

Disclosure and the Pace of Drug Development

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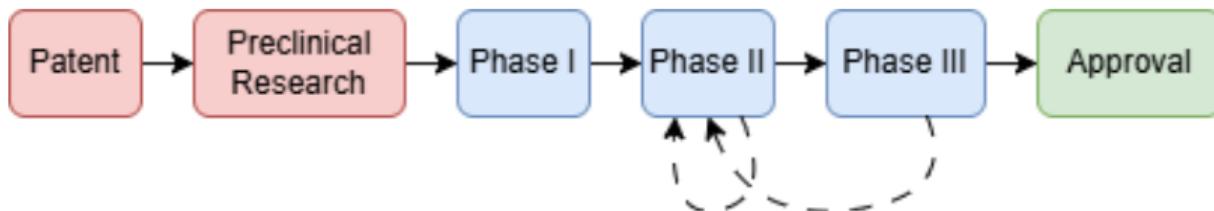
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§Yale University

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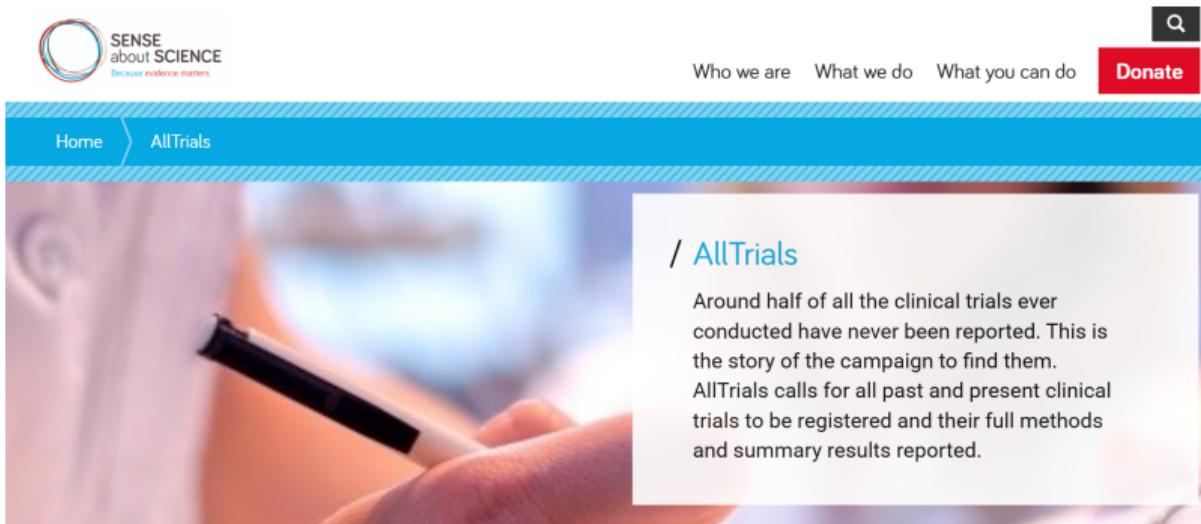
Clinical Trials: Regulation



- In the United States, clinical research and the approval on new drugs is regulated by the FDA.
- In 2007, the FDA Amendments Act required the public registration of all Phase II+ trials (clinicaltrials.gov).
 - ▶ Molecule under investigation, target disease, trial protocol, completion date, etc.
- **No explicit mandate to disclose results.**

Clinical Trials: Disclosure

- Lack of trial results disclosure is a source of controversy.



nature

Social Selection | Published: 16 April 2015

WHO calls for full disclosure of clinical trials

Clinical Trials: Disclosure

- FDA implements the “Final Rule” on clinical trial results disclosure in 2017.
 - ▶ Implementation occurred after a public comment period in 2015-16.
- Results of all Phase II+ trials must disclosed **one year** after trial completion.
 - ▶ Non-compliance is punishable by daily fines.

Information Externalities

- Existing discussion of disclosure policy focuses on the benefits:
 - ▶ Positive **information externality** of research.
 - ▶ More disclosure allows faster learning **across firms**.
 - ▶ Cumulative research; Reduction in duplicative investment.
- However, increased disclosure may also lead to slower research because of a **free-riding** incentive:
 - ▶ If firms anticipate learning from rivals' trials of "similar" drugs.
 - ▶ Plausible given the high cost of running trials ($\sim \$10$ million for Phase II) and the high failure rate ($\sim 70\%$).
- In addition, disclosure might allow competitors to "catch up", reducing the expected value of investment.

Research Questions

- ① What was the effect of the final rule on **results disclosure**?
- ② What was the effect of the final rule on **investment in clinical trials**?
- ③ How should **information disclosure policy** be designed?

To answer these questions we analyze data on the history of all industry-sponsored clinical trials from 2010 to 2020.

Preliminary Findings

- ① Final Rule increases disclosure of trial results around the one-year deadline.
 - ▶ Mostly unsuccessful trials.
- ② Phase 2 research is around 33% *slower* after the policy change.
 - ① Length of P2 trials.
 - ② Time between P2 and P1.
 - ③ Opening of sites.
- ③ Heterogeneous effects consistent with free-riding mechanism.
 - ① Slowdown is more significant for drugs where the potential information externality is larger.
- ④ Build a structural model of the pharmaceutical firm's dynamic trial investment problem.
 - ① Policy functions consistent with descriptive findings.
 - ② To do: estimate model to quantify the effects of counterfactual disclosure policy.

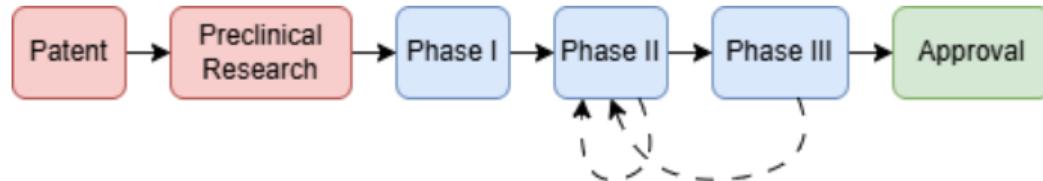
Outline

- ① Data
- ② Descriptive Patterns
- ③ Mechanisms
- ④ Dynamic Model of Trial Investment

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Data



① Citeline Pharma Projects and TrialTrove (2010-2020)

- ▶ Drug level: molecule, mechanism of action, history of patent, trials, and approval.
- ▶ Trial level: sponsoring firm, target disease, date started, date complete, date results published.
- ▶ For trials with reported results: outcome measures.

