

Clinical Trials, the Market for Observations, and the Cost of Medical R&D

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Abstract

A major cost of drug R&D is the delay in patient access to new treatments. Part of this delay is due to FDA regulations. Although economists have analyzed the time it takes for the FDA to approve new drug applications, the majority of R&D time and expenditures is devoted to clinical testing that is required before a new drug application can be filed. Yet there is little economic analysis of what determines the length and costs of clinical trials.

This paper fills the gap with a positive theory of clinical trials that stresses two features of these studies. First, they involve costly search – patients looking for trials and trials looking for patients – in a larger market for clinical data. Unlike other markets, however, bioethical rules impose wage regulations that prevent the market for trial subjects from clearing. Second, medical R&D has the unique feature that the input supply market (subjects) and the output demand (patients) market coincide. We derive the implications of these features for the length and costs of trials. An important finding is that R&D by one drug company slows down R&D of other companies because it makes it more difficult to recruit patients into trials.

We find empirical support for our predictions using data from *clinicaltrials.gov*, the largest registry of cancer trials available. We find that an increase in the number of trials have slowed down clinical trials and largely offset potential gains in the duration of trials due to improved internet technology for matching patients to trials and reductions in the size of individual trials. In particular, we find that accelerated innovation has increased the time it takes to recruit a subject by 400 percent.

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1 Introduction

Improvements in health have been a major component in the overall gain in economic welfare during the last century (Murphy & Topel 2006). Much of the gains are due to medical research and development (R&D), including drugs. There is growing evidence, however, of diminishing returns to drug R&D. For example, while the amount spent on drug R&D has doubled since 1993, the number of drugs for which the pharmaceutical industry has sought or obtained marketing approval has remained flat (GAO 2006).²

In order to market a drug, a drug company must conduct clinical trials to demonstrate a drug is safe and effective. The cost of these trials is a major factor in the slowdown in the productivity of drug R&D. Historically, clinical testing has accounted for about one-third of the costs of drug development. But studies such as DiMasi et al. (2003) suggest that it now accounts for over one-half (\$467 of \$802 million) of development costs. One-half of the costs of clinical testing, in turn, can be attributed to the time it takes to complete clinical trials. The average duration of phase II and phase III trials – the trials which focus on the target population for a drug – is 25.7 and 30.5 months, respectively. These trials account for nearly 80% of the average 72.1 months it takes to complete clinical testing (DiMasi et al. 2003, Adams & Brantner 2006).

Indeed, the time it takes to conduct Phase II and III clinical trials dwarfs the average 18.2 months it takes for the Food and Drug Administration (FDA) to review the evidence of the trials before granting marketing approval. Part of the reason is that recent reforms, namely the Prescription Drug User Fee Acts (PDUFA), have focused on improving the time it takes for the FDA to approve a drug. Even before these reforms, however, the FDA's approval times at their height were only one half (average 30.3 months) the duration of phase II and III testing (DiMasi et al. 2003).

Despite the importance of clinical trials to the productivity of drug development, there is no positive economic theory of clinical trials. In particular, there exists no explicit analysis of what determines how long trials take and how much they cost. Given that U.S. National Institutes of Health (NIH) registry of clinical trials, clinicaltrials.gov, reports that over 2 thousand phase II and III trials started each year between 1996 and 2007, it is surprising how poorly this component of medical R&D is understood.

This paper attempts to fill this gap in the economic literature on medical R&D. Building on previous work (Philipson 1997; Philipson and Malani 1999; Malani 2008), we interpret the recruitment of subjects for clinical trials as a labor market with subjects making up the supply side and investigators making up the demand side for observations. In contrast to previous

² There are three steps to marketing a drug. A company must first find a chemical entity and show medical value in *in vitro* and animal testing. After this pre-clinical research, the company files an Investigational New Drug (IND) application with the Food & Drug Administration (FDA). Second, if the FDA approves the IND, the company conducts three phases of clinical testing. Phase I includes small studies of the toxicity of the drug in healthy subjects. Phase II includes medium-sized studies of drug efficacy among subjects with the disease targeted by the drug. Phase III includes large-scale randomized clinical trials of the efficacy and safety of the drug in subjects with the disease. If the results of clinical testing are positive, the company files a New Drug Application (NDA) with FDA. Finally, the FDA reviews the data in the NDA to determine whether the drug is safe and effective. If it is, the FDA approves the NDA and the company may market the drug.

analyses, we consider impact of two important features of this market. First, there is costly search in the market for human subjects. Were it not for this search process, clinical development times would be determined merely by the length of patient follow-up and the major delay of new products would be due to FDA review of trials. Second, medical R&D differs from other types of R&D in that a firm's input supply market (human subjects) coincides with its output demand market (patients). This unique link between input and output markets for medical R&D generates important implications for the ability to recruit subjects in trials.

In section 2, we present a one-sided model of patients' search for a clinical trial that generates our central predictions about the duration of clinical trials. Due to the coincidence of input and output markets for drug R&D, existing trials compete with each other and with successes of prior R&D for patients. In the typical market, this competition would produce efficient outcomes due to the price mechanism. The market for clinical observations, however, is subject to wage controls that flow from bioethical regulation of medical research. Trials are barred from recruiting patients by offering patients a higher monetary wage for participation. As a result, patients are not sorted to trials based on the value of those trials and participation rates among eligible patients are low. Instead, past and present R&D by one company has negative recruitment externalities on R&D by other companies. In section 3, we extend the analysis to the demand side of the market and model investigators' search for patients to enroll in trials. In this model, the duration of trials is related to the tightness of the market for observations, defined by the ratio of the number of trials being conducted and the prevalence of a disease.

In section 4, we test the predictions of our analysis using data on cancer trials from *clinicaltrials.gov*, a registry of all clinical trials concerning drugs for serious and life-threatening conditions that was created by the FDA Modernization Act of 1997 and is maintained by the NIH. We find that, despite the introduction and improvement of internet technologies to match patients to clinical trials, the duration of cancer trials has been relatively flat over the last decade. The reason is that there has been a tremendous growth in the number of cancer trials being conducted and this has slowed down trial recruitment. We estimate that, had the level competition among trials been frozen at 1996 levels, cancer trials would now take about 80% less time to complete. To put in another way, the growth in competition for recruitment is responsible for increasing the time it takes to recruit a patient by about 400 percent.

The main point of our analysis is that a better understanding of the determinants of the length and costs of clinical trials is crucial for understanding the medical R&D process in general and the slowdown in productivity of drug R&D in particular. Our analysis stresses the economic, rather than scientific, forces that lower medical R&D productivity over time. We believe that search costs and the coincidence of input- and output-markets for drugs are as critical to understanding the R&D productivity slowdown as the diminishing returns from pharmacology.

2 One Sided Search by Patients

This section presents a simple analysis of patients' search for new treatments offered through clinical trials – the supply side of the market for clinical observations – that offers a surprising number of testable implications about the duration of trials. We employ a modified

version of a standard one-sided labor search model in which patients maximize expected “full income”, which includes health and non-health consumption. In our modification, leisure or unemployment corresponds to remaining on conventional treatment and employment to enrolling in a trial.

While a patient is searching for a trial, he remains on conventional treatment, which offers per-period utility

$$\theta_0 - c_0$$

where θ_0 is the patient’s health when on conventional therapy and c_0 is the cost or price of conventional therapy. When a patient enrolls in a randomized clinical trial of a new treatment, he obtains utility

$$q\theta + w$$

where q is the probability that the patient is assigned to the new treatment, θ is the patient’s health under the new treatment, and w is the monetary compensation the patient receives for participating in the trial. This wage is net of the cost of the new treatment so that, if the only compensation is free access to the new treatment, $w = 0$. We assume, without loss of generality, that the trial is placebo-controlled and blinded. Since placebo does not improve health, randomization to the control arm offers no utility.³ Because of blinding, the subject does not know which group he is in and values the trial as a lottery.⁴

We assume that once a patient enrolls in a trial he receives randomized treatment plus compensation for one period, and then returns to conventional therapy and the search for another trial. Thus the present expected value of enrolling in a trial is

$$A(\theta) = q\theta + w + \beta U$$

where U is the present expected value of payoff from continued search. If the patient continues to search he stays on the conventional treatment and, each period, receives an offer to participate in a trial with probability α . When he receives an offer, he draws a belief about the value of new treatment from the distribution F of treatment effects. We assume these draws on treatment effects are i.i.d. over time. Therefore, the Bellman equation for continued search is

$$U = \theta_0 - c_0 + \beta[\alpha \int \max\{A(\theta), U\} dF(\theta) + (1 - \alpha)U]$$

As the value of accepting enrollment A is strictly increasing in the anticipated treatment effect θ , it follows that there is a reservation level of anticipated treatment effect R defined by

³ For a model of placebo effects, see Malani (2006).

⁴ For subject-learning through consumption, see Philipson & DeSimone (1997) and Philipson & Hedges (1998).

$$A(R) = U$$

above which the patient enters the trial and below which he does not. The probability that a patient on conventional treatment enrolls in a trial – more succinctly the hazard rate of enrollment in trials – is the arrival rate of offers to enroll times the acceptance rate of these offers,

$$H = \alpha[1 - F(R)]$$

This implies that the expected duration a patient searches before entering a trial is

$$T = \frac{1}{H}$$

For the moment we assume that trials accept any patient who seeks to enroll. This suppresses analysis of the demand side of the market for observations, but still yields a number of direct and important predictions about the conduct of clinical trials.

Mortality and Recruitment

Patients facing life threatening diseases such as cancer discount the future more heavily because they have lower survival rates. We can model these patients with lower β , and use this to compare R&D for life-threatening diseases with R&D for other diseases. A more life-threatening disease implies more discounting, which in turn lowers the option value of searching for a trial and implies a shorter duration of search

$$\frac{dR}{d\beta} > 0 \Rightarrow \frac{dH}{d\beta} < 0$$

Other things constant, subjects are more eager to enroll in trials when they are in serious conditions because waiting is not an option. This reduced option value lowers the cost of medical R&D for life-threatening diseases.

Sample Size and Recruitment

Suppose a trial requires the enrollment of n subjects but is able to recruit only one subject per period. How long will this trial take to complete recruitment? Each period, the trial obtains a new enrollee with probability H . Thus, the trial's expected duration is the expected number of draws required to obtain n successes from a binomial distribution with success probability H . Because this is just the expected value of a variable drawn from a negative binomial distribution with parameters (n, H) , the expected duration is

$$\zeta(n, H) = n / H \tag{1}$$

Clearly, a larger trial size raises the length of trials, $d\zeta/dn > 0$, while a higher rate of subject enrollment lowers it, $d\zeta/dH < 0$.

