. (2016), who conclude that biomarkers can accelerate drug development while reducing costs. The differences may be explained by our wider definition of a trial that uses biomarkers and the use of more than ten times the number of trials in our study. We provide a more detailed analysis of these differences in Appendix B.

4.4 Probability of Success for Orphan Drugs

Table 6 contains POS estimates for drugs that treat rare diseases, also known as 'orphan drugs'. Rare diseases can belong to any therapeutic group, and the computations for the statistics for orphan drugs are identical to those used for the trials used in Table 3.

Our data source reveals that that most orphan drug trials are in oncology. In general, orphan drug development has significantly lower success rates than in general, with only 9.9% of drug development projects reaching the market. Comparing these results with those for all drug development, we see that, while the Phase 1 POS increased from 66.4% to 75.9%, Phase 2 and Phase 3 success rate fell from 58.3% to 48.8% and 59.0% to 46.7% respectively, leading to a decline in the overall POS.

Our overall POS of 9.9% is lower than the 25.3% reported in Thomas et al. (2016). The discrepancy can be attributed to the fact that they identified only non-oncology indications as "rare diseases," and did not use the path-by-path method of computing POS. Our estimated orphan-drug POS increases to 21.8% after excluding all oncology indications from the calculations, which is more in line with the findings of Thomas et al. (2016).

Orphan Drugs (Industry, All indications)								
	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic Groups	Total Paths	$POS_{1,2}$, % (SE, %)	Total Paths	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total Paths	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	1,245	72.0	535	39.4	2.8	104	14.4	1.9
		(1.3)		(2.1)	(0.5)		(3.4)	(0.4)
Metabolic/ Endocrinology	89	84.3	45	66.7	31.1	18	77.8	29.8
		(3.9)		(7.0)	(4.9)		(9.8)	(4.8)
Cardiovascular	115	69.6	58	77.6	43.1	30	83.3	32.1
		(4.3)		(5.5)	(4.6)		(6.8)	(4.4)
CNS	160	85.0	96	56.3	8.3	25	32.0	8.8
		(2.8)		(5.1)	(2.2)		(9.3)	(2.2)
Autoimmune/ Inflammation	228	76.3	114	57.0	8.8	32	31.3	7.4
		(2.8)		(4.6)	(1.9)		(8.2)	(1.7)
Genitourinary	14	100.0	13	46.2	38.5	6	83.3	38.5
		(0.00)		(13.8)	(13.0)		(15.2)	(13.0)
Infectious Disease	157	89.2	104	53.8	28.8	39	76.9	28.8
		(2.5)		(4.9)	(3.6)		(6.7)	(3.6)
Ophthalmology	19	73.7	7	71.4	0.0	0	0.0	0.0
		(10.1)		(17.1)	(0.00)		(0.00)	(0.00)
Vaccines (Infectious Disease)	57	89.5	43	53.5	51.2	22	100.0	45.8
		(4.06)		(7.6)	(6.6)		(0.0)	(6.6)
Overall	2,084	75.9	1,015	48.8	12.7	276	46.7	9.9
		(0.9)		(1.6)	(0.7)		(3.0)	(0.7)
All except oncology	839	81.5	480	59.2	23.8	172	66.3	21.8
		(1.3)		(2.2)	(1.5)		(3.6)	(1.4)

Table 6. The probability of success of orphan drug development. We computed the results using the algorithm shown in Figure 2, which traces drug development and calculates the proportion of drug developments that advance from one phase to another. While we used the entire dataset from January 1, 2000 to October 31, 2015, it has to be noted that there are only 3,548 data points relating to orphan drugs, with the majority (95.3%) of the trials' statuses observed on or after Jan 1, 2005.

4.5 Completion Rates

An alternative measure of performance for clinical trials is the completion rate. It answers the question, "How likely is a trial to complete?". The completion rate of Phase *i* trials (CR_i) is computed by dividing the number of trials in Phase *i* that were tagged as 'completed' by the number of trials that have been initiated in Phase *i*. This metric is useful in real option valuation, whereby uncertain possible outcomes with various endpoints are implicitly modeled in order to provide a more robust and comprehensive cost-benefit analysis. Our data shows that clinical trial completion rates are high across all phases, averaging at 85.8% (Table 7). Phase 2 trials have the lowest tendency to complete, with only 81.1% of all trials being completed. On the other hand, 91.3% of all Phase 1 trials are completed. While Phase 3 trials are often larger-scale replications of Phase 2 trials, and thus potentially riskier and costlier, they have a higher completion rate than Phase 2 trials. Possible explanations include selection bias and commitment, as only the most promising trials in Phase 2 are selected for Phase 3 trials and given sufficient resources to complete the trials, since they are paramount in getting marketing approval.

	Phase 1			Phase 2			Phase 3			Phase 4		
	Completed	Failed	CR_1	Completed	Failed	CR_2	Completed	Failed	CR_3	Completed	Failed	CR_4
Oncology	3910	885	81.5%	6278	2501	71.5%	1439	706	67.1%	403	149	73.0%
Metabolic/ Endocrinology	2602	145	94.7%	1939	292	86.9%	2267	370	86.0%	1564	227	87.3%
Cardiovascular	1884	110	94.5%	1349	249	84.4%	1679	290	85.3%	1373	199	87.3%
CNS	3233	185	94.6%	2862	432	86.9%	3091	453	87.2%	2100	245	89.6%
Autoimmune/ Inflammation	2449	132	94.9%	2986	432	87.4%	2681	343	88.7%	1984	234	89.4%
Genitourinary	507	16	96.9%	419	56	88.2%	450	53	89.5%	324	43	88.3%
Infectious Disease	2424	140	94.5%	1715	268	86.5%	1698	243	87.5%	1111	220	83.5%
Ophthalmology	161	18	89.9%	424	72	85.5%	307	51	85.8%	336	45	88.2%
Vaccines (Infectious Disease)	414	37	91.8%	752	69	91.6%	850	63	93.1%	337	34	90.8%
Total	17584	1668	91.3%	18724	4371	81.1%	14462	2572	84.9%	9532	1396	87.2%

Table 7. Completion rates of industry-sponsored clinical trials (i.e. the number of trials that were tagged as completed divided by the number of trials that were initiated) by phases and therapeutic groups, using the entire data from January 1, 2000 to October 31, 2015.

Differences emerged after breaking down the completion rates of clinical trials by therapeutic group. With the exception of cancer-treating drugs, most drug development projects had a trial completion rate between 84.4% and 93.1%. Oncology trials performed much more poorly than average, with only 73.9% of all trials concluding

successfully. A closer look spotted that their lower completion rates were lower across all phases, pointing to a possible bottleneck in the development of oncology drugs.

Chapter 5 Non-Industry Sponsored Trials

The non-industry clinical research sector is an integral part of the drug R&D sector. Not only is this sector actively involved with industry in conducting trials, but academics and hospitals also conduct fundamental research that furthers understanding of basic pharmacokinetics, among other phenomena measured in clinical trials. We thus seek to quantify the performance of this sector.

5.1 Few Approved Drugs

As our database does not record non-industry approvals, we supplement our dataset with data from *Drugs@FDA*, the U.S. Food and Drug Administration's (FDA) approved drugs database. In all, 53 drug approvals for 17 unique compounds were awarded to non-industry organizations (see Table 27 in Appendix C). Of these, only three compounds were non-generic: two were awarded to the U.S. Army and the remaining compound is a PET imaging diagnostic agent. The remaining drugs are generic compounds whose patents have expired and have been awarded to hospitals and non-profits.

5.2 Completion Rates

Given the altruistic aims of organizations outside the industry and the fact that virtually no novel drugs have been granted by the FDA to these organizations, we look at only the completion rates for non-industry trials. We find that, although Phase 1 trials conducted outside the industry have lower completion rates than those within the industry, non-industry organizations outperform the latter in completing Phase 2, Phase 3 and Phase

	Phase 1			Phase 2			Phase 3			Phase 4		
	Completed	Failed	CR_1	Completed	Failed	CR_2	Completed	Failed	CR_3	Completed	Failed	CR_4
Oncology	2,327	511	82.0%	12,199	2,474	83.1%	1,379	527	72.4%	592	83	87.7%
Metabolic/ Endocrinology	323	26	92.6%	2,351	157	93.7%	1,073	134	88.9%	5,446	280	95.1%
Cardiovascular	461	32	93.5%	4,676	178	96.3%	1,340	144	90.3%	7,106	318	95.7%
CNS	564	60	90.4%	5,677	404	93.4%	2,068	257	88.9%	7,507	537	93.3%
Autoimmune/ Inflammation	431	37	92.1%	4,046	236	94.5%	1,589	105	93.8%	6,156	210	96.7%
Genitourinary	84	9	90.3%	918	45	95.3%	334	47	87.7%	1,741	126	93.3%
Infectious Disease	702	76	90.2%	2,264	220	91.1%	1,030	146	87.6%	4,887	374	92.9%
Ophthalmology	60	7	89.6%	1,238	28	97.8%	361	22	94.3%	1,642	50	97.0%
Vaccines (Infectious Disease)	335	60	84.8%	450	50	90.0%	192	15	92.8%	807	73	91.7%
Total	5,287	818	86.6%	33,819	3,792	89.9%	9,366	1397	87.0%	35,884	2,051	94.6%

Table 8. Completion rates of non-industry-sponsored trials based on data from January 1, 2000 to October 31, 2015.