② Within-trial investment data collected from clinicaltrials.gov change logs.

- ▶ Changes in the number of active and recruiting **sites** within each trial over time.
- ▶ For now: only Phase II oncology.

Data: Clinicaltrials.gov

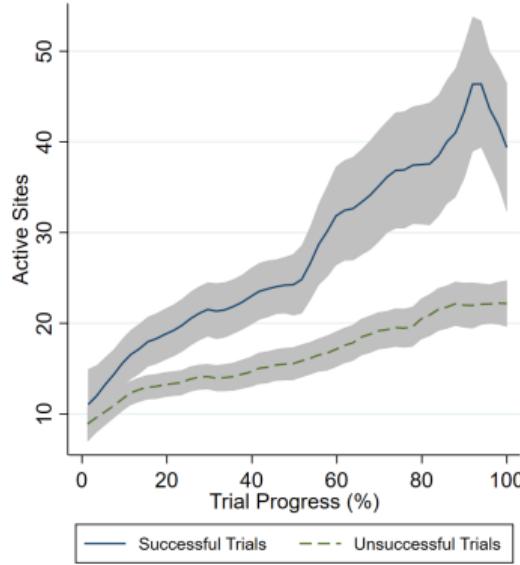
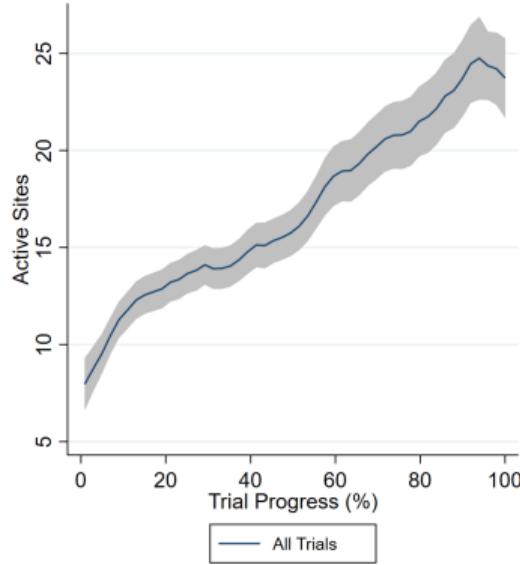
Study Status

| | |
|--|---------------------------|
| Record Verification | 2018-09-11 |
| Overall Status | Active, not recruiting |
| Study Start | 2016-06-01 [Actual] |
| Primary Completion | 2018-11-15 [Estimated] |
| Study Completion | 2019-01-31 [Estimated] |
| First Submitted | 2016-04-28 |
| First Submitted that Met QC Criteria | 2016-04-28 |
| First Posted | 2016-04-29 [Estimated] |
| Last Update Submitted that Met QC Criteria | 2018-09-11-14:06 |
| Last Update Posted | 2018-09-11-17:07 [Actual] |

Location

- Oceanside, California, United States, 92056
Facility: North County Oncology
- Redondo Beach, California, United States, 90277
Facility: Torrance Health Association
- San Luis Obispo, California, United States, 93401
Facility: PHC-SLO Oncology and Hematology
- Valencia, Spain, 46009
Facility: Fundacion Instituto Valenciano de Oncologia
- Valencia, Spain, 46010
Facility: Hospital Clinico Universitario de Valencia
- Valencia, Spain, 46015
Facility: Hospital Universitari Arnau de Vilanova de Valencia

Data: Clinicaltrials.gov



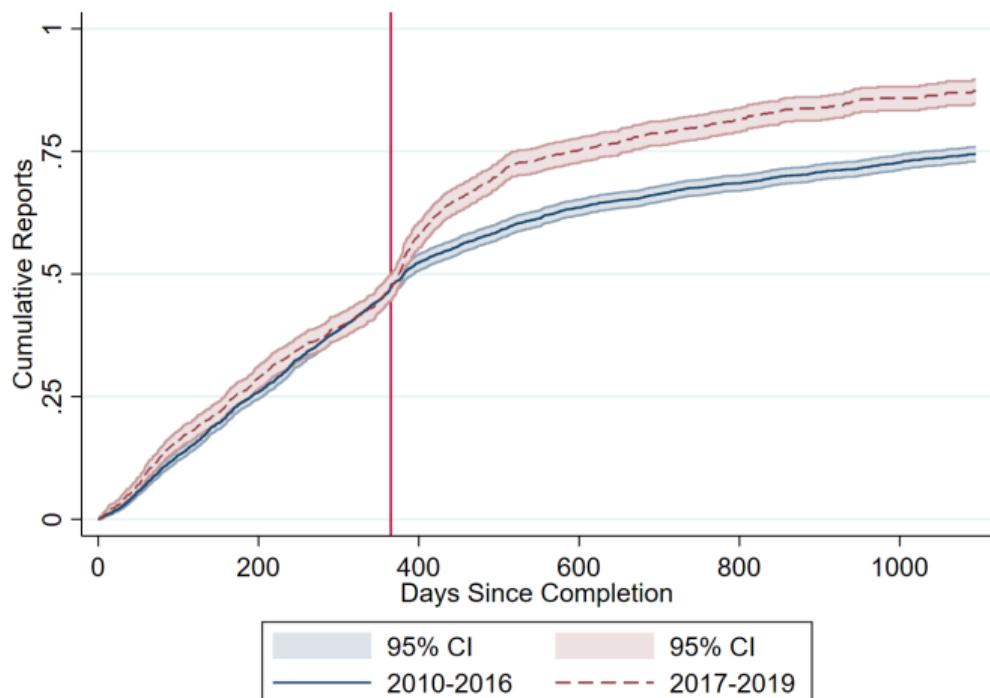
- Trial progress: % of time from opening of first site to trial completion.
- Unsuccessful trials add fewer sites (also terminate earlier).
- Decision to scale up trial likely responds to interim results.
 - ▶ Note: “triple-blinding” is rare.