Matching Technology & Services to Match Patients with Trials

A number of organizations offer patients services to help them find trials in which to enroll. Many, like the NIH's clinicaltrials.gov database that we employ in section 4, are web-based. The effect of these services is to increase the arrival rate α of offers to enroll in trials. The impact on the duration of trials, however, is ambiguous. The α parameter has two offsetting effects on the length of the trial

$$\frac{d\zeta}{d\alpha} = \frac{\partial\zeta}{\partial H} \frac{dH}{d\alpha} = \frac{\partial\zeta}{\partial H} \left[(1-F) - \alpha f \frac{dR}{d\alpha} \right]$$

Enrollment requires two steps: a patient must find the trial and then he must decide to enroll in the trial. Improved matching increases the rate at which patients find a trial, but it lowers the rate which they enroll once they find a trial. Since trials are more easily found, the optional value R of waiting rises with improved matching.

The Effect of Disease Prevalence and Competing R&D

The arrival rate α in our analysis depends not only on matching technologies but also on the number of patients not already enrolled in a trial and the number of trials with open slots for patients. Other things constant, we assume that the arrival rate of offers to enroll in a trial is decreasing in non-enrolled patients and increasing in the number trial vacancies. Since overall patient supply rises with the prevalence of disease and overall demand by trials is increasing in the number of new treatments being researched, the arrival rate is decreasing in disease prevalence and increasing in competing medical R&D.⁵

Just as in the case of improved matching technologies, the effect of changes in the arrival rate due to greater disease prevalence or rising numbers of competing trials is ambiguous. For example, an increase in the number of trials increases the number of trials patients may encounter, but it also encourages patients to be more selective about the trials in which they ultimately enroll. If the latter effect outweighs the former, medical R&D may have a negative externality on other medical R&D because it hinders recruitment into clinical trials.

The pace of current and past R&D

The amount of prior, successful medical innovation also affects the cost of current R&D. If we interpret past medical innovation as an increase in the effectiveness of conventional treatment, then such innovation will make it more difficult to recruit patients because they will

⁵ These relationships will be derived, rather than assumed, in the two-sided analysis in Section 3.

demand more from trials

$$\frac{dH}{d\theta_0} = -\alpha f \frac{dR}{d\theta_0} < 0$$

To put it another way, it is not difficult to line up enrollees if patients do not have any alternative treatment. But as innovation improves their alternative, recruitment will slow down and trials will take longer to complete, holding sample size constant. This slowdown on current innovation induced by past successes is a negative externality of past R&D on current R&D. This is due to the input-output market link of medical R&D. Because clinical trials enroll the same patients who ultimately purchase the product once it is approved for sale, the input supply function into R&D is the same as the output demand function for that R&D.

If new trials could lure patients away from conventional treatment or competing trials by offering higher wages, then the negative externality from past R&D and other trials would be a pecuniary externality and have no efficiency consequences. This is not the case, however, as bioethical rules cap wages. We will discuss this below.

Pricing of Treatments and Insurance Rates

The input-output link for medical R&D also has important implications for regulations of output markets for the pace of R&D. In particular, the utility from conventional treatment depends not just on past innovation but also on the price at which those innovations are sold. It is straightforward to show that the price of conventional treatment raises the hazard rate into recruitment

$$\frac{dH}{dc_0} = -\alpha f \frac{dR}{dc_0} > 0$$

There two important influences on the price of conventional treatment: government price controls and the availability of insurance. Both lower the price of that treatment at the time of service and thereby increase the duration of trials. In other words, not only do price controls have the familiar effect of lowering the *benefits* to R&D, they have the less obvious implication of raising the *costs* of R&D by slowing down subject recruitment. As for insurance rates, while prior research has highlighted that moral hazard from health insurance increases the returns to medical innovation (Lakdawalla & Sood 2006), we observe that it also increases the cost of that innovation by delaying clinical trials.⁶

Medical ethics and wage regulations in the labor market for observations

Due largely to a number of highly offensive studies conducted on humans during World War II, there are a number of bioethical regulations of clinical trials. These are usually

⁶ This is consistent with results from surveys of patients that enroll in trials (Klabunde et al. 1999).

implemented through public or private review of trial protocols. In the main, this oversight requires trials obtain the informed consent of patients before enrollment and that trials not offer patients excessive financial compensation for enrollment. Even though we let many professions accept higher wages for larger mortality risk at work, this is considered unethical in the area of investigational research, even when patients consent to enroll is more informed than acceptance of most other mortality-inducing professions. Be that as it may, bioethical regulations implicitly impose wage-caps in the labor market for clinical observations.

In our framework, bioethical rules induce trade under the so-called non-transferable utility model in which companies cannot induce enrollment by sharing their surplus. Trade is possible only when both parties must gain from a match without compensation. In the transferable utility model, applicable to most other jobs, trade occurs when wages compensate sellers. In our framework, it is straightforward to show that regulations permitting higher trial compensation shorten trial durations

$$\frac{dH}{dw} < 0$$

Thus, wage-caps raise the cost of R&D by slowing down trial recruitment. This is likely to induce inefficiencies in trade between current and future patients. The surplus of drug companies comes from future patients, and those patients would benefit from the faster trials that would be possible if wage caps were eliminated and current patients were offered higher wages for enrollment. Wage caps are especially problematic in the trial context because current patients who enroll in trials provide positive external effects for future patients that get to learn from their results. Enrollment is therefore under-provided without additional compensation.

Post-marketing Studies

Our analysis also has strong implications for the feasibility and costs of randomize trials after a drug has been approved for marketing. Post-marketing studies are called Phase IV trials and are meant to uncover long term side effects of drugs. Ideally these studies, like pre-approval clinical trials, should be randomized and placebo-controlled to maximize their informational value.

However, after approval, the output market for a drug competes directly with the input supply for Phase IV studies so that

$$\theta_0 = k \quad \& \quad F(\theta) = 1_k$$

where k is the treatment effect of the new treatment. Patients now have a choice between obtaining the new treatment outside the trial versus perhaps only a probability of obtaining the new treatment in a trial. Because health consumption is always lower in a Phase IV trial, the trial must compete on non-health consumption. Unless the cost of the new treatment is very high or the trial wage is increased, marketing approval will increase the duration of trials.

Indeed, given insurance coverage for approved drugs and the bioethical cap on trial wages, it may be impossible to recruit patients into randomize, placebo-controlled post-marketing trials. To sum up, unless the value of subsidized treatment outweighs the lower likelihood of receiving the new treatment

$$c + w > (1 - q)k$$

we predict that no Phase IV trial will exceed the reservation wage of patients and therefore Phase IV trials will have infinite length.

3 Two Sided Search by Subjects and Investigators

In this section we show that the implications from the simple one-sided search analysis largely generalize to the two-sided case in which both patients and investigators engage in search. Investigators may not want to enroll all willing patients because of medically-dictated inclusion and exclusion criteria or because they want to enroll patients with the most favorable treatment effects to maximize the probability of obtaining marketing approval. In this context, the effect of changes in parameters such as the number of competing trials or the productivity of meeting technology on the duration of trials will depend not just on whether patients are willing to supply observations, but also whether investigators actually demand those observations.

Because the equilibrium of two-sided search model is easier to analyze in continuous time,⁷ we shall make two changes to the patient's search process. First, we assume offers to enroll in a trial now arrive according to a Poisson process with parameter α_p , where the p -subscript signifies the patient. Second, we assume that if the patient enrolls in a trial, instead of receiving randomized treatment for one period, he receives it for duration τ .

As for the investigator, we assume it makes no profits while it searches for a patient to enroll into its trial. Potential enrollees arrive according to a Poisson process with parameter α_t , where the t -subscript signifies the trial. Once it finds a patient to enroll, it has to pay wage w and cost of new treatment c for the duration τ that the patient is enrolled. In return it obtains information $i > 0$ from the patient. We assume, for convenience, that each trial enrolls just one subject.⁸ When the trial ends, the investigator can file for marketing approval, which has value M after accounting for the risk of regulatory approval. Thus an investigator searches for one enrollee and, once it has found an enrollee, never needs to search again.

We assume that the value and cost of conventional treatment is fixed across patients, and that the probability of treatment q and wage w are announced ahead of matches.⁹ From

⁷ Our two-sided model is based on the non-transferable utility model of Burdett and Wright (1998).

⁸ This implies no loss of generality because we can just reinterpret the number of trials as the number of patients needed in trials to discuss the case where trials require multiple patients. Increasing the number of patients needed in trials will have the same effect as increasing the number of trials in our simple one enrollee per trial model.

⁹ They may be the result of bargaining between the drug company and patient advocates at a research site that we model in a future draft.

the patient's perspective, each offer to enroll in a trial is characterized by an independent draw of anticipated relief θ from cumulative distribution function F_p , which is differentiable and has finite support. From the company's perspective, each potential enrollee is characterized by an independent draw of information i from distribution F_i , which obeys the same regularity conditions as F_p . A successful match requires that the patient prefers enrolling in a trial given his independent draw of θ and that the company prefers enrolling the patient given its independent draw of i .

In the appendix, we describe how this model yields reservation values for each side of the market, R_p for patients (supply-side) and R_i for investigators (demand side). Both reservation values will depend on the arrival rates of offers. Because the arrival rate for patients will depend on the actions of investigators and vice versa, we must derive each side's arrival rates from a matching process. We assume a simple random matching technology $m = \gamma u_p u_i$ that determines the number of meetings m per unit time as a function of γ the productivity of search, u_p the number of patients not enrolled in trials, and u_i the number vacancies in trials. From the patient's perspective, the arrival rate of trials equals the contact rate for patients times the probability that the patient is suitable to trial,

$$\alpha_p = \gamma u_i [1 - F_i(R_i^*)] \quad (2)$$

Likewise, the arrival rate of patients to trials is

$$\alpha_i = \gamma u_p [1 - F_p(R_p^*)] \quad (3)$$

Following Burdett & Wright (1998), it can be shown that there exists an equilibrium (R_p^*, R_i^*) that satisfies Nash's conditions. Indeed, if (F_p, F_i) are log concave, this equilibrium is unique. Because a successful match requires approval of both the patient and the investigator, the equilibrium reservation values imply that the hazard rate at which patients enroll in trials is

$$H_p = \gamma u_i [1 - F_i(R_i^*)][1 - F_p(R_p^*)] \quad (4)$$

and the hazard rate at which trials enroll patients

$$H_i = \gamma u_p [1 - F_i(R_i^*)][1 - F_p(R_p^*)] \quad (5)$$

The one-sided model of the previous section can be obtained as a special case where the reservation value of the demand side is low enough to lead to acceptance of all patients that want to enroll, i.e., $F_i(R_i^*) = 0$. In this case, the rate of enrollment depends only on the reservation values of subjects.