4 trials (see Table 7 and Table 8).

5.3 Jointly-Sponsored Trials

The completion rates of the industry sponsored and non-industry sponsored trials suggest that each group has a relative advantage in completing different phases of clinical trials, and that there may be exploitable synergies to be gained when working together. Computing the POS of drug development projects conditioned on the status and the number of non-industry partners (Table 9) shows that drug development projects involving non-industry partners have a 5% higher chance of getting marketing approval for their drugs. These results update the findings by Danzon et al. (2005) and suggest that a possible pathway for improving success rates would be for more collaboration between industry and partners outside the industry.

Overall			
Number of non-industry partners	Advanced	Failed or Terminated	POS
0	9,631	10,250	48.4%
1	11,338	8,328	57.7%
2	3,645	2,290	61.4%
3	9,86	398	71.2%
4	3,20	106	75.1%
5	1,37	35	79.7%
6	73	7	91.3%
>6	65	17	79.3%
Joint (>0 partners)	16,564	11,181	59.7%

Table 9. Overall success rates of trials with non-industry partners, based on data from January 1, 2000 to October 31, 2015

Phase I			
Number of non-industry partners	Advanced	Failed or Terminated	POS
0	4,235	4,207	50.2%
1	2,350	1,444	61.9%
2	918	592	60.8%
3	173	100	63.4%
4	40	15	72.7%
5	9	4	69.2%
6	8	2	80.0%
>6	1	0	100.0%
Joint (>0 partners)	3,499	2,157	61.9%

Table 10. Phase I success rates of trials with non-industry partners, based on data from January 1, 2000 to October 31, 2015

Phase II			
Number of non-industry partners	Advanced	Failed or Terminated	POS
0	3,063	4,779	39.1%
1	5,314	5,953	47.2%
2	1,667	1,418	54.0%
3	459	241	65.6%
4	157	64	71.0%
5	55	22	71.4%
6	22	3	88.0%
>6	19	11	63.3%
Joint (>0 partners)	7,693	7,712	49.9%

Table 11. Phase II success rates of trials with non-industry partners, based on data from January 1, 2000 to October 31, 2015

Phase III			
Number of non-industry partners	Advanced	Failed or Terminated	POS
0	2,333	1,264	64.9%
1	3,674	931	79.8%
2	1,060	280	79.1%
3	354	57	86.1%
4	123	27	82.0%
5	73	9	89.0%
6	43	2	95.6%
>6	45	6	88.2%
Joint (>0 partners)	5,372	1,312	80.4%

Table 12. Phase III success rates of trials with non-industry partners, based on data from January 1, 2000 to October 31, 2015

Chapter 6 Duration of Trials

One principal component of the cost of conducting a trial is its expected duration. All else being equal, one would expect that a longer trial would require more man-hours of labor and supplies, resulting in a higher cost. In addition, from a financial perspective, a longer trial is exposed to more uncertainties. We quantify the distribution of the duration of trials in order to inform companies and investors of the potential risk in a project. In order to do so, we assume that there is no underlying process that induces gaps in the data. We drop trial data without date-stamps for the start or the end of the trial, as we cannot make a statement on the time spent in development for these trials. After data processing, 99,363 trials remain for our computations. Our data has a resolution of 1 calendar month.

The distribution of duration varies widely across different therapeutic groups and phases (Table 13). A typical trial takes a median time of 1.61, 2.94 and 3.84 years to complete Phase 1, Phase 2 and Phase 3 respectively. While the median durations for other therapeutic groups lie between 5.94 to 7.15 years, oncology trials take 13.11 years. This causes higher risks in oncology projects, and may explain their low approval rate. The empirical distributions and the gamma-kernelled non-parametric density estimates introduced by Malec & Schienle (2014) are plotted in Appendix D.

	Oncology	Metabolic/ Endocrinology	Cardiovascular	CNS	Autoimmune/ Inflammation	Genitourinary	Infectious Disease	Ophthalmology	Vaccines (Infectious Disease)	Overall
Phase 1	1216	325	379	334	335	378	562	546	714	586.6
Phase 2	1490	946	1025	932	980	787	951	823	827	1072.6
Phase 3	2080	976	1208	1034	979	1005	1067	1028	798	1271.8
Phase 4	1394	1036	1174	1068	1207	913	1180	935	900	1171.8

Table 13. Median duration of trials in days. The entire dataset from January 1, 2000 to October 31, 2015 that has complete date entries is used.

Taking cues from Abrantez-Metz et al. (2005), we also compute the duration of trials conditioned on their eventual status ('advanced' or 'terminated') using a 5-year rolling window (Figure 8). With our larger dataset, we found that Phase 2 trials that were terminated tend to be concluded 8.1 months earlier than Phase 2 trials that did (Table 14). Terminated Phase 3 trials, however, tend to conclude about 3.2 months after Phase 3 trials that successfully advanced. The difference within the Phase 1 group is insignificant (while we see a difference of 53 days, this is within our margin of error because the resolution for a time period is 2 calendar months or

60 days). By composing a time series using 5-year rolling windows (see Figure 8), we see that the differences (or lack thereof) remain constant over time.

	Terminated	Advanced	Difference ('Advanced' – 'Terminated')
Phase I	487	540	53.0
Phase II	823	1065	242.0
Phase III	1035	941	-94.0

Table 14. Median duration of trials conditioned on eventual status, in days

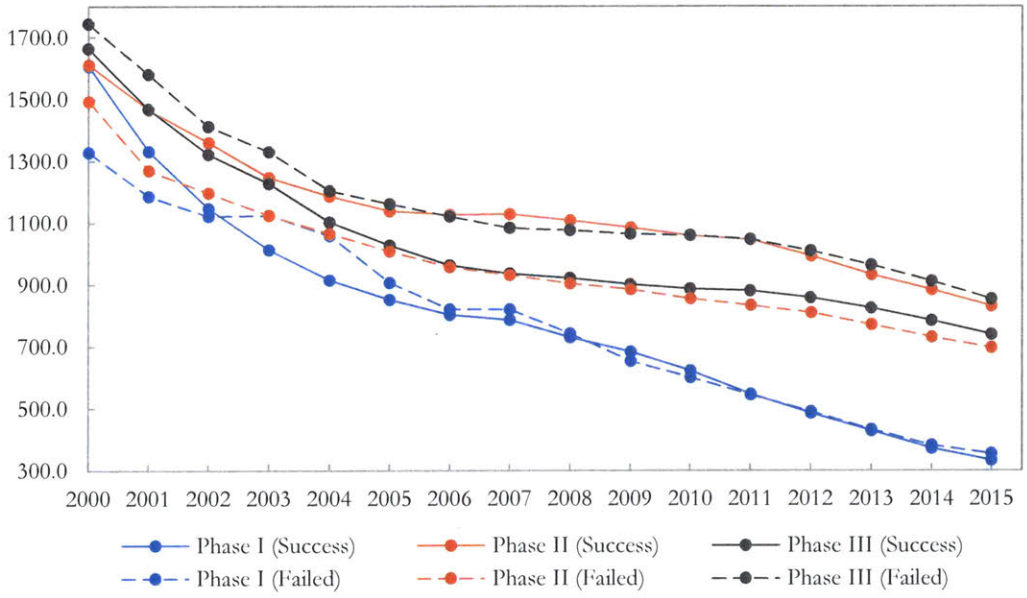


Figure 8. Plot of median duration of trials across time

Chapter 7 Robustness Check

In this paper, we attempt to use trial data to trace every drug/indication/sponsor triplet from first trial to last. While our method is arguably more accurate than earlier ones, it faces other issues such as the need to process machine-readable trial information using heuristics, and to deal with corrupted and missing data by interpolation and estimation, which may introduce errors of their own. We perform two experiments to test the robustness and stability of our algorithm across different time windows and datasets.

In our first experiment, we attempt to replicate Thomas et al. (2016) by using only data between 2006 and 2015. We find that the POS from the truncated sample differ from the full sample by less than 2.1 percentage points for all therapeutic groups. The overall POS is 0.6 percentage points lower than in the full sample. Compared to Thomas et al., we find that our Phase POS is higher in Phases 1 and 2, but lower in Phase 3. This is due to us using the path-by-path method of calculating POS. Our 13.8% overall POS is higher than their 9.6%.

In our second experiment, we run our algorithm using data tagged as originating from FDA's trial repository, clinicaltrials.gov. The computed success rates are comparable to those from our original dataset (deviations of less than 2.1 percentage points) despite having approximately 30% fewer data points. This indicates that our algorithm produces similar results even when a different dataset is used. Details of our robustness results are provided in Appendix E.