Outline

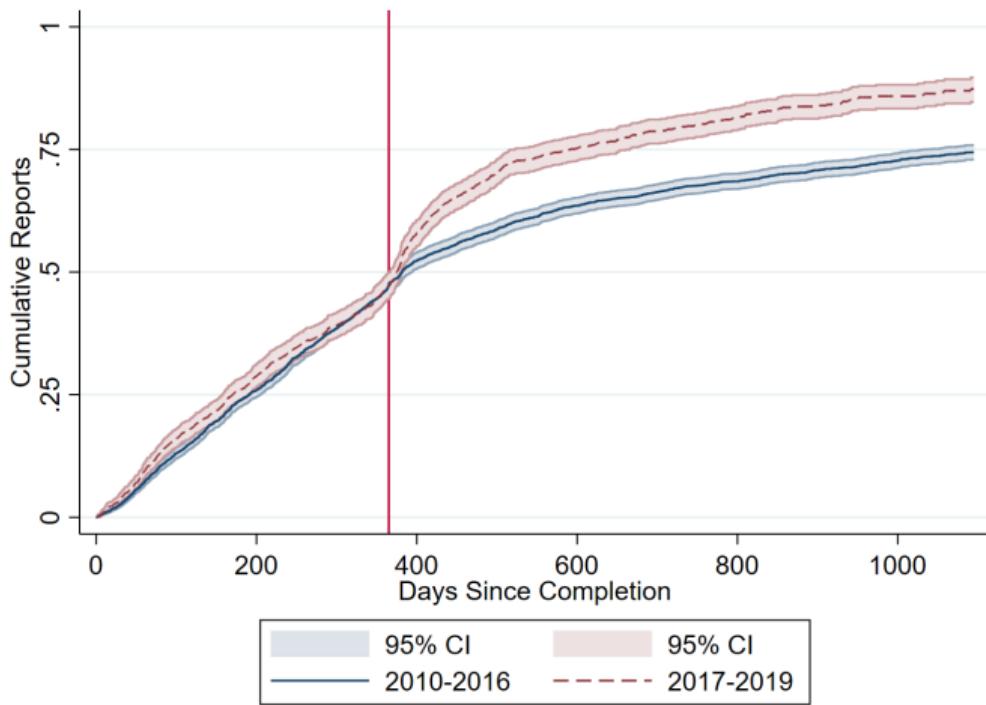
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- ③ Mechanisms
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Does Disclosure Policy Bite?

- Plot the cumulative probability that a trial is reported by days since trial completion for the pre- and post-policy periods.
- Kaplan-Meier curves account for truncation of the data.

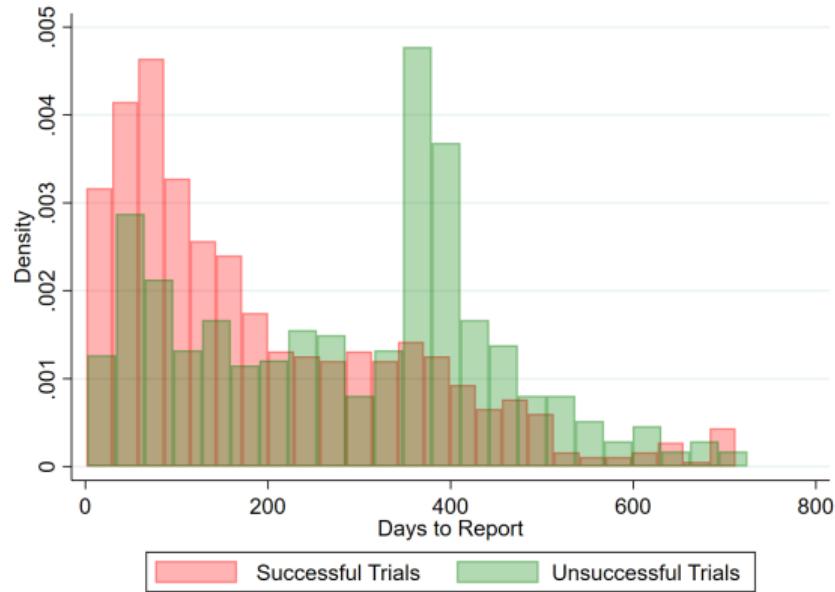


Does Disclosure Policy Bite?



- Probability of disclosure by two years since completion increases from $\sim 60\%$ to $\sim 80\%$.
- Mass of disclosure around the one year deadline.

Does Disclosure Policy Bite?

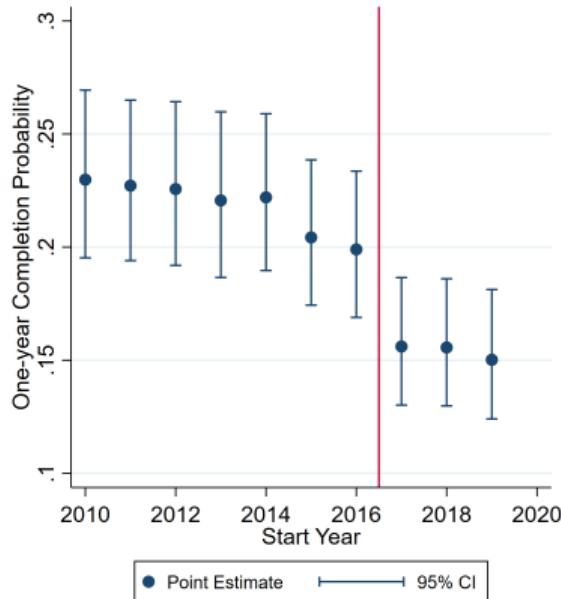
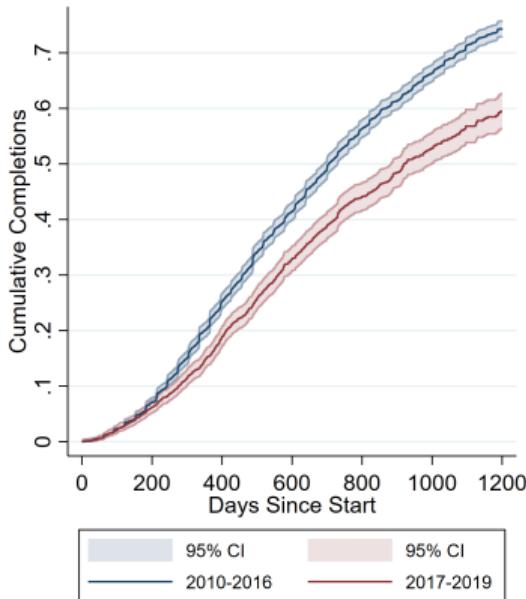