In order to determine the steady state levels of trial enrollment, we must analyze the dynamics

of matched and unmatched patients (e_p, u_p) and trials (e_t, u_t) . Starting with the supply-side of the market, we assume the total number of patients $N = e_p + u_p$ is fixed. Patients flow into enrollment at rate H_p and return to non-enrollment after duration τ , which can be operationalized as a flow at rate τ^{-1} . This yields the dynamic system

$$\begin{aligned}\dot{u}_p &= -H_p u_p + \tau^{-1} e_p \\ \dot{e}_p &= H_p u_p - \tau^{-1} e_p\end{aligned}$$

The steady state of this system is

$$\bar{u}_p = \frac{N}{\bar{H}_p \tau + 1}, \quad \bar{e}_p = \frac{\bar{H}_p \tau}{\bar{H}_p \tau + 1} \quad (6)$$

Turning to the demand side, we assume that new trials start at rate ϕ , which is interpreted as the rate of innovation. Trials begin vacant u_t but enroll patients and become filled at rate H_t . Trials end at rate τ^{-1} . This yields the dynamic system

$$\begin{aligned}\dot{u}_t &= \phi - H_t u_t \\ \dot{e}_t &= H_t u_t - \tau^{-1} e_t\end{aligned}$$

The steady state of this system is

$$\bar{u}_t = \phi \bar{H}_t, \quad \bar{e}_t = \phi \tau \quad (7)$$

Our primary interest is the steady state duration of trials, or

$$\bar{T} = \frac{1}{\bar{H}_t} + \tau \quad (8)$$

In the appendix, we prove a series of results that lead to the following proposition which summarizes the effect that changes in key parameters have on the duration of trials.

Proposition. Suppose (i) that investigators' reservation value R_t^* is positive and (ii) that the distribution F_p of anticipated treatment effects and the distribution F_t of information from patients are each log-concave. Then,

- A) An increase in the quality of conventional treatment (θ_0), the cost of the new treatment (c), the rate of medical innovation (ϕ), or the duration of enrollment in trials (τ) increase the steady state duration (\bar{T}) of trials.

- B) An increase in the cost of conventional treatment (c_0), the probability of being randomized to the treatment arm (q), the value of an application for market approval (M), the matching technology (γ), or disease prevalence (N) decreases the steady state duration of trials.
- C) If the wage from participating in a trial (w) and the value of applying for marketing approval (M) are sufficiently low, then an increase in discounting (r) will decrease the duration of trials. If w and M are high, then an increase in discounting may increase the steady state duration of trials.
- D) An increase in the wage from participating in a trial (w) may increase or decrease the steady state duration of trials.
- E) An increase in the number of subjects required to complete a trial (n) increase the steady state duration of trials.

This proposition generalizes the implications of the one-sided search analysis to two-sided search. There are two important changes that follow from consideration of the demand side of the market for observations. First, an increase in wage does not always speed up trials. An increase in wage decreases the surplus of the investigator. It responds by becoming more selective about the patients it admits into trials. This could increase the duration of trials.¹⁰ Second, greater discounting may delay trials. While patients are quicker to enroll, higher discounting increases the relative cost of the wage payment and reduces the present value of applying for marketing approval (M). This may cause investigator to become more selective about enrolling patients, delaying trials.

There are also three results in the proposition above that appear to refine the results from one-sided search but do not, in fact, do so. The three results are that improved search technology or greater prevalence of disease reduce duration and increased innovation increases duration. We are able to sign these effects only by assuming that the distributions of anticipated treatment effect and information (F_p, F_t) are long-concave. If we had also assumed in the one-sided that the distribution of anticipated treatment effects was log concave, however, we would have reached the analogous conclusions that an increase in the arrival rate (α) or greater prevalence of disease reduce duration and increased numbers of trials increase duration.

4 Empirical Analysis

The previous two sections derived the effects of improved matching technology and increased medical innovation on the durations of clinical trials. In this section we examine data that quantify these two opposing forces on the rate of recruitment into cancer trials. Our main finding is that improved matching sped up recruitment from 218 to 45 days per 10 subjects and that competing medical innovation slowed down recruitment from 9 to 45 days per 10 subjects,

¹⁰ In a world without wage caps, the investigator would choose a wage which maximized it's utility in the non-matched state in which it starts. Assuming R_t^* is concave in wage, this would yield an interior optimum. [Explain $R'(w)$ at optimum.]

holding other factors constant.

Data

Our data are drawn from a registry of clinical trials available at ClinicalTrials.gov and maintained by the NIH. The database was created by the FDA Modernization Act (FDAMA) of 1997, Section 113, which requires that clinical trials evaluating certain drugs for serious or life-threatening diseases be registered at ClinicalTrials.gov.¹¹ While the FDAMA does not define serious or life-threatening conditions and there are no legal sanctions for failure to register a trial, an evaluation study has shown the database covers 48% of industry-sponsored and 91% of NIH cancer trials (Toigo 1004).

As of May 6, 2008, there were over 52,000 trials in the database. Our empirical analysis will focus on the roughly 7,200 Phase II, III and IV trials¹² examining drugs for cancer that began during the period 1996 – 2008.¹³ Figure 1 and Figure 2 describe the number and enrollment in trials based on the year they were started and, for those that are completed, the year they were completed.

The trials are categorized by phase. Phases II and III are described in footnote 2. Phase II/III trials are a hybrid of phase II and phase III trials. Phase IV trials are conducted after a drug has been approved for marketing and are meant to uncover long term side effects of drugs. Our data are dominated by phase II and phase III trials. Though there are roughly twice as many phase II trials (4,797) as phase III trials (1,802), total enrollment in phase III trials (1,366,213) is nearly three times enrollment in phase II trials (380,022). Table 1 reports the median size (number of enrollees) of trials by the year they were started and by phase. As expected, phase II trials have smaller median enrollment than Phase III trials (50 versus 400).

The clinicaltrials.gov database provides basic data on the conduct of trials. In addition to the start and stop dates and planned enrollments, it provides information on the specific type of cancer targeted by the drug being investigated, the design of the trial, whether the trial targets adults, children or seniors, and whether it is funded by industry.¹⁴ Table 2 presents information on the specific cancers targeted by the trials in our sample. Table 3 provides summary statistics for most of the remaining variables by phase of trial.¹⁵

¹¹ The Act requires that drugs being tested for efficacy under an IND be registered. This generally corresponds to drugs for which marketing approval is sought. However, it is accepted by both drug sponsors and the FDA that certain drugs that are unlikely to be approved or profitably marketed may remain available under an IND so that patients may access them for purpose of “compassionate use.”

¹² We omit Phase I trials because they target a different population group. Outside cancer, they target healthy subjects. Within cancer, they target only terminal patients. Phases II – IV, however, target the broader market of patients likely to use the drug if approved.

¹³ An investigator may register a trial that began before the database was started. We focus on cancer trials that began between Jan. 1, 1996 and May 6, 2008. We exclude trials that merely facilitate compassionate use and trials that are observational. In observational trials, the investigator does not choose which treatment each enrollee gets.

¹⁴ Although we do not use them in the present draft, the database also provides data on the location of trials. A more complete description of the database can be found in Zarin et al. (2005).

¹⁵ Note that Phase II trials are rarely blinded and placebo-controlled (6%). The main source of variation in design during Phase II is whether a trial is single arm (41%) or otherwise uncontrolled (27%). Phase III trials are almost

The dependent variable in our analysis is the duration of trials, measured in days. Roughly a quarter of trials in our sample are completed before 2007, the rest are censored.¹⁶ The duration of completed trials is simply the completion date minus the start date. For censored trials, we measure censored duration as the time from the start date to May 6, 2008, the date we obtained the clinicaltrials.gov data.

In order to examine the role of meeting technology, we calculate for each “reference” trial the total number of trials (including the reference trial) added to the clinicaltrials.gov database by the year the reference trial was started. In order to explore the effects of competition across trials for enrollees, we construct for each reference trial variables that count the total number of other trials that are ongoing during the reference trial and the number of enrollees in the other trials.¹⁷ We also calculate these competition variables counting as competition only trials targeting the same types of cancer as the reference trial.

Graphical analysis

Figure 3 summarizes the main trends in oncology trials during 1996-2007. It plots three variables (duration, enrollment and competition) along the left axis, and one variable (matching technology) along the right axis. The key outcome variable, trial duration (as measured by the fraction of trials that last 2 or more years), declined slightly – roughly 7% – during the last decade.¹⁸ During the same period, however, enrollment declined by nearly 35%¹⁹ and the size of the clinicaltrials.gov registry, a key technology for matching patients to trials, grew dramatically, increasing 10-fold between 1999 and 2007.²⁰ In other words, although enrollment fell and match technology improved, the duration of trials did not substantially decline. One possible explanation is the increase in the number of competing trials. The number of trials for all cancers, for example, increased over 170% during the last decade. This

always randomized (88%) and controlled. The main source of variation is whether the trials employ an active control (47%) and whether they give enrollees the new treatment on an open label basis (48%) when the randomized evaluation of that treatment is completed. We shall focus on those phase-specific design features that vary enough to identify effects on trial duration in our empirical analysis.

¹⁶ Investigators sometimes report a future date (past May 6, 2008, the date we obtained the data) as the date of completion. We assume that investigators can only accurately predict end dates for trials during the last year of the trial because the last year involves only follow-up of patients, not recruiting. Therefore, we count as completed any trial investigators report as predicted completed before May 6, 2009.

¹⁷ The amount of overlap between a reference trial and a competing trial is equal to fraction of the duration of a reference trial during which the competing trial is not yet completed. The total number of competing trials is the sum of these fractions across all competing trials. Competing enrollees is the number of enrollees in a competing trials multiplied by the fractional overlap. Total competing enrollees is the sum of these competing enrollees across all competing trials.