	All data	2006-2015	ClinicalTrials.gov
Oncology	3.4%	2.9%	2.6%
Metabolic/Endocrinology	19.6%	17.5%	19.2%
Cardiovascular	25.5%	23.8%	26.6%
CNS	15.0%	13.6%	15.1%
Autoimmune/Inflammation	15.1%	13.9%	14.6%
Genitourinary	21.6%	21.0%	24.4%
Infectious Disease	25.2%	25.6%	27.2%
Ophthalmology	32.6%	31.3%	34.8%
Vaccines (Infectious Disease)	33.4%	34.8%	35.5%
Overall	13.8%	13.2%	13.4%

Table 15. Robustness checks: comparison of various datasets against the entire dataset.

Chapter 8 Conclusion

Our results point to a worrisome trend in the development of oncology drugs. These projects have a depressing approval rate of 3.4%, a figure that is significantly lower than previous estimates. While it may well be the case that fighting cancer is an inherently difficult task, our research points to some possible remedies to change this trend. First, since biomarkers have shown promise of being able to increase the success rates of oncology research, we advocate their development and use in trials. Second, it may be worthwhile for pharmaceutical companies to collaborate with non-industry partners such as academia and other non-profit organizations to leverage their expertise. Our study has shown that this may increase the chances of trial success by 11.3 percentage points. Third, given that the median time to completion for oncology trials is twice as long as for non-oncology trials, it may be prudent to review the oncology drug development process frequently in order to manage the cost and risk of the project.

By providing greater risk transparency to drug developers, investors, policymakers, and patients, all stakeholders in the healthcare ecosystem will be able to make more informed decisions regarding the design and implementation of clinical trials.

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Appendices

Appendix A Success Rates over time

The following tables supplements the analysis in section 4.2. We tabulate the POSs over time for every therapeutic group.

Oncology										
Year	Phase 1			Phase 2			Phase 3			$POS_{1,APP}$
	Success	Failure	$POS_{1,2}$	Success	Failure	$POS_{2,3}$	Success	Failure	$POS_{3,APP}$	
2005	812	1297	38.5%	410	771	34.7%	155	176	46.8%	6.3%
2006	946	1410	40.2%	486	909	34.8%	144	212	40.4%	5.7%
2007	1014	1368	42.6%	496	1022	32.7%	142	241	37.1%	5.2%
2008	1005	1419	41.5%	509	1112	31.4%	142	269	34.5%	4.5%
2009	1026	1640	38.5%	490	1237	28.4%	145	270	34.9%	3.8%
2010	1083	1942	35.8%	511	1369	27.2%	139	291	32.3%	3.1%
2011	1098	2344	31.9%	488	1516	24.4%	120	251	32.3%	2.5%
2012	1091	2739	28.5%	481	1752	21.5%	116	298	28.0%	1.7%
2013	1067	2830	27.4%	449	1843	19.6%	131	248	34.6%	1.9%
2014	1006	2727	26.9%	423	1505	21.9%	139	193	41.9%	2.5%
2015	862	1733	33.2%	399	843	32.1%	118	33	78.1%	8.3%

Table 16. POS for oncology trials between the years of 2005 and 2015, computed using a rolling window of 3 years.

Metabolic/ Endocrinology										
Year	Phase 1			Phase 2			Phase 3			$POS_{1,APP}$
	Success	Failure	$POS_{1,2}$	Success	Failure	$POS_{2,3}$	Success	Failure	$POS_{3,APP}$	
2005	154	65	70.3%	206	167	55.2%	142	168	45.8%	17.8%
2006	204	85	70.6%	207	208	49.9%	164	168	49.4%	17.4%
2007	231	146	61.3%	180	233	43.6%	179	187	48.9%	13.1%
2008	257	216	54.3%	183	283	39.3%	171	219	43.8%	9.4%
2009	241	262	47.9%	171	305	35.9%	159	227	41.2%	7.1%
2010	270	324	45.5%	178	365	32.8%	171	208	45.1%	6.7%
2011	266	332	44.5%	173	363	32.3%	172	188	47.8%	6.9%
2012	275	339	44.8%	173	358	32.6%	179	181	49.7%	7.3%
2013	240	346	41.0%	144	298	32.6%	177	136	56.5%	7.5%
2014	213	306	41.0%	134	223	37.5%	208	92	69.3%	10.7%
2015	193	201	49.0%	105	115	47.7%	179	13	93.2%	21.8%

Table 17. POS for metabolic/ endocrinology trials between the years of 2005 and 2015, computed using a rolling window of 3 years.

Cardiovascular										
Year	Phase 1			Phase 2			Phase 3			$POS_{1,APP}$
	Success	Failure	$POS_{1,2}$	Success	Failure	$POS_{2,3}$	Success	Failure	$POS_{3,APP}$	
2005	113	87	56.5%	147	129	53.3%	168	93	64.4%	19.4%
2006	143	105	57.7%	151	139	52.1%	167	116	59.0%	17.7%
2007	171	148	53.6%	145	157	48.0%	170	143	54.3%	14.0%
2008	191	173	52.5%	129	180	41.7%	188	146	56.3%	12.3%
2009	199	208	48.9%	124	188	39.7%	178	145	55.1%	10.7%
2010	192	222	46.4%	131	229	36.4%	187	130	59.0%	10.0%
2011	198	251	44.1%	139	244	36.3%	151	139	52.1%	8.3%
2012	178	257	40.9%	129	236	35.3%	166	138	54.6%	7.9%
2013	163	292	35.8%	120	195	38.1%	152	106	58.9%	8.0%
2014	140	266	34.5%	93	125	42.7%	191	65	74.6%	11.0%
2015	122	174	41.2%	88	63	58.3%	189	10	95.0%	22.8%

Table 18. POS for cardiovascular trials between the years of 2005 and 2015, computed using a rolling window of 3 years.

CNS										
Year	Phase 1			Phase 2			Phase 3			$POS_{1,APP}$
	Success	Failure	$POS_{1,2}$	Success	Failure	$POS_{2,3}$	Success	Failure	$POS_{3,APP}$	
2005	191	107	64.1%	245	269	47.7%	170	164	50.9%	15.5%
2006	235	146	61.7%	269	331	44.8%	194	177	52.3%	14.5%
2007	252	208	54.8%	254	363	41.2%	222	222	50.0%	11.3%
2008	282	286	49.6%	233	439	34.7%	218	241	47.5%	8.2%
2009	344	439	43.9%	211	451	31.9%	228	249	47.8%	6.7%
2010	400	537	42.7%	215	480	30.9%	225	236	48.8%	6.4%
2011	385	579	39.9%	206	468	30.6%	217	225	49.1%	6.0%
2012	345	546	38.7%	186	456	29.0%	219	207	51.4%	5.8%
2013	307	498	38.1%	177	455	28.0%	225	175	56.3%	6.0%
2014	293	439	40.0%	184	362	33.7%	207	108	65.7%	8.9%
2015	238	281	45.9%	146	228	39.0%	178	18	90.8%	16.3%

Table 19. POS for central nervous system (CNS) trials between the years of 2005 and 2015, computed using a rolling window of 3 years.

Autoimmune/ Inflammation										
Year	Phase 1			Phase 2			Phase 3			$POS_{1,APP}$
	Success	Failure	$POS_{1,2}$	Success	Failure	$POS_{2,3}$	Success	Failure	$POS_{3,APP}$	
2005	208	169	55.2%	188	350	34.9%	198	104	65.6%	12.6%
2006	246	193	56.0%	191	388	33.0%	200	117	63.1%	11.7%
2007	267	233	53.4%	177	400	30.7%	206	118	63.6%	10.4%
2008	296	274	51.9%	166	444	27.2%	213	126	62.8%	8.9%
2009	301	362	45.4%	186	471	28.3%	227	147	60.7%	7.8%
2010	310	487	38.9%	183	500	26.8%	227	159	58.8%	6.1%
2011	316	544	36.7%	184	490	27.3%	202	150	57.4%	5.8%
2012	299	612	32.8%	191	489	28.1%	211	156	57.5%	5.3%
2013	292	600	32.7%	186	466	28.5%	201	121	62.4%	5.8%
2014	289	580	33.3%	172	387	30.8%	189	76	71.3%	7.3%
2015	250	354	41.4%	142	212	40.1%	158	19	89.3%	14.8%

Table 20. POS for autoimmune/ inflammation trials between the years of 2005 and 2015, computed using a rolling window of 3 years.