- Most of this mass is disclosure of unsuccessful trials.
- Why do firms have more of an incentive to delay disclosure of failures?
 - ▶ Stock price? Recruiting patients? Manipulating competitors' beliefs?

Changes in Investment

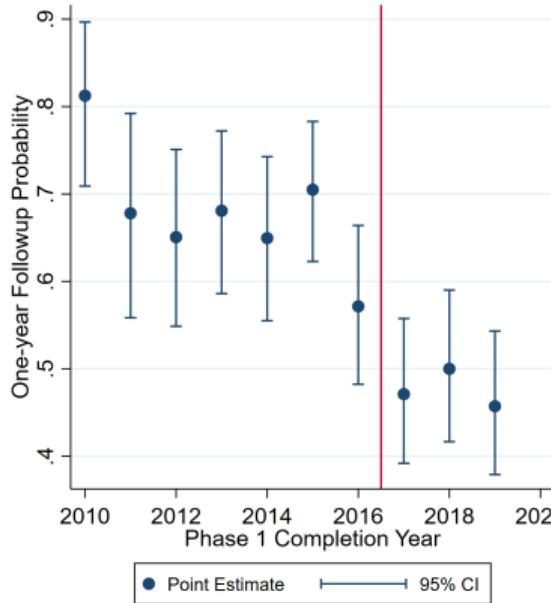
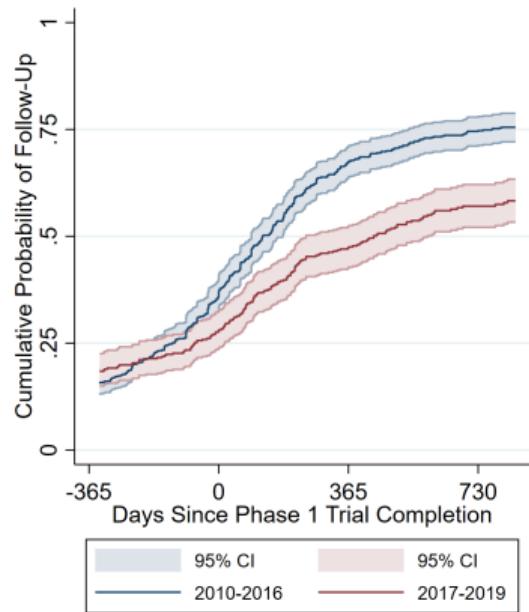
- Final Rule on disclosure brings information (especially on failures) forward in time.
- How does this change in the information environment affect trial investment?
- Time-series evidence on three measures of the **pace of research**:
 - ① Time to complete Phase 2 trials.
 - ② Time to start Phase 2 after end of Phase 1.
 - ③ Investment in trial sites within Phase II trials.
- Sample includes all industry-sponsored Phase 2 trials.
 - ▶ No control group (yet).

Changes in Investment 1: Time to Complete



- Median time to complete increases from around 750 days to around 900 days.
- One-year completion rate falls discontinuously after policy change.

Changes in Investment 2: Time to Start



- Median time between end of Phase 1 and start of Phase 2 increases from around 50 days to around 400 days.
- One-year “follow up” probability falls discontinuously.

Time to Complete & Time to Start

- To test whether these changes are driven by composition of trials, run Cox proportional hazard models controlling for disease category.

Table A2: Cox Model Estimates

| Start Year | Compete | Complete | Start | Start |
|------------|---------------------|---------------------|---------------------|---------------------|
| 2011 | 1.023 (0.063) | 1.043 (0.063) | | |
| 2012 | 0.967 (0.064) | 0.935 (0.064) | 1.003 (0.180) | 1.025 (0.181) |
| 2013 | 0.952 (0.065) | 0.997 (0.065) | 0.948 (0.178) | 0.975 (0.180) |
| 2014 | 0.937 (0.064) | 0.912 (0.064) | 0.842 (0.177) | 0.851 (0.179) |
| 2015 | 0.903 (0.063) | 0.903 (0.063) | 0.827 (0.172) | 0.831 (0.173) |
| 2016 | 0.714*** (0.066) | 0.761*** (0.066) | 0.679* (0.176) | 0.668* (0.178) |
| 2017 | 0.524*** (0.069) | 0.613*** (0.069) | 0.483*** (0.174) | 0.487*** (0.176) |
| 2018 | 0.599*** (0.074) | 0.640*** (0.074) | 0.466*** (0.180) | 0.497*** (0.183) |
| 2019 | 0.524*** (0.092) | 0.564*** (0.093) | 0.430*** (0.181) | 0.429*** (0.183) |
| Disease FE | NO | YES | NO | YES |