¹⁸ This trend is replicated within Phase, so that the durations of Phase II and III trials each fall slightly during the last decade. The trend is also replicated using longer survival (at least 3 or 4 years) as a measure of duration.

¹⁹ Much of this decline is due to a composition effect. The fraction of trials that are Phase III (as opposed to Phase II) fell by half and, according to Table 3, median enrollment in Phase III trials is eight-times that in Phase II trials.

²⁰ One possible reason for the tremendous growth in clinicaltrials.gov starting in 2005 is since September 2005 the editors of influential medical journals throughout the world have required investigators prospectively register their trials as a condition for publication of their trial results in these journals. See http://www.icmje.org/clin_trial07.pdf and Zarin et al. (2005).

is the basic empirical story that drives the regression results below.

Another way to document the impact of matching technology and competition on duration is to estimate Kaplan-Meier survival curves for cancer trials. Figure 4 plots separate survival curves for trials that began when the size of the clinicaltrials.gov database was less than and was more than (dotted line) its median size (916 trials) during the sample period.²¹ The survival curve for trials starting when the registry was above its median size lies *below* the curve for remaining trials. This suggests these trials are significantly shorter when clinicaltrials.gov is larger, i.e., when matching technology is better.

Figure 5 examines the effect of the number and size of competing trials on the duration of trials. The first column of plots focuses on the effects of all competing trials. The second column looks at competing trials only in the same cancer category as the reference trial. Each plot graphs the survival curve of trials facing above (dotted line) and below the median level of competition of the type indicated in the title. The above-median curves lie *above* the below-median competition curves.²² This suggests that competition delays trials.

Regression analysis

In order to examine the relative effects of matching technology and competition on duration, controlling for enrollment, design, and other variables, we estimated an advanced failure time model of the form

$$\begin{aligned}\ln T &= \ln n - \ln H \\ \ln H &= X\beta + e\end{aligned}$$

where D is survival time and e is assumed to have a mean zero normal distribution with standard deviation σ .²³ The first equation is simply the log form of (1), the equation for the duration of a trial seeking n subjects. This system implies survival and density functions of the form

$$S(T) = 1 - \Phi[(\ln T - \ln n - X\beta) / \sigma] \quad f(T) = (T\sigma\sqrt{2\pi})^{-1} \exp[-(\ln T - \ln n - X\beta)^2 / 2\sigma^2]$$

We will estimate (β, σ) via maximum likelihood. A trial that ends at time t contributes to the likelihood function the value of density function at t . An observation censored at t contributes the probability of surviving to that point. Therefore, the log likelihood can be written

²¹ The above median line ends just before 3000 days, or roughly 8 years. The reason is that all above median trials start in the last 7 years of the sample and are censored before completion.

²² The above median lines in the left column of plots end just before 2000 days, or roughly 6 years. The reason is that all above median all-cancer competition trials start in the last 5 years of the sample and most are censored before completion.

²³ We chose a normal distribution for e because a plot of the hazard function for trials resembled that of a log-normal survival time model. We confirmed this by estimating a model with a generalized gamma distribution and failing to reject the hypothesis that $\kappa = 0$.

$$\ln L = \sum_j [d_j \ln f(T_j) + (1 - d_j) \ln S(T_j)]$$

where j indexes observations and d_j indicates whether a trial was completed rather than censored. We estimated parameters for ten different specifications of the covariate matrix X . Each specification includes competition variables and year fixed effects to account for omitted variables such as changes in FDA requirements for trials. Importantly, specification 3 adds matching technology and specifications 6 and 8 include cancer-type fixed effects. The remaining specifications are transparent from the table.²⁴

The results, presented in Table 4, are consistent with our previous description of the main trends in oncology trials. Better search technology, measured by the size of the ClinicalTrials.gov database, tends to reduce the duration of trials. Doubling the number of trials reduces duration by 80-90%. In contrast, competing trials tend to delay a reference trial. For example, doubling the number of competing trials targeting any cancer increases the duration of the reference trial by roughly 120%.

There are two surprises associated with the effects of competition on trial durations. One is that, after adjusting competition by enrollment, competition among trials targeting the same cancer has much less of an effect than the number of trials themselves. Perhaps patients (or their doctors) are more aware of the number of trials available rather than the number of open slots in these trials. Another surprise is that competition from trials that are targeting any cancer has a much bigger effect than competition from trials targeting the same cancer as the reference trial. For example, doubling competition from trials targeting the same cancer as the reference trial increases duration by only 12%. Perhaps patients have multiple cancers so that they are eligible to participate in trials from many categories. Thus a reference trial in one category actually faces competition from trials in another category. Neither surprise changes the overall point that competition tends to delay trials.

Discussion

A useful exercise to quantify the benefits from better matching technology and the cost from competition is to ask how much slower trials would have been if clinicaltrials.gov had not grown and how much faster trials could be completed if competition had remained flat. To answer this question, we use our regression results (specifically column 8 of Table 4) to predict the duration of an average trial begun in 2007 under four scenarios

- Clinicaltrials.gov frozen at median or 2002 level
- Clinicaltrials.gov at 2007 levels

²⁴ Specification 7 requires some explanation. It includes fixed effects for the year that a trial was reported to the registry. No trials – even those begun in 1996 – were reported before 1999. In 1999, investigators retroactively reported trials that began in 1996 and were still active. As a result, early trials are left truncated. Since the database became more populated over time, there is also a greater duration-independent under-reporting in the early years of the registry. The purpose of the year registered fixed effects is to capture selection effects due to these reporting anomalies.

- Competition from all other cancer trials frozen at 1996 levels
- Competition at 2007 levels

Table 7 reports the results of this exercise. The penultimate column suggests that, whereas the average trial now takes nearly 3 years to complete, it would take nearly 14 years to complete had clinicaltrials.gov been frozen at its median size of 916 trials in 2002. That is an increase in duration of roughly 380%. Another way to put this is that, whereas it now takes 45 days to recruit 10 subjects, the same recruitment would take over 7 months with 2002 matching technology. We get almost the exact opposite result with competition. The penultimate column reports that, whereas the average trial now takes nearly 3 years to complete, it would take only about 7 months under 1996 levels of competition, a decrease of nearly 80%. In other words, whereas it now takes 45 days to recruit 10 subjects, the same recruitment would take just 9 days under 1996 competition.

5 Conclusion

Our analysis discussed the impact of search in the market for human subjects on the cost and length of clinical research. Given the large component of delay in the introduction of drugs is due to clinical testing prior to FDA review, this topic seems relatively poorly understood by economists. We investigated these effects empirically using the most comprehensive data set available on the length and characteristics of oncology clinical trials.

Although we believe search issues are central to an understanding of the length of investigational research, and thus the major cost of medical R&D, there were several issues we did not address. The issues that we ignored, and many others, suggest a rich future research agenda. First, our analysis will have implications for a normative analysis of the optimal rate of medical progress or medical research as defined by the annual number of new investigations that take place. Critical to this optimal rate is the negative externalities from past innovations and competition for human subjects between current innovations, a feature that is unique to medical R&D. Second, it is important to develop a better understanding of the role of multi-center trials and the international trade in observations – better known as the outsourcing of trials – in reducing trial durations. Third, our empirical analysis was limited to cancer trials due to data constraints. However, a more general analysis for a broader range of diseases seems warranted.

Appendix

Elaboration of Two-Sided Model

Let $A_p(\theta)$ denote the expected lifetime utility of a patient enrolled in a trial with anticipated treatment effect θ and U_p denote his expected lifetime utility when he is not currently enrolled in a trial. The value of enrolling in a trial is

$$A_p(\theta) = \int_0^\tau e^{-rt} (q\theta + w) dt + e^{-r\tau} U_p \quad (9)$$

The first term reflects the value of enrollment for duration τ and the second term reflects the discounted value of renewed search. If the length of a period is Δ , then the Bellman's equation for the value of continued search can be written

$$U_p(\theta) = (\theta_0 - c_0)\Delta + \frac{1}{1+r\Delta} [\alpha_p \Delta \int_\theta \max\{A_p(\theta), U_p\} dF_p(\theta) + (1 - \alpha_p \Delta) U_p] \quad (10)$$

Subtracting $(1+r\Delta)^{-1}U_p$ from both sides and taking limits as $\Delta \rightarrow 0$ yields

$$rU_p = \theta_0 - c_0 + \alpha_p \int_\theta \max\{A_p(\theta) - U_p, 0\} dF_p(\theta) \quad (11)$$

Because the value of being enrolled in a trial is increasing in the anticipated value of the new treatment ($A'_p(\theta) = \int_0^\tau e^{-rt} q dt$), the patient's optimal strategy is to enroll in any trial where θ is greater than reservation value R_p which satisfies $A_p(R_p) = U_p$. Evaluating $A_p(\theta)$ at $\theta = R_p$ reveals $U_p = (qR_p + w)/r$. Plugging this back into (11), integrating by parts, and using the expression for $A'_p(\theta)$ yields

$$R_p = \frac{\theta_0 - c_0 - w}{q} + \frac{(1 - e^{-r\tau})}{r} \alpha_p \int_{R_p}^{\bar{\theta}} [1 - F_p(\theta)] d\theta \quad (12)$$

Let $A_i(i)$ denote the expected present value of profits of an investigator that has recruited a patient with information value i into its trial and U_i denote the expected present value of its profits when it is still searching for a patient to enroll in its trial. The investigator's profits once it has found a patient is

$$A_i(i) = -\int_0^\tau e^{-rt} (w + c) dt + \int_i e^{-rt} idt + e^{-r\tau} \int_r^\infty M dt \quad (13)$$

The first term captures the payment of the patient's wage for the duration of the trial. The

second term is the present value of information from the patient. The third term is the value of applying for marketing approval after the trial is completed. Since the investigator can file for marketing approval after one trial, the profit to an investigator of enrolling a patient does not – in contrast to the value to a patient of enrolling a trial – depend on the value of continued search. That value of search during interval Δ is

$$rU_t = \frac{1}{1+r\Delta} [\alpha_t \Delta \int_i \max\{A_t(i), U_t\} dF_t(i) + (1-\alpha_t \Delta) U_t]$$