Genitourinary										
Year	Phase 1			Phase 2			Phase 3			$POS_{1,APP}$
	Success	Failure	$POS_{1,2}$	Success	Failure	$POS_{2,3}$	Success	Failure	$POS_{3,APP}$	
2005	25	26	49.0%	34	35	49.3%	32	11	74.4%	18.0%
2006	30	41	42.3%	39	48	44.8%	51	18	73.9%	14.0%
2007	46	67	40.7%	35	52	40.2%	53	25	67.9%	11.1%
2008	46	89	34.1%	36	68	34.6%	59	33	64.1%	7.6%
2009	56	86	39.4%	32	73	30.5%	60	26	69.8%	8.4%
2010	45	78	36.6%	31	81	27.7%	63	26	70.8%	7.2%
2011	47	77	37.9%	23	67	25.6%	57	26	68.7%	6.7%
2012	40	77	34.2%	21	55	27.6%	51	30	63.0%	5.9%
2013	37	68	35.2%	25	43	36.8%	41	24	63.1%	8.2%
2014	27	68	28.4%	22	44	33.3%	35	13	72.9%	6.9%
2015	31	47	39.7%	18	34	34.6%	33	3	91.7%	12.6%

Table 21. POS for genitourinary trials between the years of 2005 and 2015, computed using a rolling window of 3 years.

Infectious Disease										
Year	Phase 1			Phase 2			Phase 3			$POS_{1,APP}$
	Success	Failure	$POS_{1,2}$	Success	Failure	$POS_{2,3}$	Success	Failure	$POS_{3,APP}$	
2005	134	124	51.9%	170	191	47.1%	159	97	62.1%	15.2%
2006	170	137	55.4%	170	195	46.6%	201	110	64.6%	16.7%
2007	212	166	56.1%	189	215	46.8%	252	88	74.1%	19.4%
2008	234	185	55.8%	188	249	43.0%	291	96	75.2%	18.1%
2009	253	284	47.1%	194	309	38.6%	347	115	75.1%	13.6%
2010	239	355	40.2%	185	352	34.5%	343	109	75.9%	10.5%
2011	258	454	36.2%	197	349	36.1%	332	81	80.4%	10.5%
2012	287	497	36.6%	187	368	33.7%	299	83	78.3%	9.7%
2013	314	475	39.8%	154	344	30.9%	283	68	80.6%	9.9%
2014	326	472	40.9%	140	265	34.6%	276	42	86.8%	12.3%
2015	282	312	47.5%	113	153	42.5%	230	7	97.0%	19.6%

Table 22. POS for infectious disease trials between the years of 2005 and 2015, computed using a rolling window of 3 years.

Ophthalmology										
Year	Phase 1			Phase 2			Phase 3			$POS_{1,APP}$
	Success	Failure	$POS_{1,2}$	Success	Failure	$POS_{2,3}$	Success	Failure	$POS_{3,APP}$	
2005	7	5	58.3%	21	25	45.7%	28	13	68.3%	18.2%
2006	13	8	61.9%	28	30	48.3%	37	16	69.8%	20.9%
2007	20	16	55.6%	31	29	51.7%	33	17	66.0%	18.9%
2008	26	27	49.1%	35	39	47.3%	29	25	53.7%	12.5%
2009	31	36	46.3%	36	53	40.4%	38	23	62.3%	11.7%
2010	32	28	53.3%	42	69	37.8%	48	31	60.8%	12.3%
2011	29	21	58.0%	45	82	35.4%	49	28	63.6%	13.1%
2012	36	22	62.1%	46	78	37.1%	41	26	61.2%	14.1%
2013	40	34	54.1%	43	68	38.7%	44	11	80.0%	16.8%
2014	38	32	54.3%	41	53	43.6%	75	3	96.2%	22.8%
2015	26	21	55.3%	33	28	54.1%	76	1	98.7%	29.5%

Table 23. POS for ophthalmology trials between the years of 2005 and 2015, computed using a rolling window of 3 years.

Vaccines (Infectious Disease)										
Year	Phase 1			Phase 2			Phase 3			POS
	Success	Failure	$POS_{1,2}$	Success	Failure	$POS_{2,3}$	Success	Failure	$POS_{3,APP}$	
2005	23	58	28.4%	71	89	44.4%	80	30	72.7%	9.2%
2006	43	63	40.6%	85	88	49.1%	116	38	75.3%	15.0%
2007	69	73	48.6%	116	107	52.0%	172	31	84.7%	21.4%
2008	90	91	49.7%	111	134	45.3%	217	34	86.5%	19.5%
2009	106	114	48.2%	106	180	37.1%	239	31	88.5%	15.8%
2010	93	116	44.5%	103	216	32.3%	248	32	88.6%	12.7%
2011	95	120	44.2%	111	210	34.6%	236	30	88.7%	13.6%
2012	100	145	40.8%	99	205	32.6%	239	31	88.5%	11.8%
2013	97	172	36.1%	72	190	27.5%	203	29	87.5%	8.7%
2014	98	171	36.4%	63	148	29.9%	187	17	91.7%	10.0%
2015	78	110	41.5%	44	92	32.4%	157	2	98.7%	13.3%

Table 24. POS for vaccines (infectious disease) trials between the years of 2005 and 2015, computed using a rolling window of 3 years.

Appendix B Comparison of result for biomarker trials against other papers

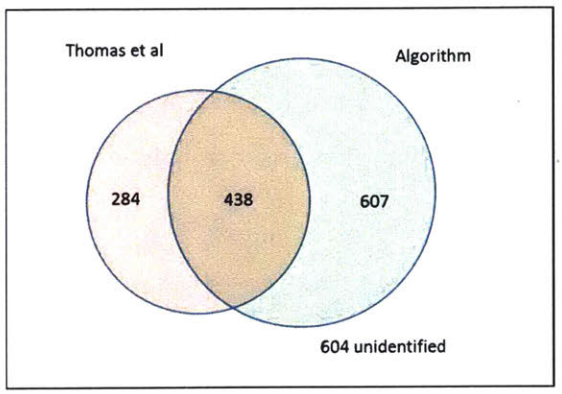
Our result for trials using biomarkers is very different from extant papers such as Thomas et al. (2016). As the authors of the Thomas et al. (2016) has kindly shared their analysis, we were able to compare and contrast the methodologies and results.

The main differences between the two analyses are how phase transitions are identified, which filters are applied, and how much data was involved (see Table 25).

	Thomas et al. (2016)	**This paper**
Identification of phase transitions	From BioMedTracker database	Using Algorithm 1 in Figure 4
What constitutes a biomarker trial?	Considered only biomarkers in patient selection	Considered a trial to involve biomarkers if it includes an objective of evaluating or identifying the use of any novel biomarkers as indicators of therapeutic efficacy or toxicity, or to use biomarkers in the selection of patients includes an objective of evaluating or identifying the use of any novel biomarkers as indicators of therapeutic efficacy or toxicity, or to use biomarkers in the selection of patients
Data source	Merges BioMedTracker with Amplion's BiomarkerBase. Only trials from clinicaltrials.gov were used as NCT numbers were used as trial identifiers. Analysis consists of 512 phase transitions.	Uses trials tagged as 'involve biomarker' by Informa. Both clinicaltrials.gov and private information were used, summing up to 10,650 phase transitions.

Table 25. Differences between the biomarker study in Thomas et al. (2017) and this paper.

The authors provided a sample of 1,593 trial entries for comparison. Of these 722 entries are used in their analysis. We merged our algorithm output with this subset of trials to produce tag outcomes for 1,065 of the 1,953 entries. Only 438 data-points exist in both analyses. Our algorithm is unable to produce outcomes for some trials that Thomas et al. did because insufficient period has passed since the conclusion of the trial. This relates to the t_1, t_2 and t_3 parameters in the algorithm.



Of the 438 overlapping data points, our algorithm arrived at the same conclusion as Thomas et al. for 90.0% of the data, showing that our algorithm identifies phase transitions accurately.

We compared our result using this dataset of 1,065 identified data entries against Thomas et al.'s result in Table 26. We see that our algorithm tends to identify more failures compared to Thomas et al., and this may be due to our method of counting a trial that is in limbo for an extended period of time as "terminated".

	Phase I		**Phase II**		**Phase III**	
	Advanced	Terminated	Advanced	Terminated	Advanced	Terminated
Thomas et al. (2016)	57	34	102	100	92	31
Our algorithm	37	23	172	170	164	102

Table 26. Comparison of identified phase transitions

Given these checks, we conclude that our results differ from Thomas et al. (2016) mainly due to the use of Algorithm 1 to process more trial data to produce POS estimates.