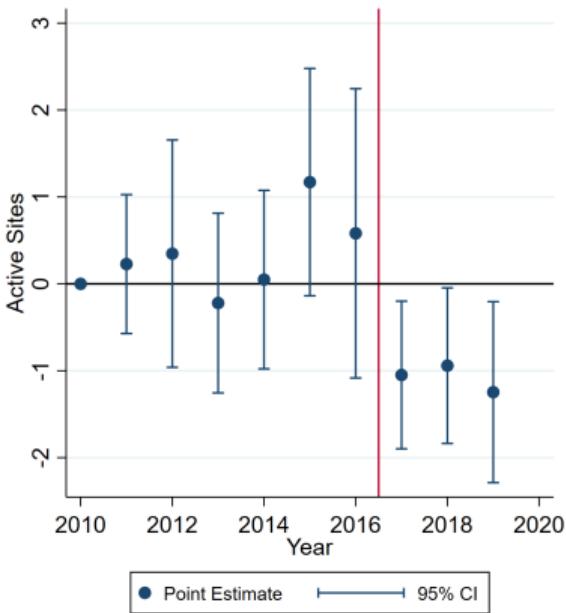
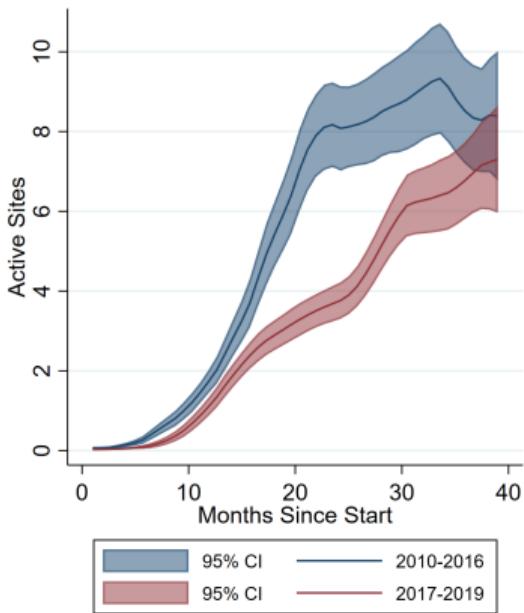
Changes in Investment 3: Trial Sites

- Does the slowdown in Phase 2 start/completion reflect a reduction in trial-specific investment?
 - ▶ Alternatively, trials could be getting slower because drug efficacy is becoming “harder” to learn.
- Direct measure of investment: number of sites opened t months since the start of the trial.
- For trial-month (j, t) let $\tau(j, t)$ be months since trial start and $y(t, j)$ be the year of a trial-month observation.

$$Sites_{jt} = \sum_{y=2011}^{2019} \alpha_y 1(y(t, j) = y) + \sum_{\tau=1}^T \gamma_\tau 1(\tau(j, t) = \tau) + \varepsilon_{jt}$$

- Coefficients α_y measure the average number of trial sites opened in year y relative to baseline year (2010), controlling for trial duration.

Changes in Investment 3: Trial Sites



- Significant reduction in site investment in the post-policy period.
- Consistent with longer time to complete Phase 2.

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Cross-Drug Learning

- Significant decline in trial investment contemporaneous with increased disclosure of trial results.
 - Hypothesis: cross-drug information externality leads to delayed investment due to free-riding.
 - ▶ If drugs A and B belong to the same “technology group”, the results of a trial on drug A are informative for drug B .
 - ▶ Condition decision to invest in trial B on the outcome of trial A → free riding, delay.
 - ▶ More disclosure (of failures) → slower investment.
- ➊ Is there evidence of cross-drug learning from results disclosure?
 - ➋ Is the slowdown in investment larger from drugs where we expect the information externality to be more important?

Cross-Drug Learning

- For each drug j , define two groups of related drugs:
 - ▶ $j \in M_j$, where M_j is the set of drugs with the same **Mechanism of Action**.
 - ▶ $j \in T_j$, where T_j is the set of drugs in the same **Therapeutic Class** (target disease).
- How does the decision to start a trial respond to the results of trials in groups M_j and T_j ?

$$\begin{aligned} Start_{jt} = & \beta_1^{Same} Suc_{jt} + \beta_2^{Same} UnSuc_{jt} + \beta_1^{TC} \sum_{k \in T_j} Suc_{kt} + \beta_2^{TC} \sum_{k \in T_j} UnSuc_{kt} \\ & + \beta_1^{MOA} \sum_{k \in M_j} Suc_{kt} + \beta_2^{MOA} \sum_{k \in M_j} UnSuc_{kt} + \alpha_j + \gamma_t + \epsilon_{jt} \end{aligned}$$

Cross-Drug Learning

Table 3: Response of Trial Start to Results Disclosure

| | | Phase 2 Start | Phase 1 Start | Phase 3 Start |
|--------------------------|----------------------|------------------------|------------------------|------------------------|
| Same Drug | Successful Phase 2 | 0.0104 (0.0080) | 0.0044 (0.0042) | 0.0029** (0.0013) |
| | Unsuccessful Phase 2 | -0.0167*** (0.0052) | -0.0075** (0.0030) | -0.0053*** (0.0012) |
| Same Therapeutic Class | Successful Phase 2 | -0.0108* (0.0064) | -0.0064 (0.0042) | 0.0019 (0.0026) |
| | Unsuccessful Phase 2 | 0.0186** (0.0072) | 0.0084* (0.0045) | 0.0021 (0.0025) |
| Same Mechanism of Action | Successful Phase 2 | 0.0165*** (0.0055) | 0.0081*** (0.0026) | 0.0030* (0.0016) |
| | Unsuccessful Phase 2 | -0.0117*** (0.0041) | -0.0064*** (0.0023) | -0.0022* (0.0013) |
| Time FE | | YES | YES | YES |
| Drug FE | | YES | YES | YES |
| <i>N</i> | | 1,617,366 | 1,617,366 | 1,617,366 |
| <i>R</i> ² | | 0.1892 | 0.0999 | 0.0719 |
| Mean of Dep. Var. | | 0.0098 | 0.0128 | 0.0061 |

- Coefficients measured in standard deviations.
- Results suggest learning within MOA group, consistent with Krieger (2021).