Subtracting $(1+r\Delta)^{-1}U_p$ from both sides and taking limits as $\Delta \rightarrow 0$ yields

$$rU_t = \alpha_t \int_i \max\{A_t(i) - U_t, 0\} dF_t(i) \quad (14)$$

Because the profit from enrolling a patient is increasing in the value of information ($A'_t(i) = 1/r$), the company's optimal strategy is to enroll any patient that provides information greater than reservation value R_t which satisfies $A_t(R_t) = U_t$. Evaluating $A_t(i)$ at $i = R_t$ reveals $rU_t = -(1-e^{-r\tau})(w+c) + R_t + e^{-r\tau}M$. Plugging this back into (14), integrating by parts, and using the expression for $A'_p(\theta)$ yields

$$R_t = (1-e^{-r\tau})(w+c) - e^{-r\tau}M + \frac{1}{r} \alpha_t \int_{R_t}^{\bar{i}} [1-F(i)] di \quad (15)$$

Plugging the arrival rates (2) and (3) into the reservation values just derived yields

$$R_p = \frac{\theta_0 - c_0 - w}{q} + \frac{(1-e^{-r\tau})}{r} \gamma_u [1-F_t(R_t)] \int_{R_p}^{\bar{\theta}} [1-F_p(\theta)] d\theta \quad (16)$$

$$R_t = (1-e^{-r\tau})(w+c) - e^{-r\tau}M + \frac{1}{r} \gamma_u [1-F_p(R_p)] \int_{R_t}^{\bar{i}} [1-F(i)] di \quad (17)$$

These two equations implicitly define the patient's and the company's reaction functions $R_p = \rho_p(R_t)$ and $R_t = \rho_t(R_p)$, respectively, to each others' reservation values. Following Burdett and Wright (1998), it can be shown that there exists an equilibrium in which $R_p^* = \rho_p(R_t^*)$ and $R_t^* = \rho_t(R_p^*)$. Indeed, it can be shown that if F_p and F_t are log concave, then there is a unique equilibrium.

To simplify notation for subsequent analysis, we define

$$\mu_p(R_p) = \int_{R_p}^{\bar{\theta}} [1-F_p(\theta)] d\theta > 0 \quad \mu_t(R_t) = \int_{R_t}^{\bar{i}} [1-F_t(i)] di > 0 \quad (18)$$

These imply that $\mu'_p(R_p) = -[1 - F_p(R_p)] < 0$ and $\mu'_t(R_t) = -[1 - F_t(R_t)] < 0$. It can also be verified that $\mu''_p(R_p) = f_p(R_p) > 0$ and $\mu''_t(R_t) = f_t(R_t)$.

Combining steady state conditions (6) and (7) with hazards (4) and (5) and using the notation from (18) yields the steady state equilibrium reservation value and hazard rates

$$R_p^* = \left[\frac{\theta_0 - c_0 - w}{q} \right] - \frac{1 - e^{-r\tau}}{r} \frac{\phi}{N - \phi\tau} \frac{\mu_p(R_p^*)}{\mu'_p(R_p^*)} \quad (19)$$

$$R_t^* = [(1 - e^{-r\tau})(w + c) - e^{-r\tau}M] - \frac{\gamma(N - \phi\tau)}{r} \mu_p(R_p^*) \mu'_t(R_t^*)$$

$$\bar{H}_p = \frac{\phi}{N - \phi\tau} \quad (20)$$

$$\bar{H}_t = \gamma(N - \phi\tau) \mu_p(R_p^*) \mu'_t(R_t^*)$$

While the patients' reservation wage is always positive, investigators may have a negative reservation value if the value of applying for market approval is large enough. In other words, if the probability of approval or the market value of an approved drug is large enough, investigators might accept any patient that wants to enroll because every patient provides positive information ($i > 0$). In this case the two-sided model collapses to the one-sided model from the previous section.²⁵

There are two things to note about the hazard rates. Since $\bar{u}_t \geq 0$ and so $\bar{H}_t > 0$, the steady state only exists if the number of patients is greater than the rate of innovation times the duration of trials, i.e., $N > \phi\tau$. This condition is very likely to be satisfied since only a fraction of patients receive treatment in trials. Second, the hazard rate at which patients enroll in trials does not depend on reservation values. This contrasts with the one-sided search problem. The duration of time a patients waits to enroll in a trial is, simply, rising in the number of patients, falling the rate of innovation, and falling in the length of enrollment in a trial.

The following propositions summarizes the effect that changes in key parameters have on the steady state reservation values of patients and investigators, respectively.

Proposition 1 (Patient's Reservation Value). Suppose that the distribution of anticipated treatment effects (F_p) is log-concave. Then,

- A) An increase in discounting (r), disease prevalence (N), the cost of conventional treatment outside the trial (c_0), or the wage from participating in a trial (w) decreases the patient's steady state reservation price R_p^* . If $\theta_0 - c_0 - w > 0$, then an increase in the probability of receiving the new treatment in a trial (q) also decreases R_p^* .
- B) An increase in the amount of medical innovation (ϕ), the quality of existing medical

²⁵ This may also happen if patients do not remain in trials very long (τ very low) or investigators have poor outside investment opportunities (r very low or 0).

treatments (θ_0), or the duration of enrollment in a trial (τ) increases R_p^* .

Proposition 2 (Investigator's Reservation Value).

- A) An increase in the value of being able to apply for marketing approval (M) decreases the trial's steady state reservation price R_t^* and an improvement in matching technology (γ) increases R_t^* .
- B) An increase in the interest rate (r) or an increase in the duration (τ) of enrollment may increase or decrease R_p^* .

Suppose that the distribution of anticipated treatment effects (F_p) is log-concave. Then,

- C) An increase in disease prevalence (N), the cost of conventional treatment outside the trial (c_0), the cost of new treatment (c), the wage from participating in a trial (w), or the probability of receiving the new treatment in a trial (q) increases the trial's steady state reservation price R_t^* .
- D) An increase in the amount of medical innovation (ϕ) or the quality of existing medical treatments (θ_0) decreases R_t^* .

Proof of Propositions

Proof of Proposition 1. Define

$$X_p = 1 + \frac{1 - e^{-r\tau}}{r} \frac{\phi}{N - \phi\tau} \left[1 - \frac{\mu_p \mu_p''}{(\mu_p')^2} \right]$$

If F_p is log concave, then $X_p > 0$. Taking derivatives of R_p^* in (19) and rearranging yields

$$\frac{dR_p^*}{dr} = -\frac{1}{X_p} \left[\frac{d}{dr} \int_0^\tau e^{-rt} dt \right] \frac{\phi}{N - \phi\tau} \frac{\mu_p}{\mu_p'} = \frac{1}{X_p} \left[\int_0^\tau r e^{-rt} dt \right] \frac{\phi}{N - \phi\tau} \frac{\mu_p}{\mu_p'} < 0$$

$$\frac{dR_p^*}{dN} = \frac{1}{X_p} \frac{1 - e^{-r\tau}}{r} \left[\frac{\phi}{(N - \phi\tau)^2} \right] \frac{\mu_p}{\mu_p'} < 0 \quad \frac{dR_p^*}{dc_0} = \frac{dR_p^*}{dw} = \frac{-dR_p^*}{d\theta_0} < 0$$

$$\frac{dR_p^*}{dq} = \frac{-(\theta_0 - c_0 - w)/q^2}{X_p} < 0$$

if $\theta_0 - c_0 - w > 0$.

$$\frac{dR_p^*}{d\theta_0} = \frac{1/q}{X_p} > 0 \quad \frac{dR_p^*}{d\tau} = -\frac{1}{X_p} \left[e^{-r\tau} + \frac{1-e^{-r\tau}}{r} \frac{\phi}{N-\phi\tau} \right] \frac{\phi}{N-\phi\tau} \frac{\mu_p}{\mu_p'} > 0$$

$$\frac{dR_p^*}{d\phi} = -\frac{1}{X_p} \frac{1-e^{-r\tau}}{r} \left[\frac{N}{(N-\phi\tau)^2} \right] \frac{\mu_p}{\mu_p'} > 0$$

Proof of Proposition 2. Define

$$X_t = 1 + \frac{\gamma(N-\phi\tau)}{r} \mu_p' \mu_t' > 0$$

Taking derivatives of R_t^* in (19) and rearranging yields

$$\frac{dR_t^*}{dM} = \frac{-e^{-r\tau}}{X_t} < 0 \quad \frac{dR_t^*}{d\gamma} = \frac{1}{X_t} \left[-\frac{(N-\phi\tau)}{r} \mu_p' \mu_t' \right] > 0$$

$$\frac{dR_t^*}{dr} = \frac{1}{X_t} \left[\tau e^{-r\tau} (w+M) + \frac{\gamma(N-\phi\tau)}{r^2} \mu_p' \mu_t' - \frac{\gamma(N-\phi\tau)}{r} \mu_p'' \mu_t' \frac{dR_p^*}{dr} \right]$$

$$\frac{dR_t^*}{d\tau} = \frac{1}{X_t} \left[\overbrace{re^{-r\tau} (w+M)}^{>0} + \gamma \frac{\phi}{r} \mu_p' \mu_t' - \gamma \frac{(N-\phi\tau)}{r} \mu_p'' \mu_t' \frac{dR_p^*}{d\tau} \right]$$

If F_p is log concave, then

$$\frac{dR_t^*}{dN} = \frac{1}{X_t} \left[-\frac{\gamma}{r} \mu_p' \mu_t' - \gamma \frac{(N-\phi\tau)}{r} \mu_p'' \mu_t' \frac{dR_p^*}{dN} \right] > 0$$

$$\frac{dR_t^*}{dc_0} = \frac{1}{X_t} \left[-\gamma \frac{(N-\phi\tau)}{r} \mu_p'' \mu_t' \frac{dR_p^*}{dc_0} \right] > 0$$

$$\frac{dR_t^*}{dq} = \frac{1}{X_t} \left[-\gamma \frac{(N-\phi\tau)}{r} \mu_p'' \mu_t' \frac{dR_p^*}{dq} \right] > 0 \quad \frac{dR_t^*}{dc} = \frac{1}{X_t} (1-e^{-r\tau}) > 0$$

$$\frac{dR_t^*}{dw} = \frac{1}{X_t} \left[(1 - e^{-r\tau}) - \gamma \frac{(N - \phi\tau)}{r} \mu_p'' \mu_t \frac{dR_p}{dw} \right] > 0$$

$$\frac{dR_t^*}{d\phi} = \frac{1}{X_t} \left[\frac{\gamma\tau}{r} \mu_p' \mu_t - \gamma \frac{(N - \phi\tau)}{r} \mu_p'' \mu_t \frac{dR_p}{d\phi} \right] < 0$$

Proof of Proposition 3. If F_t is log-concave, it will be the case that

$$(\mu_t')^2 - \mu_t'' \mu_t > 0$$

We will use this result repeatedly below.