Generic?	SponsorName	ApplNo	drugname
No	BIOMEDCL RES FDN	204352	AMMONIA N 13
No	BIOMEDCL RES FDN	203710	FLUDEOXYGLUCOSE F18
Yes	BIOMEDCL RES FDN	204351	SODIUM FLUORIDE F-18
No	BRIGHAM WOMENS	203816	FLUDEOXYGLUCOSE F18
No	BRIGHAM WOMENS HOSP	203783	AMMONIA N 13
No	CHILDRENS HOSP MI	204385	FLUDEOXYGLUCOSE F18
No	FEINSTEIN	22119	AMMONIA N 13
No	FEINSTEIN	21870	FLUDEOXYGLUCOSE F18
No	FEINSTEIN	21870	FLUDEOXYGLUCOSE F18
No	HEALTHPOINT	84698	NUTRACORT
No	HOUSTON CYCLOTRON	203543	AMMONIA N 13
No	HOUSTON CYCLOTRON	203665	FLUDEOXYGLUCOSE F18
Yes	HOUSTON CYCLOTRON	203544	SODIUM FLUORIDE F-18
No	JOHNS HOPKINS UNIV	204514	AMMONIA N 13
No	KETTERING MEDCTR	204759	FLUDEOXYGLUCOSE F18
No	KREITCHMAN PET CTR	203938	AMMONIA N 13
No	KREITCHMAN PET CTR	203942	FLUDEOXYGLUCOSE F18
Yes	KREITCHMAN PET CTR	203936	SODIUM FLUORIDE F-18
No	MA GENERAL HOSP	207025	AMMONIA N 13
No	MA GENERAL HOSP	204333	FLUDEOXYGLUCOSE F18
No	METHODIST HOSP RES	203904	FLUDEOXYGLUCOSE F18
No	NIH NCI DCTD	22494	SODIUM FLUORIDE F 18
No	POPULATION COUNCIL	20544	JADELLE
No	POPULATION COUNCIL	19897	NORPLANT
No	QUEEN HAMAMATSU PET	203771	FLUDEOXYGLUCOSE F18
Yes	THE FEINSTEIN INST	204328	SODIUM FLUORIDE F-18
No	TRUSTEES UNIV PA	203801	FLUDEOXYGLUCOSE F18
No	UCLA BIOMEDICAL	203812	AMMONIA N 13
No	UCLA BIOMEDICAL	203811	FLUDEOXYGLUCOSE F18
No	UIHC PET IMAGING	203990	FLUDEOXYGLUCOSE F18
Yes	UIHC PET IMAGING	204462	SODIUM FLUORIDE F-18
No	UNIV AZ CANCER CTR	19940	ACTINEX
No	UNIV MICHIGAN	204531	FLUDEOXYGLUCOSE F18
No	UNIV NORTH DAKOTA	203994	FLUDEOXYGLUCOSE F18
No	UNIV TX MD ANDERSON	203933	AMMONIA N 13
No	UNIV TX MD ANDERSON	205690	CHOLINE C-11
No	UNIV TX MD ANDERSON	203246	FLUDEOXYGLUCOSE F18
Yes	UNIV TX MD ANDERSON	203247	SODIUM FLUORIDE F-18
No	UNIV UTAH CYCLOTRON	204498	FLUDEOXYGLUCOSE F18
Yes	UNIV UTAH CYCLOTRON	204497	SODIUM FLUORIDE F-18
No	US ARMY	21175	ATNAA
Yes	US ARMY	20056	ATROPINE SULFATE
No	US ARMY	20124	DIAZEPAM
Yes	US ARMY	20414	PYRIDOSTIGMINE BROMIDE
			SKIN EXPOSURE REDUCTION PASTE AGAINST
No	US ARMY	21084	CHEMICAL WARFARE AGENTS
No	US ARMY	20166	SODIUM THIOSULFATE
No	US ARMY WALTER REED	19578	MEFLOQUINE HYDROCHLORIDE
No	UT SW MEDCTR	19647	POTASSIUM CITRATE
No	WA UNIV SCH MED	204506	AMMONIA N 13
No	WEILL MEDCL COLL	21768	FLUDEOXYGLUCOSE F18
No	WI MEDCL CYCLOTRON	204356	AMMONIA N 13
No	WI MEDCL CYCLOTRON	203709	FLUDEOXYGLUCOSE F18
No	WUSM CYCLOTRON	203935	FLUDEOXYGLUCOSE F18
No	BIOMEDCL RES FDN	203837	FLUDEOXYGLUCOSE F18
No	UNIV TX MD ANDERSON	203246	FLUDEOXYGLUCOSE F18
No	UT SW MEDCTR	19647	POTASSIUM CITRATE

Table 27. Table of Approved Drugs to non-industry organizations, extracted from *Drugs@FDA*

Appendix D Distribution of Duration

In this section, we document the distribution of duration conditioned on the indication group and phase in order to inform interested readers.

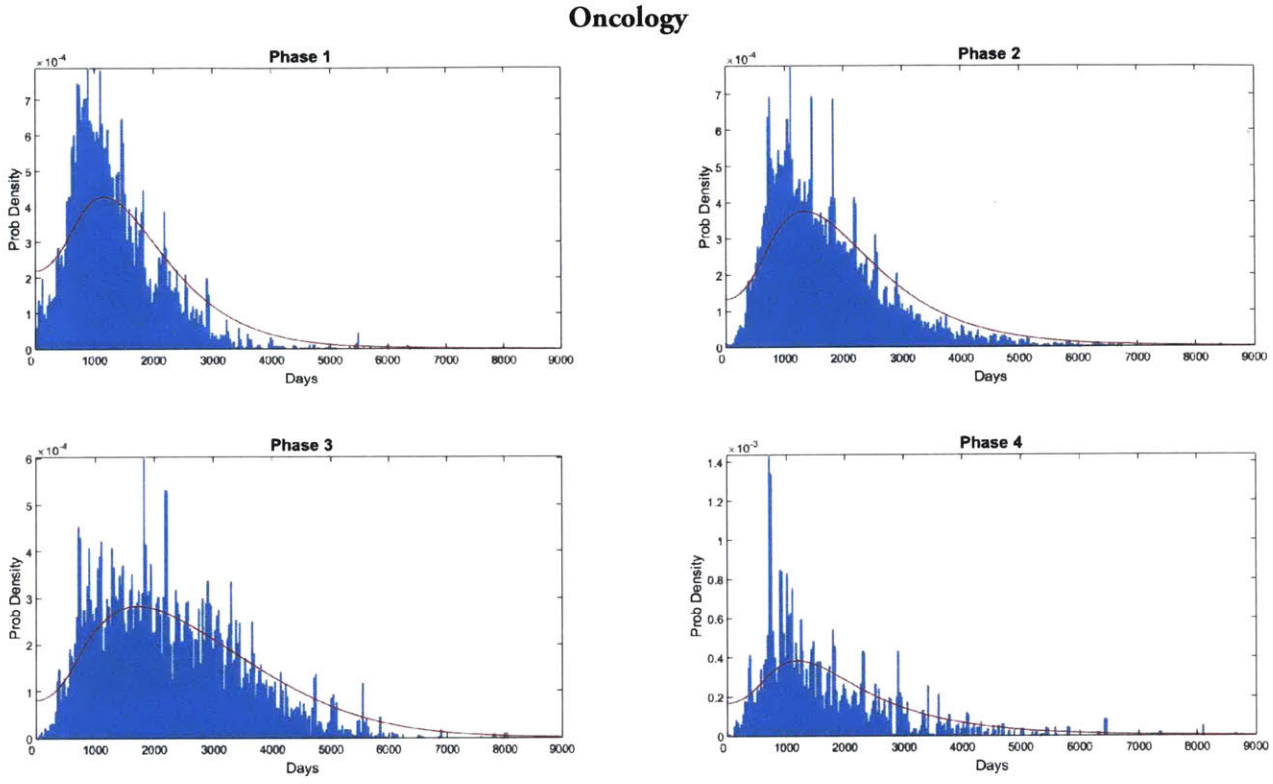


Figure 9. Distribution of duration for oncology trials conditioned on the phase.