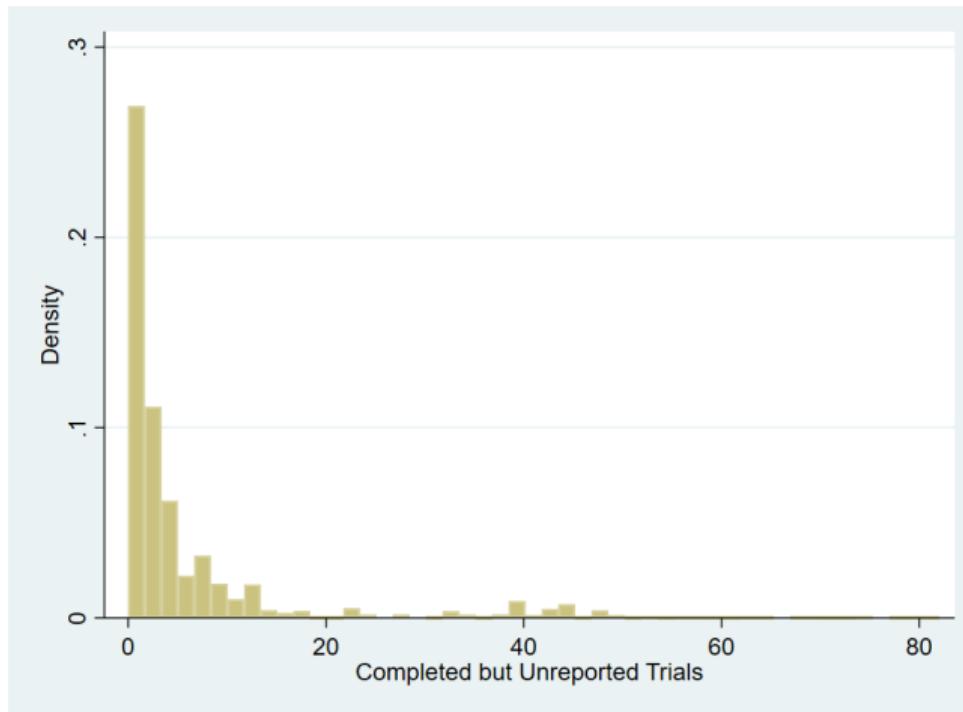
Robustness

Heterogeneous Effects of Policy

- If slowdown of investment is caused by free riding, the effect should be largest for drugs where there is more to learn from other trials.
- Consider drug $j \in M_j$. If $M_j = \{j\}$ and learning only takes place within mechanism group, there are no other trials that could inform drug j .
- Change in the disclosure policy does no affect incentive to invest in drug j *through the free riding channel*.
- For each trial-month (j, t) , count the number of **completed but unreported trials** for drugs in M_j .

Heterogeneous Effects of Policy

- $Unrep_{jt} = 0$ for 28% of observations.
- Significant variation within and across MOA groups.



Heterogeneous Effects of Policy

$$Y_{jt} = \beta_1 Post_t + \beta_2 \log(Unrep_{jt} + 1) + \beta_3 Post_t \log(Unrep_{jt} + 1) + \alpha_{\tau(j,t)} + \gamma_{M_j} + \varepsilon_{jt}$$

$Y_{jt} \in \{\text{Active Sites, Active or Recruiting Sites, Trial Completion}\}.$

Table 4: Responses to Unreported Trials by Policy Period

| | Trial Completion | Active or Recruiting Sites | | Active Sites | |
|---|----------------------|----------------------------|----------------------|----------------------|----------------------|
| Start Year ≥ 2017 | -0.004*** (0.002) | 0.003 (0.002) | -1.375*** (0.473) | 0.543 (0.890) | -1.544*** (0.210) |
| Log Unreported | -0.002** (0.001) | 0.001 (0.001) | -0.890** (0.354) | -0.088 (0.350) | -0.289* (0.156) |
| Log Unreported \times Start ≥ 2017 | | -0.006*** (0.002) | | -1.638*** (0.494) | -0.502** (0.208) |
| Time FE | YES | YES | YES | YES | YES |
| MOA Group FE | YES | YES | YES | YES | YES |
| <i>N</i> | 64,529 | 64,529 | 64,529 | 64,529 | 64,529 |
| Mean of Dep. Variable | 0.018 | 0.018 | 13.408 | 13.408 | 3.813 |

- No significant effect on trial completion for $Unrep_{jt} = 0$.
- For mean value of $\log(Unrep_{jt} + 1)$:
 - ▶ Active sites decrease by 39% of mean.
 - ▶ Probability of completion decreases by 20% of mean.

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Structure of the Dynamic Model of Trial Investment

- Descriptive results are suggestive of cross-drug learning and a free-riding effect on investment.
- To quantify this effect, we build a dynamic model of the firm's trial investment problem.
 - ▶ Decision to add sites → improve precision of signal.
 - ▶ Potential to learn from other trials in same MOA.
- Goal:
 - ▶ Use model disentangle learning effects from changes in the cost of running trials.
 - ▶ Consider counterfactual disclosure rules → optimal policy.

Sketch of the Dynamic Model of Trial Investment

- Drug j in MOA group M has ex-ante unknown **effectiveness** $\lambda_j = \mu_M + \lambda_j^o$.