A) Effect of θ_0 . Taking the derivative of (20) with respect to θ_0 reveals that $d\bar{H}_t/d\theta_0$ has the same sign as

$$\mu_t' - \mu_p' \mu_t'' \frac{1}{X_t} \frac{\gamma(N - \phi\tau)}{r} \mu_t$$

Using the definition of X_t from Proposition 2 and the fact that μ_p' and $\mu_t' < 0$, it can be shown that the last equation is negative because

$$\frac{\gamma(N - \phi\tau)}{r} [(\mu_t')^2 - \mu_t'' \mu_t] > -\frac{\mu_t'}{\mu_p'}$$

Effect of c . Using the expression for dR_t^*/dc , it can be shown that

$$\frac{d\bar{H}_t}{dc} = \gamma(N - \phi\tau) \left[\mu_p' \mu_t'' \frac{dR_t}{dw} \right] < 0$$

Effect of ϕ . Using the expression for $dR_t^*/d\phi$ and the definition of X_t , it can be shown that $d\bar{H}_t/d\phi$ has the same sign as

$$\begin{aligned} & -\gamma\tau \mu_p' \mu_t' - \frac{\gamma^2 \tau (N - \phi\tau)}{r} \mu_p'^2 [\mu_t'^2 - \mu_t'' \mu_t] \\ & + \gamma(N - \phi\tau) \mu_p'' \mu_t' \frac{dR_p^*}{d\phi} + \mu_p'' \mu_p' \frac{dR_p^*}{d\phi} \frac{[\gamma(N - \phi\tau)]^2}{r} [\mu_t'^2 - \mu_t'' \mu_t] \end{aligned}$$

Using the fact that $\mu_p'' > 0$, it can be verified that each term in the last expression is negative.

Effect of τ . Using the expression for $dR_t^*/d\tau$ and the definition of X_t , it can be shown

that $d\bar{H}_t/d\tau$ has the same sign as

$$\begin{aligned} & -\gamma\phi\mu'_p\mu'_t - \frac{\gamma^2\phi(N-\phi\tau)}{r}\mu_p'^2[\mu_t'^2 - \mu_t''\mu_t] \\ & + \gamma(N-\phi\tau)\left\{\mu_p''\mu_t'\frac{dR_p^*}{d\tau} + \mu_p''\mu_p'\frac{dR_p^*}{dT}\frac{\gamma(N-\phi\tau)}{r}(\mu_t'^2 - \mu_t''\mu_t)\right. \\ & \left. + \mu_p'\mu_t''[re^{-r\tau}(w+M)]\right\} \end{aligned}$$

It can be verified that each term in the last expression is negative. Because

$$\frac{dT}{d\tau} = \frac{-1}{\bar{H}_t^2} \frac{d\bar{H}_t}{d\tau} + 1$$

duration increases with τ .

B) Effect of c_0 . The sign of $d\bar{H}_t/dc_0$ is the same as the sign of

$$\mu_p''\mu_t'\frac{dR_p^*}{dc_0}$$

Because $dR_p^*/dc_0 < 0$, this is positive, implying a smaller duration of trials.

Effect of q . The sign of $d\bar{H}_t/dq$ is the same as the sign of

$$\mu_p''\mu_t'\frac{dR_p^*}{dq}$$

Because $dR_p^*/dq < 0$, this is positive, implying a smaller duration of trials.

Effect of M . The sign of $d\bar{H}_t/dM$ is the same as the sign of

$$\frac{dH_t}{dM} = \mu_p'\mu_t''\frac{dR_t^*}{dM} > 0$$

Because $dR_p^*/dM < 0$, this is positive, implying a smaller duration of trials.

Effect of γ . Using the expression for $dR_t^*/d\gamma$ and the definition of X_t , it can be shown that $d\bar{H}_t/d\gamma$ has the same sign as

$$-\frac{\gamma(N-\phi\tau)}{r}\mu_p'\mu_t''[\mu_t'^2 - \mu_t''\mu_t] - \mu_t'$$

It can be verified that each term in the last expression is positive, implying a smaller duration of trials.

Effect of N . Using the expression for dR_t^*/dN and the definition of X_t , it can be shown that $d\bar{H}_t/dN$ has the same sign as

$$\begin{aligned} & \mu'_p \mu'_t + \frac{\gamma(N - \phi\tau)}{r} \mu_p'^2 \left[(\mu'_p \mu'_t)^2 - \mu''_t \mu_t \right] \\ & + (N - \phi\tau) \left[\mu''_p \mu'_t \frac{dR_p^*}{dN} + \mu''_p \mu'_p \frac{dR_p^*}{dN} \frac{\gamma(N - \phi\tau)}{r} (\mu_t'^2 - \mu''_t \mu_t) \right] \end{aligned}$$

Using $dR_p^*/dN < 0$, it can be verified that each term in the last expression is positive, implying a smaller duration of trials.

C) Effect of r . Using the expression for dR_t^*/dr and the definition of X_t , it can be shown that $d\bar{H}_t/dr$ has the same sign as

$$\begin{aligned} = & \mu''_p \left(\mu'_t \frac{dR_p^*}{dr} \right) + \mu''_p \left(\mu'_p \frac{dR_p^*}{dr} \right) \frac{\gamma(N - \phi\tau)}{r} [\mu_t'^2 - \mu'_t \mu_t''] + \mu_p'^2 \mu''_t \mu_t \frac{\gamma(N - \phi\tau)}{r^2} \\ & + \mu'_p \mu_t'' \tau e^{-r\tau} (w + M) \end{aligned}$$

Each term of this last expression except $\mu'_p \mu_t'' \tau e^{-r\tau} (w + M)$ is positive. The whole expression is positive if

$$Y - \mu'_p \mu_t \frac{\gamma(N - \phi\tau)}{r^2} > \tau e^{-r\tau} (w + M) \quad (21)$$

where

$$Y = \frac{-\mu_p''}{\mu'_p \mu_t''} \left\{ \left(\mu'_t \frac{dR_p^*}{dr} \right) + \left(\mu'_p \frac{dR_p^*}{dr} \right) \frac{\gamma(N - \phi\tau)}{r} [\mu_t'^2 - \mu'_t \mu_t''] \right\} > 0$$

(21) holds so long as

$$w + M < \frac{1}{\tau e^{-r\tau}} \left[Y - \mu'_p \mu_t \frac{\gamma(N - \phi\tau)}{r^2} \right]$$

D) Effect of w . Using the expression for dR_t^*/dw , it can be shown that

$$\frac{d\bar{H}_t}{dw} = \gamma(N - \phi\tau) \left[\mu_p'' \mu_t' \frac{dR_p^*}{dw} + \mu_p' \mu_t'' \frac{dR_t^*}{dw} \right]$$

which has the same sign as

$$-\mu_p'' \mu_t' \frac{dR_p^*}{dw} + \mu_p' \mu_t'' \frac{1}{D_t} \left[(1 - e^{-r\tau}) - \gamma \frac{(N - \phi\tau)}{r} \mu_p'' \mu_t' \frac{dR_p^*}{dw} \right]$$

The effect through R_p^* is positive

$$\mu_p'' \mu_t' \frac{dR_p^*}{dw} + \frac{dR_p^*}{dw} \frac{\gamma(N - \phi\tau)}{r} \mu_p'' \mu_t' [\mu_t' \mu_t' - \mu_t'' \mu_t] > 0$$

But the direct effect on R_t^* is negative

$$\mu_p' \mu_t'' \frac{1}{D_t} (1 - e^{-r\tau}) < 0$$

The overall sign is ambiguous.

E) Follows directly from $\zeta(v, H) = n/H$.

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Tables and figures

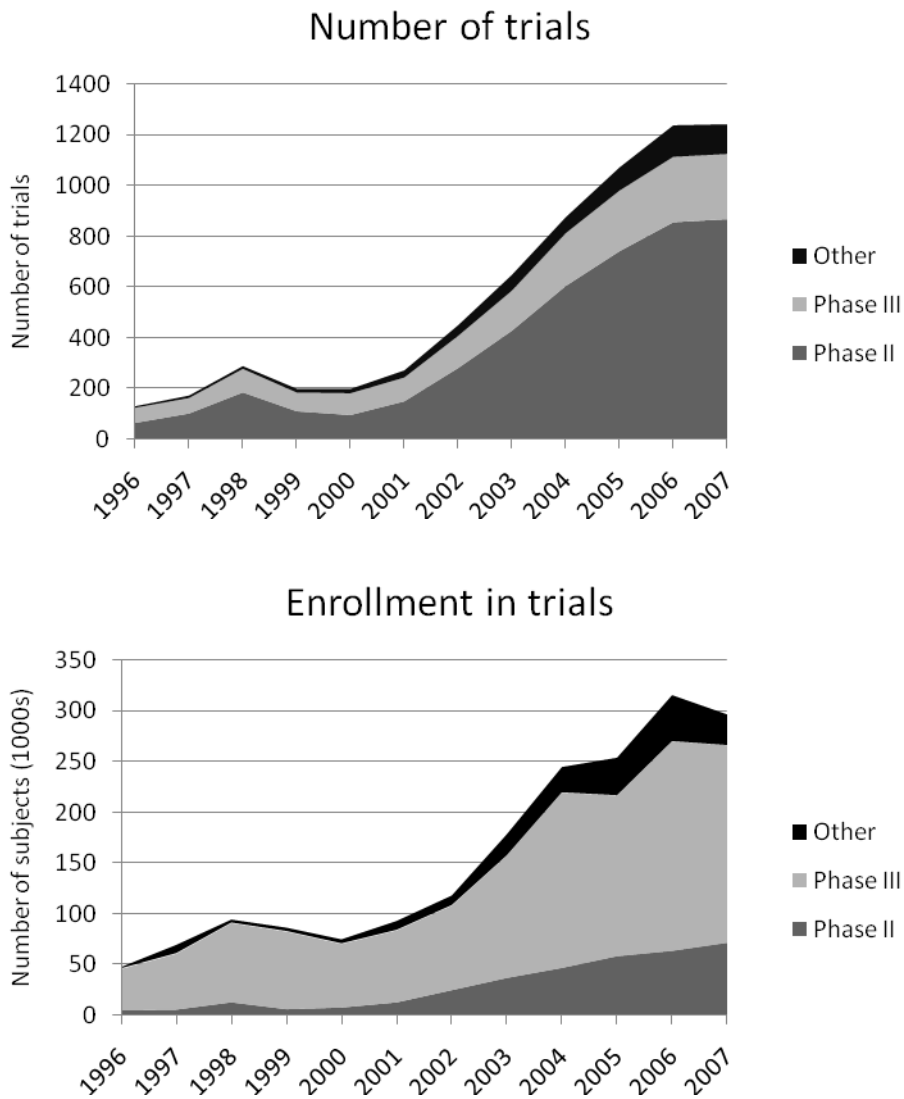


Figure 1. Number and enrollment in new clinical trials, by year started and phase.