Metabolic/Endocrinology

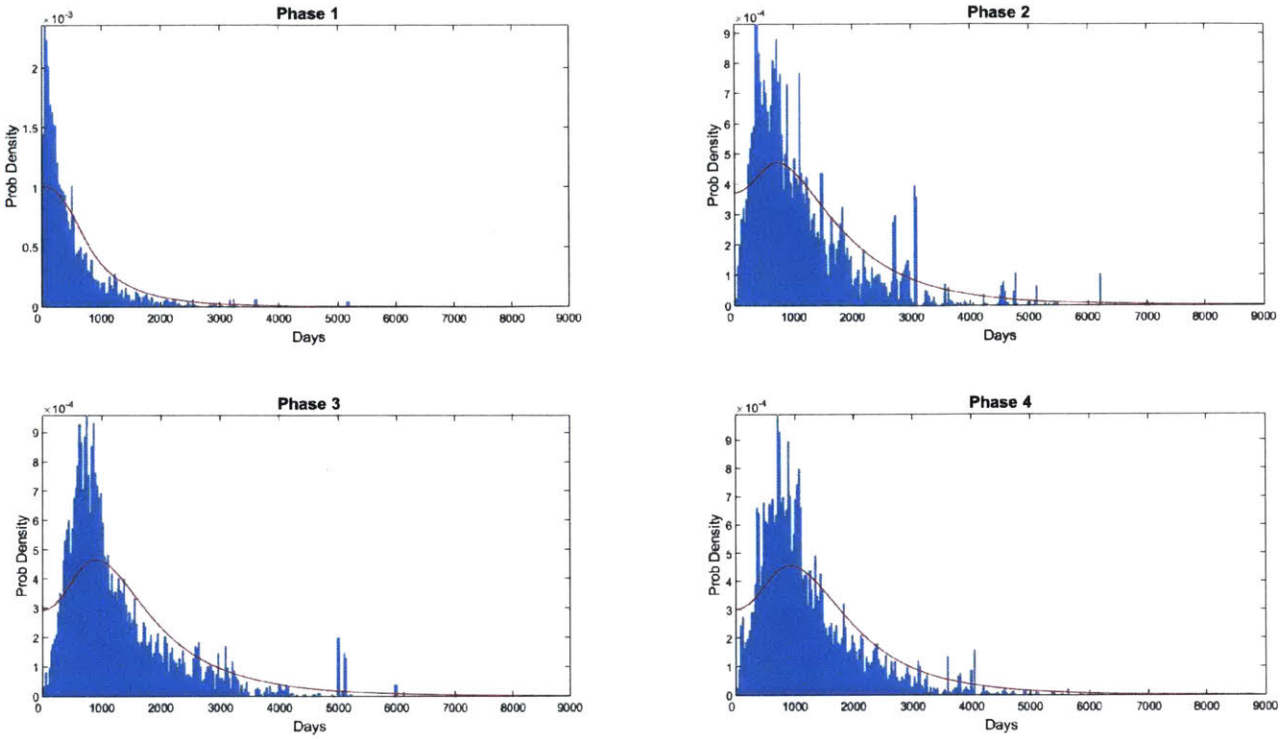


Figure 10. Distribution of duration for metabolic/endocrinology trials conditioned on the phase.

Cardiovascular

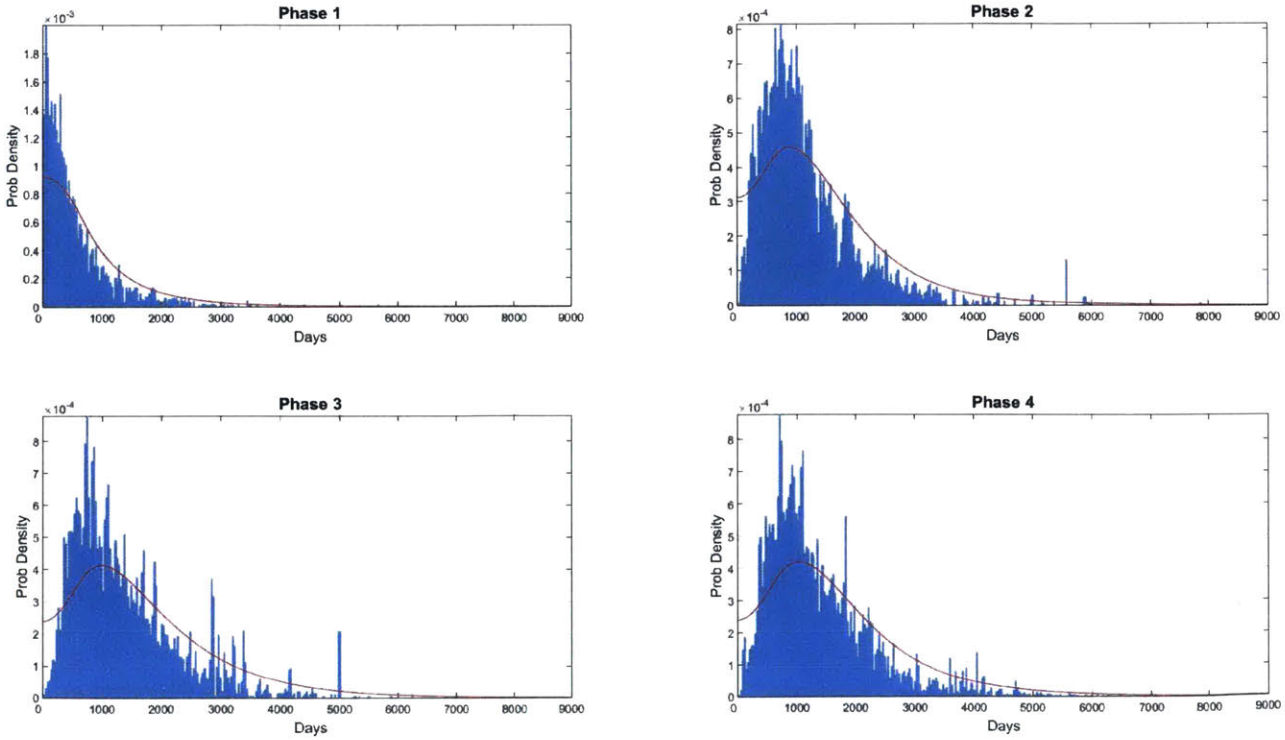


Figure 11. Distribution of duration for cardiovascular trials conditioned on the phase.

CNS

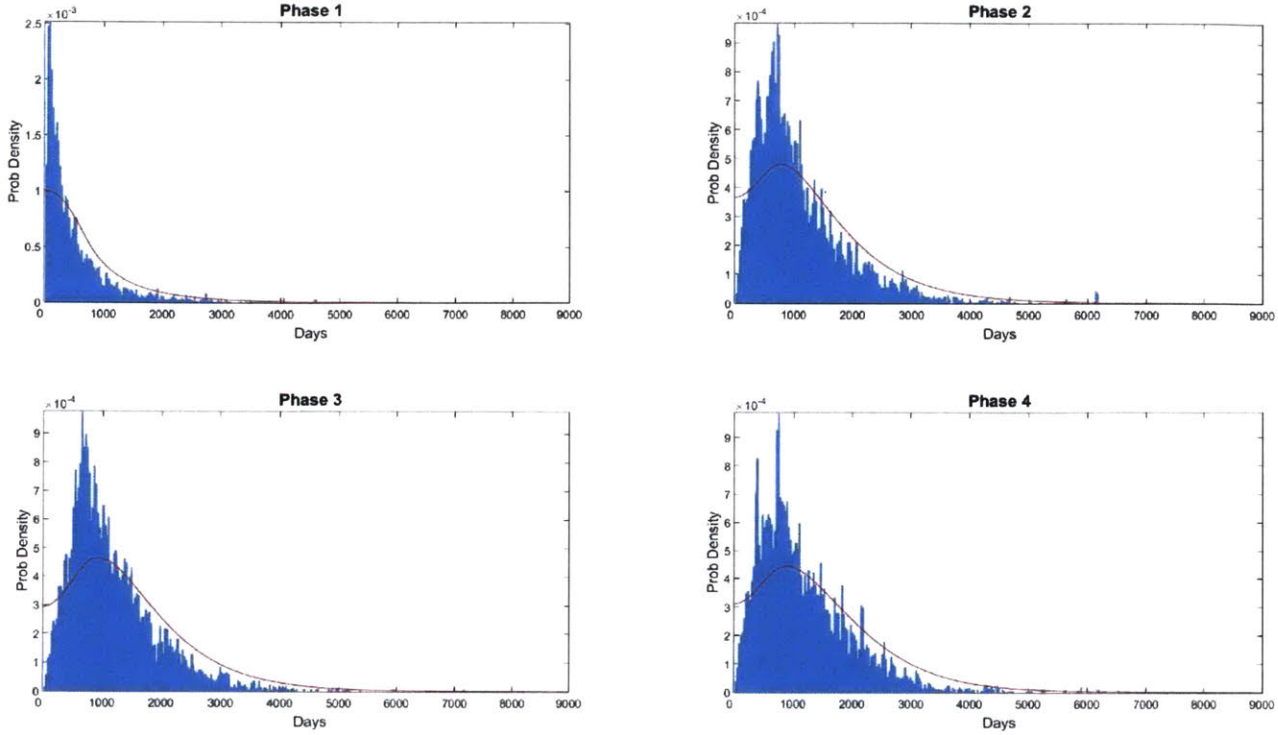


Figure 12. Distribution of duration for CNS trials conditioned on the phase.