$$\mu_M \sim N(0, \sigma_M)$$

$$\lambda_j^o \sim N(0, \sigma_\lambda)$$

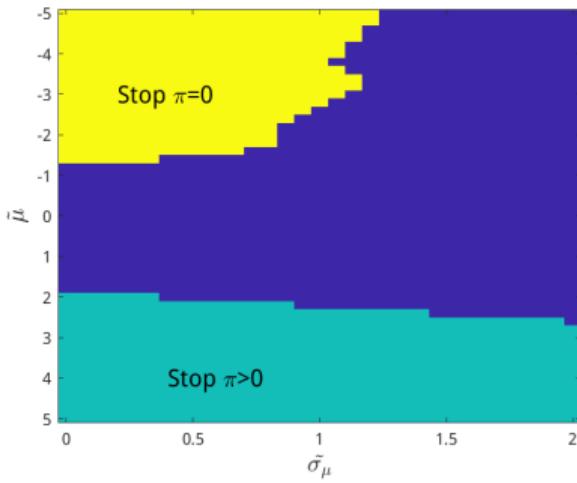
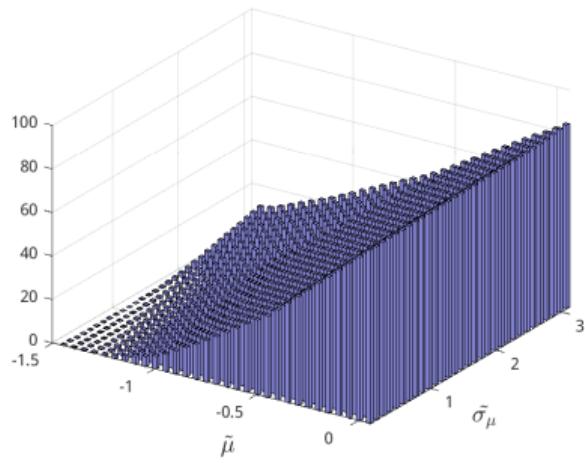
- μ_M is the component common to all drugs in M .
- λ_j^o is the drug-specific component.
- Firms (which have the same identities as drugs, j) invest in trial sites to obtain signals about λ_j .

Solving the Model

- Calibrate parameters to “match”:
 - ▶ Average number of sites.
 - ▶ Average trial length.
 - ▶ Number of site additions.
 - ▶ Response of sites to other trial results.
- Points to (future) estimation/identification strategy.
- Note: Think of α_D as policy parameter, and α_C as an equilibrium object.
- We have not yet defined an equilibrium: single-agent problem fixing α_C .

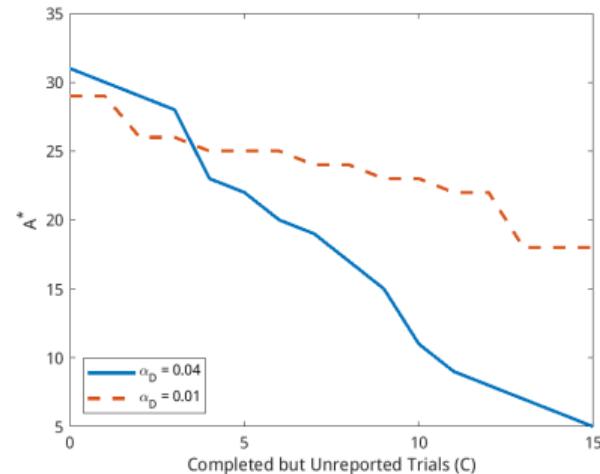
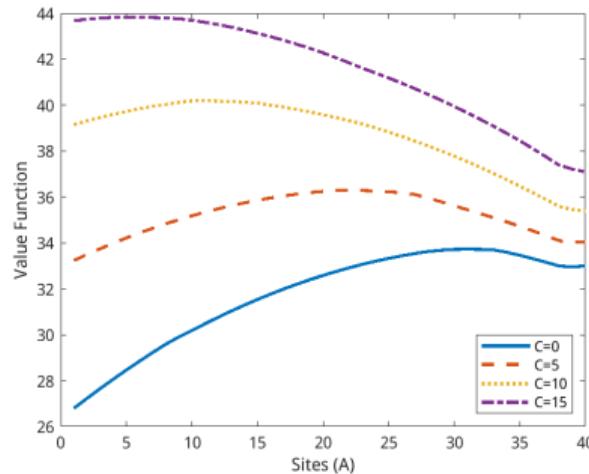
Value and Policy Functions

- Value function and stopping rule in $(\tilde{\mu}_M, \tilde{\sigma}_M)$ space:



Value and Policy Functions

- Optimal level of active sites, A^* , declines with C .
- More information flow from other trials \rightarrow lower incentive to invest.
- Consistent with slowdown of site investment under disclosure policy.