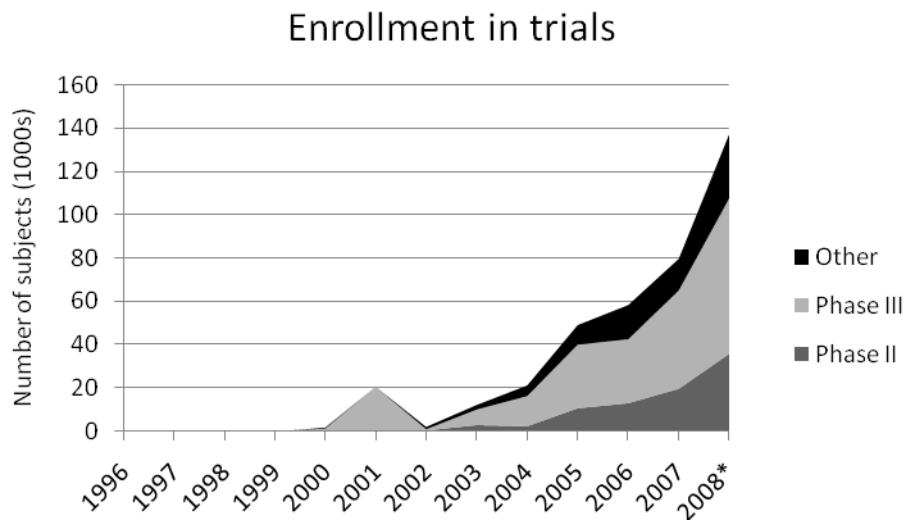
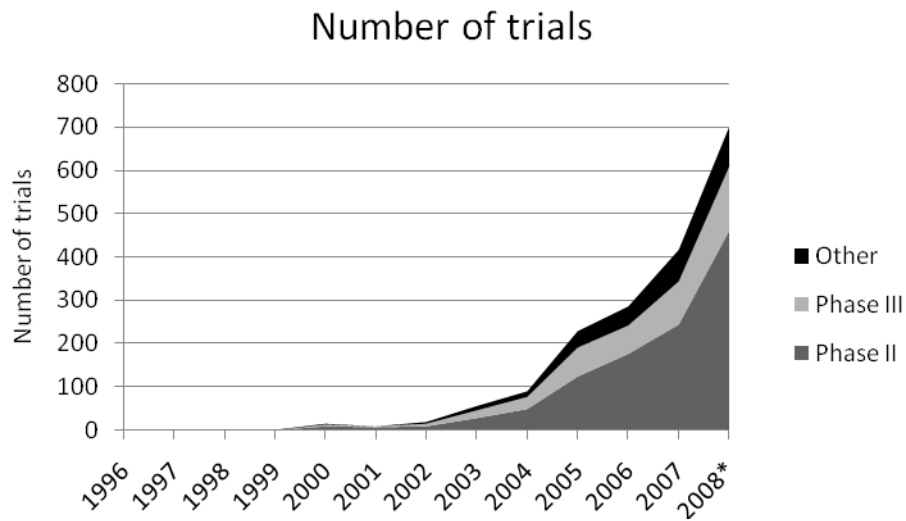


Figure 2. Number and enrollment in completed clinical trials, by year of completion and phase (* includes anticipated completions before 12/31/2008).

Table 1. Size of cancer trials, by year and date.

Year	Median enrollment				Median
	Phase II	Phase II/III	Phase III	Phase IV	
1996	40	98	384	317	100
1997	40	137	404	771	67
1998	40	452	430	45	75
1999	41	200	450	117	87
2000	53	100	451	175	120
2001	50	214	405	175	91
2002	60	200	363	152	90
2003	55	175	385	126	80
2004	50	176	400	80	66
2005	50	140	360	110	70
2006	50	112	438	118	64
2007	52	137	380	80	70
2008*	60	245	325	100	80
Median	50	144	400	108	74

* For trials through 5/6/08.

** Includes censored trials.

Table 2. Specific cancers targeted by trials in sample.

Type of cancer	Fraction of trials	Std. dev.
Adenocarcinoma	0.14	0.34
Breast Neoplasms	0.14	0.34
Carcinoma	0.09	0.28
Carcinoma, Non-Small-Cell Lung	0.27	0.45
Colorectal Neoplasms	0.06	0.24
Digestive System Neoplasms	0.15	0.36
Endocrine Gland Neoplasms	0.07	0.26
Gastrointestinal Neoplasms	0.15	0.36
Genital Neoplasms, Female	0.05	0.22
Genital Neoplasms, Male	0.07	0.26
Neoplasms, Germ Cell and Embryonal	0.10	0.29
Neoplasms, Glandular and Epithelial	0.27	0.44
Intestinal Neoplasms	0.06	0.24
Leukemia	0.05	0.23
Leukemia, Lymphoid	0.06	0.24
Leukemia, Myeloid	0.11	0.31
Lung Neoplasms	0.10	0.31
Lymphoma	0.08	0.27
Lymphoma, Non-Hodgkin	0.12	0.32
Neoplasm Metastasis	0.10	0.31
Neuroectodermal Tumors	0.09	0.29
Prostatic Neoplasms	0.07	0.25
Thoracic Neoplasms	0.11	0.31
Urogenital Neoplasms	0.16	0.37

Notes. Fractions add up to more than 1 because some trials cover multiple cancers. Moreover, not all cancers are tabulated. Only cancers covered by trials with a total of more than 1000 enrollees are tabulated.

Table 3. Summary statistics by phase.

Variable	Phase II		Phase II/III		Phase III		Phase IV	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Trial design								
Open label	0.77	0.42	0.58	0.49	0.48	0.50	0.57	0.50
Active control	0.15	0.35	0.38	0.49	0.47	0.50	0.33	0.47
Single group	0.41	0.49	0.28	0.45	0.10	0.30	0.30	0.46
Uncontrolled	0.27	0.44	0.19	0.39	0.07	0.26	0.22	0.41
Blinded	0.06	0.24	0.25	0.43	0.19	0.39	0.21	0.41
Placebo controlled	0.06	0.24	0.23	0.42	0.17	0.38	0.17	0.38
Randomized	0.24	0.43	0.68	0.47	0.88	0.33	0.56	0.50
Competing								
Trials	4,245	1,301	4,072	1,459	3,919	1,441	3,834	1,513
Enrollments (thous.)	1,491	360	1,441	408	1,397	407	1,377	428
Trials (same cancer)	955	707	817	692	781	651	558	615
Enrollments (same cancer, thous.)	338	242	290	235	305	237	220	234
Trials in clinicaltrials.gov on start date	3,431	2,390	3,421	2,339	2,867	2,411	3,466	2,333
Government funded	0.33	0.47	0.15	0.36	0.25	0.43	0.08	0.27
Industry funded	0.40	0.49	0.47	0.50	0.38	0.49	0.49	0.50
Adult subjects	0.98	0.12	0.99	0.07	0.97	0.16	0.97	0.17
Child subjects	0.16	0.36	0.18	0.39	0.22	0.42	0.20	0.40

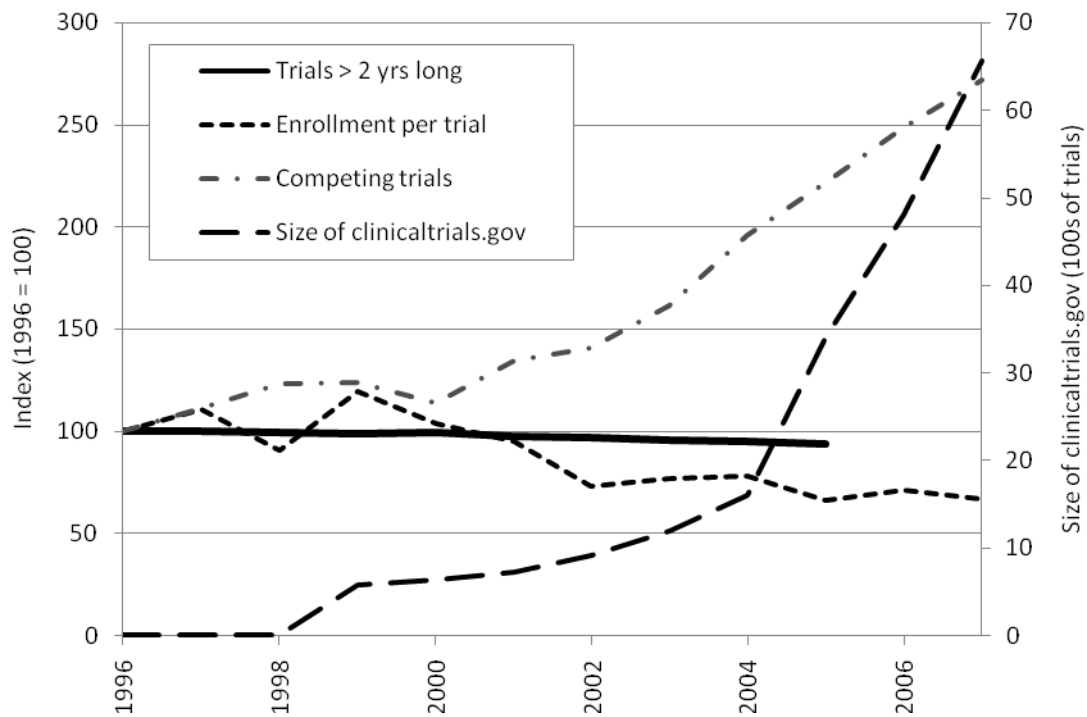


Figure 3. Trends in duration, enrollment, number of competing trials, 1996-2007.