Autoimmune/Inflammation

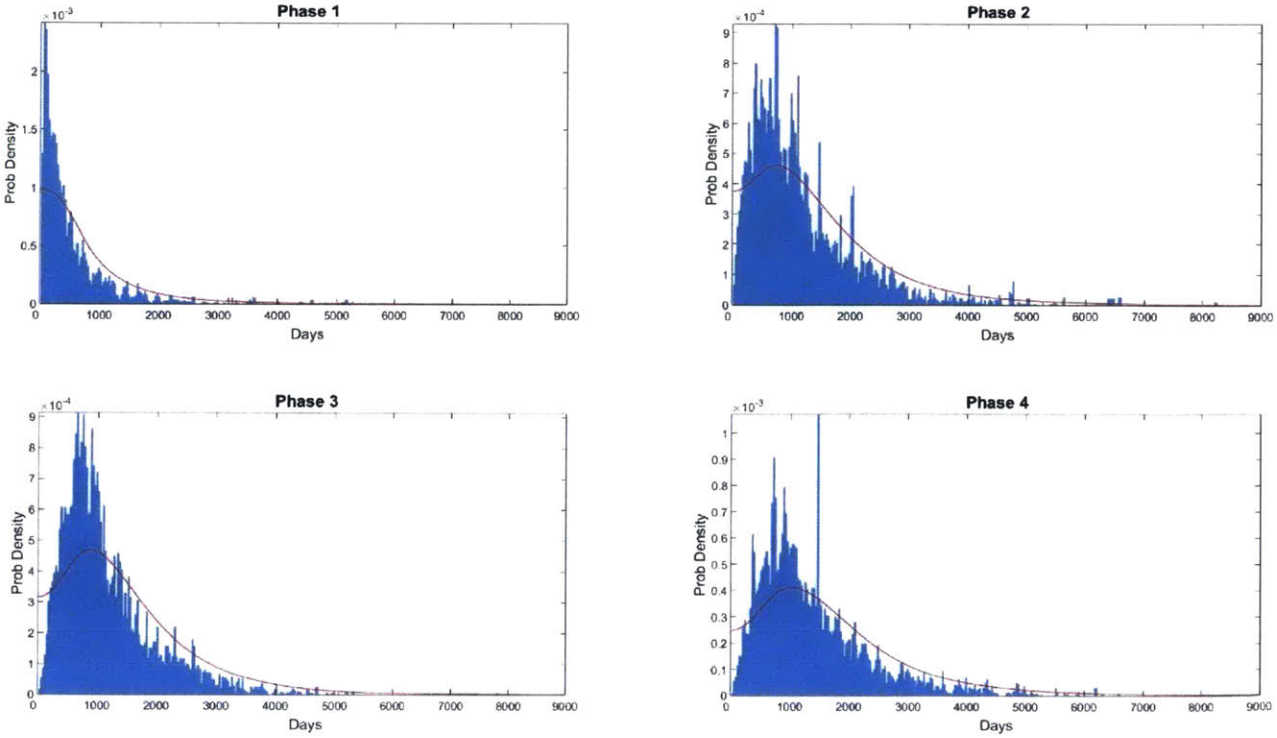


Figure 13. Distribution of duration for autoimmune/inflammation trials conditioned on the phase.

Genitourinary

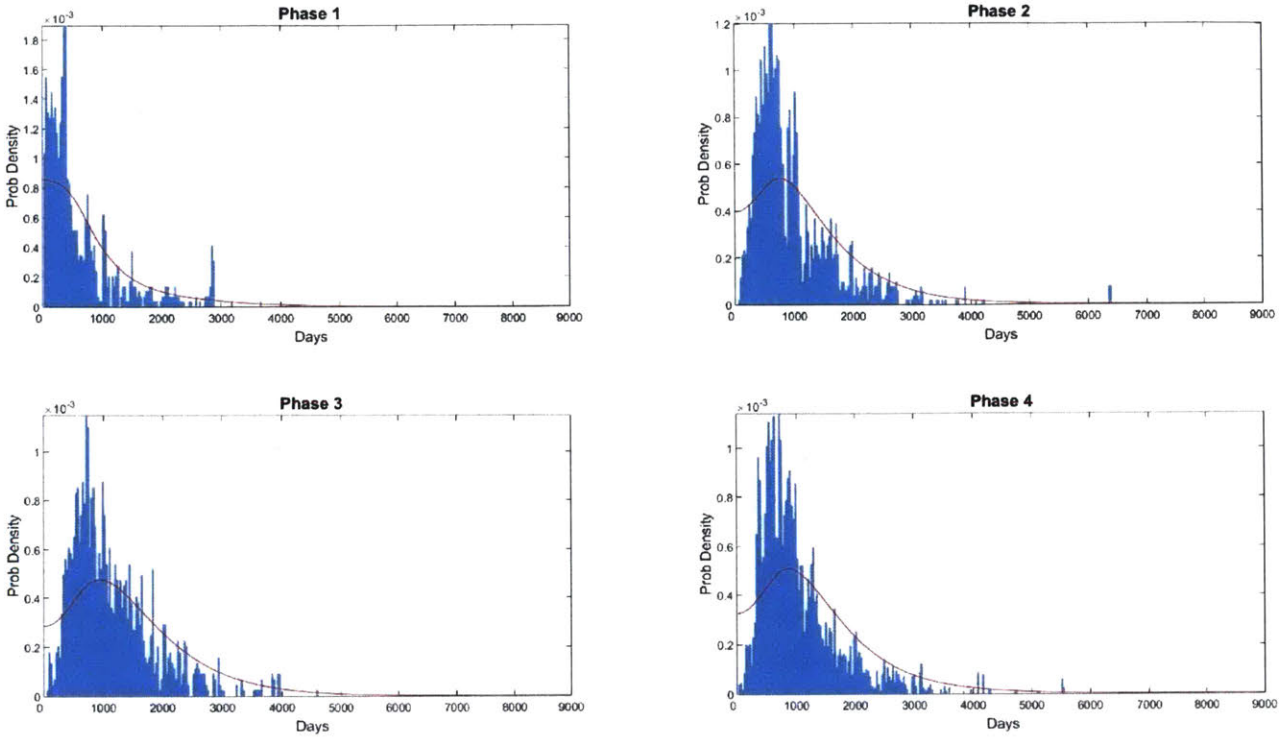


Figure 14. Distribution of duration for genitourinary trials conditioned on the phase.

Infectious Disease

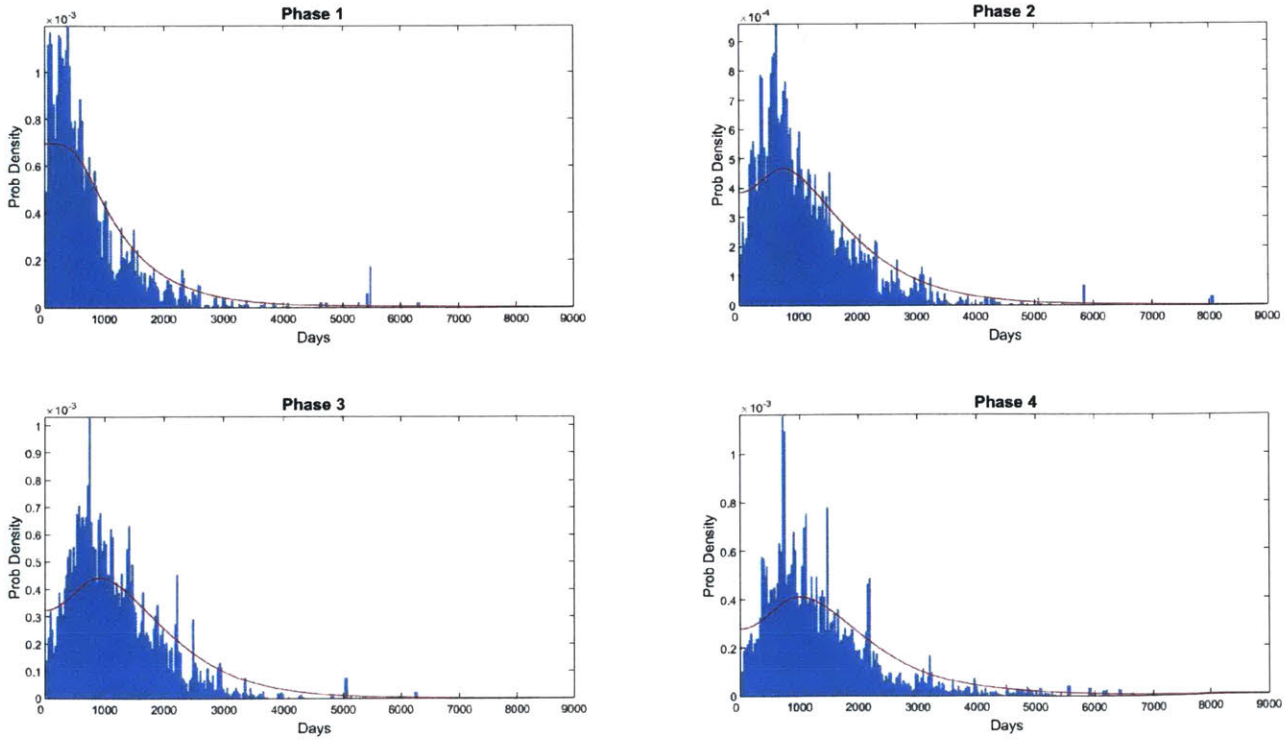


Figure 15. Distribution of duration for infectious disease trials conditioned on the phase.