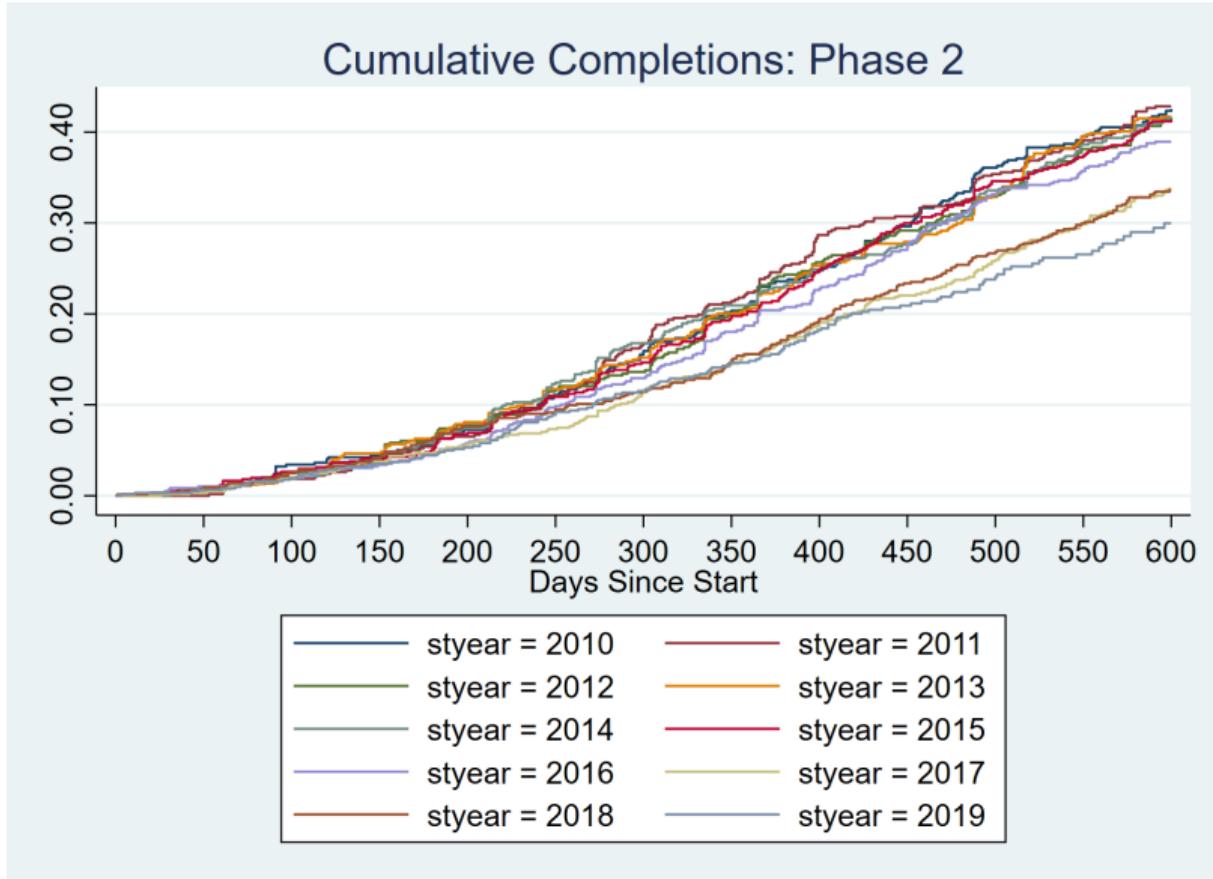
Conclusion

- We document the effects of the “**Final Rule**” on clinical trial results disclosure.
- Disclosure increases, but the start and completion rate of clinical trials decreases.
- Investment in clinical trials falls the most in technology groups where the potential for cross-drug learning is greatest.
 - ▶ Consistent with a **free riding effect**.
- We build a **dynamic model of clinical trial investment** to quantify these effects and consider counterfactual disclosure policy.
 - ▶ More results coming ... **soon**.

Thank You!

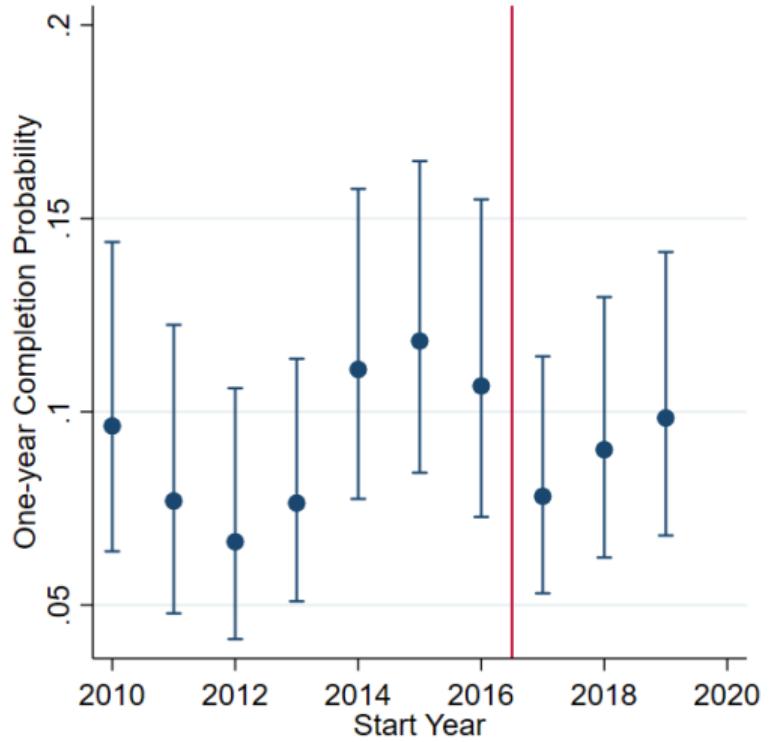


Annual Completion Curves



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Non-Industry Trials



● Point Estimate ━━━━ 95% CI

Cross-Drug Learning

Table A3: Response of Trial Start to Results Disclosure: Robustness

| | | Phase II Start | | | |
|--------------------------|--------------------------|------------------------|-----------------------|------------------------|-----------------------|
| Same Drug | Successful Phase 2 | 0.0104 (0.0080) | 0.0068 (0.0055) | 0.0104 (0.0080) | 0.0069 (0.0055) |
| | Unsuccessful Phase 2 | -0.0167*** (0.0052) | -0.0058 (0.0051) | -0.0167*** (0.0052) | -0.0058 (0.0051) |
| Same Therapeutic Class | Successful Phase 2 | -0.0106* (0.0064) | 0.0072 (0.0065) | -0.0109* (0.0064) | 0.0071 (0.0065) |
| | Unsuccessful Phase 2 | 0.0182** (0.0072) | 0.0017 (0.0069) | 0.0193*** (0.0075) | 0.0022 (0.0070) |
| Same Mechanism of Action | Successful Phase 2 | -0.0043 (0.0071) | 0.0263*** (0.0092) | -0.0155 (0.0122) | 0.0181*** (0.0066) |
| | Unsuccessful Phase 2 | -0.0182*** (0.0047) | -0.0078 (0.0055) | 0.0012 (0.0043) | -0.0134** (0.0053) |
| Completed Suc. Phase 2 | Completed Suc. Phase 2 | 0.0140 (0.0106) | 0.0022 (0.0071) | | |
| | Completed Unsuc. Phase 2 | 0.0174*** (0.0041) | -0.0139 (0.0094) | | |
| Started Phase 3 | | | | 0.0256** (0.0126) | 0.0055 (0.0065) |
| Time FE | | YES | YES | YES | YES |
| Drug FE | | YES | NO | YES | NO |
| Drug-Year FE | | NO | YES | NO | YES |
| <i>N</i> | | 1,617,366 | 1,617,366 | 1,617,366 | 1,617,366 |
| <i>R</i> ² | | 0.1893 | 0.3397 | 0.1895 | 0.3397 |

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References I

Krieger, Joshua L., “Trials and terminations: Learning from competitors’ R&D failures,” *Management Science*, 2021, 67 (9), 5525–5548.