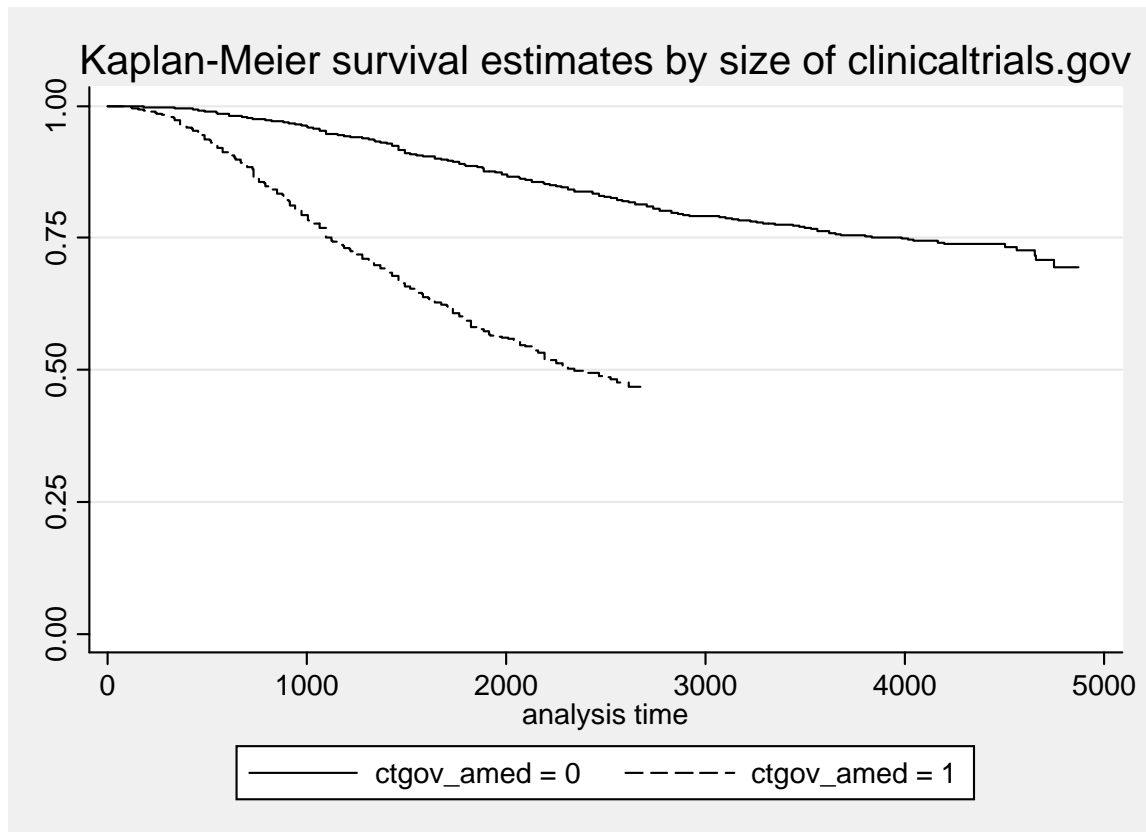


Figure 4. Survival curves by matching technology (size of clinicaltrials.gov).

Kaplan-Meier survival estimates by level of competition

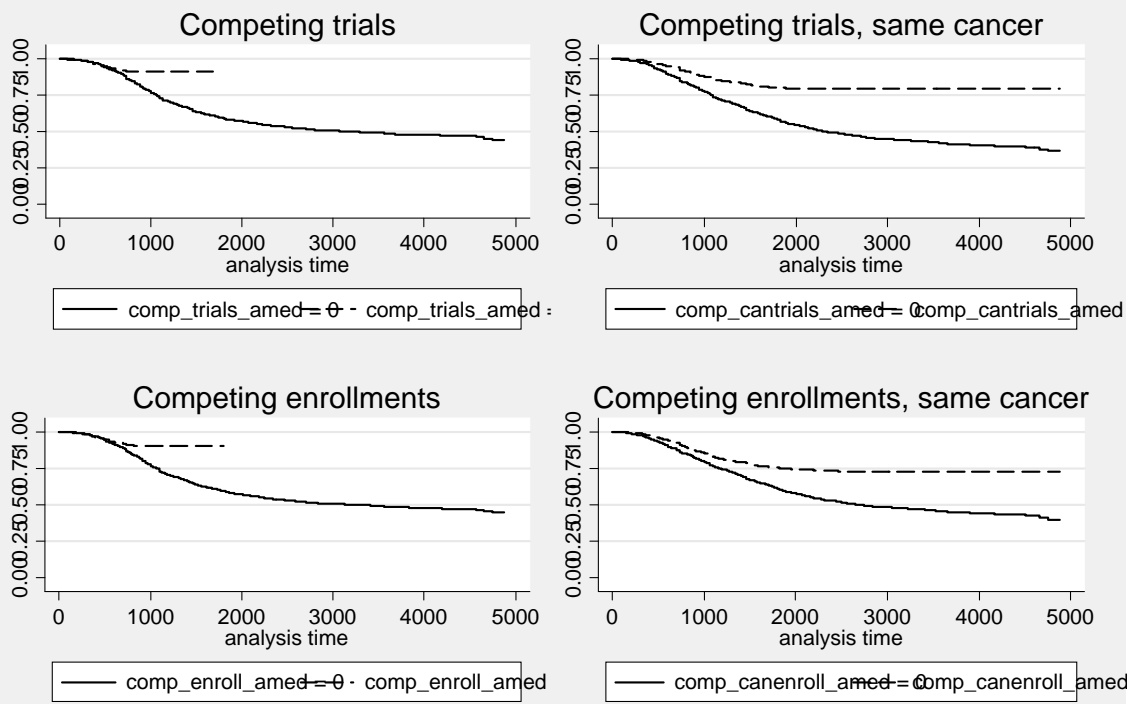


Figure 5. Survival curves by level of competition.

Table 4. Estimates from advanced failure time model with log-normal survival time.

Variable	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Log enrollment	0.035*** (0.000)	0.023*** (0.007)	0.032*** (0.000)	0.052*** (0.000)	0.069*** (0.000)	0.069*** (0.000)	0.071*** (0.000)	0.072*** (0.000)
Competing trials								
Log trials, all cancers	-0.210 (0.643)	-0.212 (0.633)	1.284*** (0.002)	1.283*** (0.001)	1.146*** (0.002)	1.137*** (0.002)	1.268*** (0.001)	1.255*** (0.001)
Log enrollment, all cancers	1.263* (0.077)	1.242* (0.076)	0.073 (0.909)	0.061 (0.922)	0.124 (0.830)	0.116 (0.840)	-0.000 (1.000)	-0.007 (0.990)
Log trials, same cancer	0.119*** (0.000)	0.122*** (0.000)	0.089*** (0.000)	0.081*** (0.001)	0.063*** (0.008)	0.066 (0.244)	0.068*** (0.004)	0.074 (0.178)
Log enrollment, same cancer	-0.055*** (0.000)	-0.055*** (0.000)	-0.037*** (0.004)	-0.035*** (0.007)	-0.025** (0.044)	-0.030 (0.283)	-0.028** (0.021)	-0.035 (0.209)
Design variables								
Single Group or Uncontrolled in Phase II		-0.102*** (0.000)	-0.054*** (0.004)	-0.107*** (0.000)	-0.015 (0.491)	-0.020 (0.350)	-0.013 (0.534)	-0.018 (0.398)
Open Label in Phase III		-0.025 (0.392)	0.012 (0.701)	0.068** (0.050)	0.083** (0.017)	0.073** (0.032)	0.083** (0.017)	0.073** (0.032)
Active Control in Phase III		-0.030 (0.376)	-0.027 (0.445)	-0.001 (0.972)	-0.016 (0.648)	-0.019 (0.584)	-0.016 (0.650)	-0.019 (0.598)
Log trials in clinicaltrials.gov			-0.913*** (0.000)	-0.904*** (0.000)	-0.832*** (0.000)	-0.828*** (0.000)	-0.804*** (0.000)	-0.800*** (0.000)
Phase II (0/1)				0.178*** (0.000)	0.134*** (0.000)	0.124*** (0.000)	0.133*** (0.000)	0.123*** (0.000)
Phase III (0/1)				-0.002 (0.961)	-0.011 (0.752)	-0.008 (0.829)	-0.015 (0.665)	-0.012 (0.739)
Adults enrolled (0/1)					-0.101** (0.039)	-0.124** (0.011)	-0.095* (0.051)	-0.118** (0.015)
Children enrolled (0/1)					-0.010 (0.690)	-0.028 (0.292)	-0.014 (0.585)	-0.033 (0.220)
Funded by govt (0/1)					0.233*** (0.000)	0.231*** (0.000)	0.226*** (0.000)	0.224*** (0.000)
Funded by industry (0/1)					-0.107*** (0.000)	-0.102*** (0.000)	-0.104*** (0.000)	-0.100*** (0.000)
Constant	-10.662* (0.099)	-10.273 (0.106)	1.663 (0.780)	1.590 (0.783)	1.277 (0.811)	1.473 (0.779)	1.801 (0.721)	1.997 (0.686)
Log sigma	-0.817*** (0.000)	-0.819*** (0.000)	-0.831*** (0.000)	-0.839*** (0.000)	-0.863*** (0.000)	-0.871*** (0.000)	-0.869*** (0.000)	-0.877*** (0.000)
Year active fixed effects	Y	Y	Y	Y	Y	Y	Y	Y
Year registered fixed effects							Y	Y
Cancer fixed effects						Y		Y
Observations	7183	7183	7183	7183	7183	7183	7183	7183

Note: Robust standard errors below coefficients. *** indicates $p < 0.01$, ** $p < 0.05$, * $p < 0.1$.

Table 5. Predicted duration of trials under different levels of competition.

	Size of clinical-trials.gov	Trials, all cancers	Prediction for 2007 trials			Duration per 10 subjects (days)
			Log duration (days)	Std dev log duration	Duration (months)	
2002 matching technology	916		8.47	0.11	173.4	218
2007 matching technology	6567		6.89	0.02	35.9	45
Percent change	-				383%	383%
1996 competition level		2000	5.29	0.19	7.2	9
2007 competition level		5442	6.89	0.02	35.9	45
Percent change		172%			-80%	-80%

Notes. Recruits per month based on average enrollment of 239 in trials started in 2007.