Ophthalmology

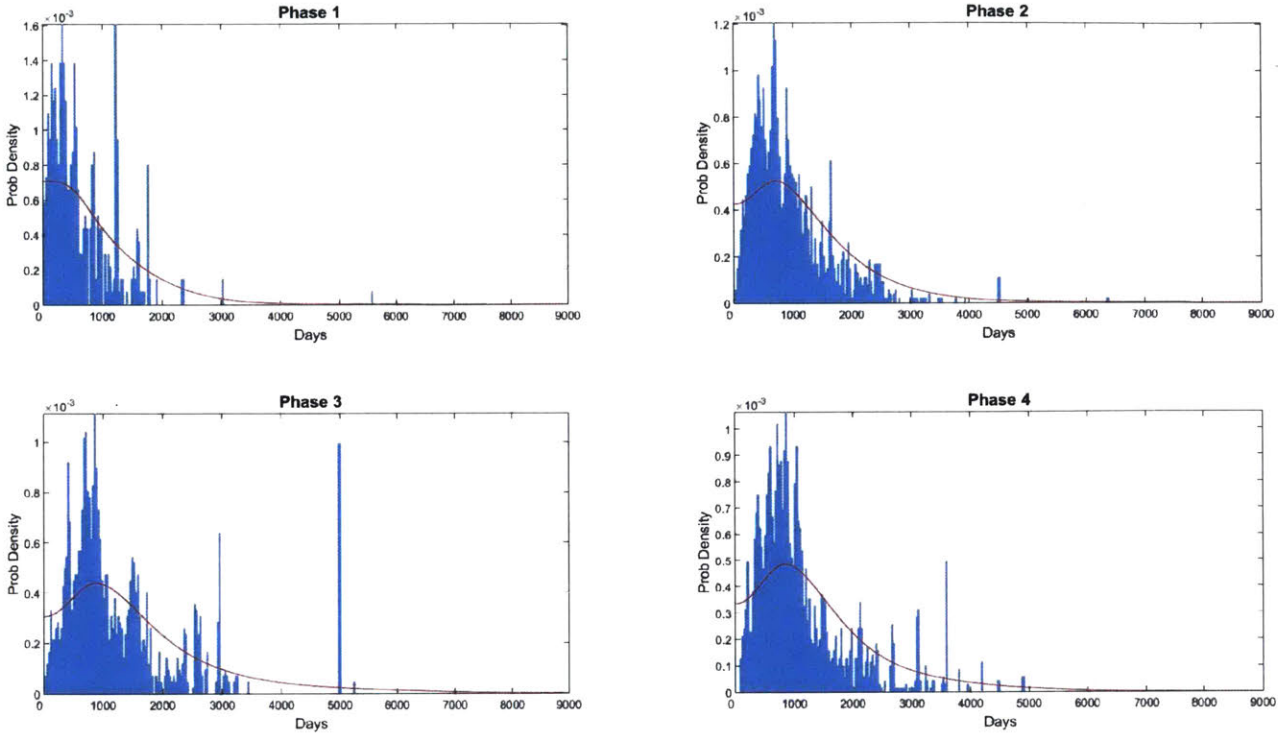


Figure 16. Distribution of duration for ophthalmology trials conditioned on the phase.

Vaccines (Infectious Disease)

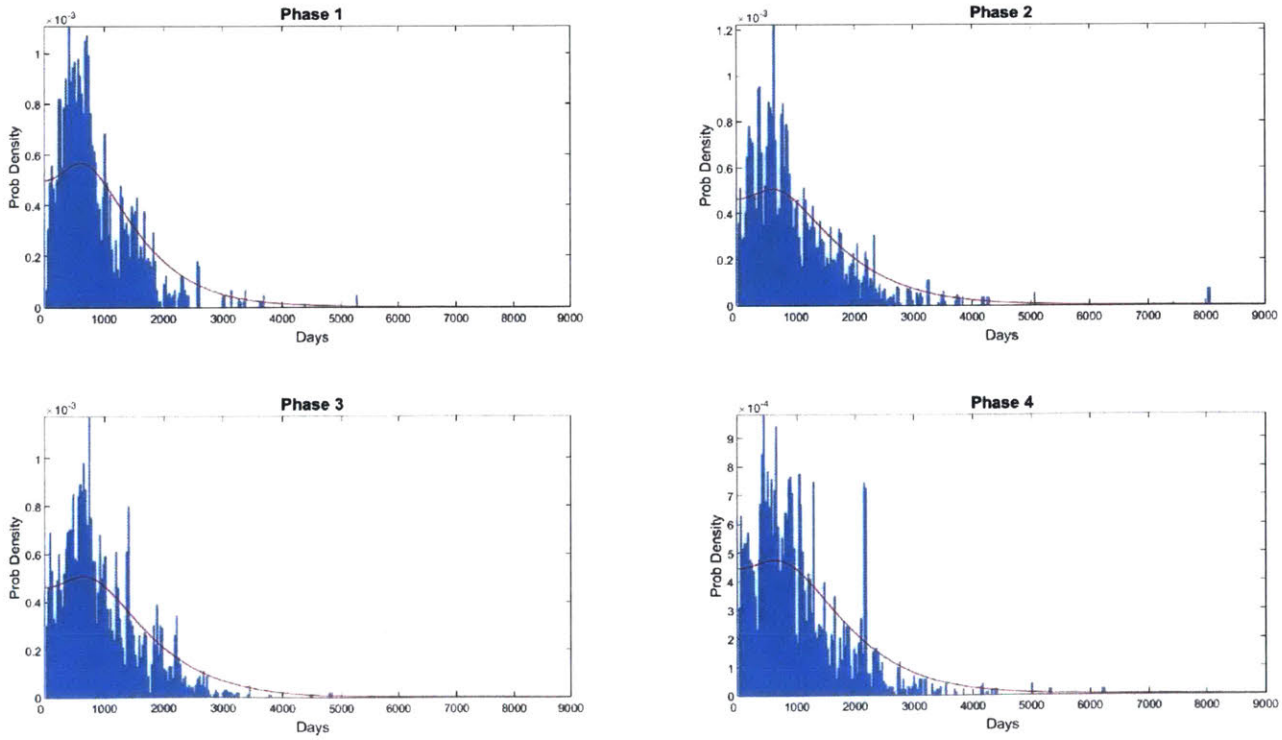


Figure 17. Distribution of duration for vaccines (infectious disease) trials conditioned on the phase.

Appendix E Detailed results of robustness checks

This table supplements the Table 15 in Chapter 7.

Trials occurring between 2006 - 2015								
	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic Groups	**Total Paths**	**$POS_{1,2}$,%**	**Total Paths**	**$POS_{2,3}$,%**	**$POS_{2,APP}$,%**	**Total Paths**	**$POS_{3,APP}$,%**	**POS,%**
Oncology	15,192	59.8	5,616	23.1	33.2	943	33.1	2.9
Metabolic/ Endocrinology	3,173	74.7	1,989	58.4	58.9	859	50.6	17.5
Cardiovascular	2,400	72.8	1,543	72.1	66.6	764	60.3	23.8
CNS	4,345	71.9	2,552	47.5	53.1	920	49.3	13.6
Autoimmune/ Inflammation	4,381	69.0	2,378	42.3	47.8	763	61.3	13.9
Genitourinary	686	67.9	421	55.2	59.1	189	64.6	21.0
Infectious Disease	3,553	69.4	1,996	46.0	60.4	929	77.3	25.6
Ophthalmology	630	86.0	416	61.5	61.5	183	73.8	31.3
Vaccines (Infectious Disease)	1,700	76.7	1,103	42.4	60.0	552	87.5	34.8
Overall	36,060	66.9	18,014	38.0	49.6	6,102	58.8	13.2
Trials originating from ClinicalTrials.gov only								
	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		
Therapeutic Groups	**Total Paths**	**$POS_{1,2}$,%**	**Total Paths**	**$POS_{2,3}$,%**	**$POS_{2,APP}$,%**	**Total Paths**	**$POS_{3,APP}$,%**	**POS,%**
Oncology	13,437	61.2	5,128	32.3	4.9	888	28.3	2.6
Metabolic/ Endocrinology	2,417	81.3	1,651	61.1	21.4	747	47.4	19.2
Cardiovascular	1,831	81.0	1,310	69.0	29.1	679	56.1	26.6
CNS	3,076	79.5	2,012	54.0	17.4	763	45.9	15.1
Autoimmune/ Inflammation	3,114	74.5	1,781	50.2	18.6	597	55.6	14.6
Genitourinary	477	74.4	320	60.0	30.0	144	66.7	24.4
Infectious Disease	2,805	72.8	1,651	61.8	36.0	790	75.2	27.2
Ophthalmology	514	90.1	358	62.0	34.1	164	74.4	34.8
Vaccines (Infectious Disease)	1,371	77.8	887	60.2	44.4	453	87.0	35.5
Overall	29,042	70.1	15,098	49.8	19.0	5,225	55.0	13.4

Figure 18. The probability of success by therapeutic groups, using truncated datasets. The top half shows the results of using only trials between Jan 1st, 2006 and Oct 31st, 2015. The bottom half shows the results of using only trials tagged as originating from clinicaltrials.gov.