Experts and Financial Ties: Evidence from FDA Advisory Committees

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Motivation

- The use of experts in decision-making is common
  - Doctors provide expertise for patients
  - Referees provide expertise for editors
- Experts may have conflicts of interest (COIs) or bias
  - Doctors generally can't dispense the drugs they prescribe
  - Referees may favor co-authors
- But COIs can also be correlated with expertise
  - Industry funding to doctors
  - Ties to co-authors may provide information

Long-term goal

- Important policy choices relevant to many regulatory bodies:
  - When to seek advice, and how to use it
  - Selection of committee members
  - Conflict of interest policies and disclosure of ties
- In order to address these, we need to start with estimates of expert quality and bias related to financial ties
- This paper tackles this first estimation problem

Institutional background: FDA

- US Food and Drug Administration regulates entry of all new drugs and medical devices
  - Sponsor submits clinical evidence of safety and efficacy
  - FDA conducts an internal review of this evidence
  - Sometimes, refers an application to a committee of experts
  - Usually, FDA follows the recommendation of this committee
- 33 Advisory Committees in total
  - 10-20 standing members per committee, appointed for 3-year terms as "special government employees"
  - Experts in the relevant disease area (oncology; cardiovascular; vaccines; etc.), patient and (non-voting) industry representatives
  - Temporary committee members serve on ad hoc basis

AC meetings

- Committees meet several times per year, depending on need
- Typically 1-3 days of discussion and votes
  - Meeting materials and questions distributed in advance
  - Presentation by sponsor, other interested parties
  - Discussion and voting
- Public information:
  - All meeting materials (summaries of clinical evidence)
  - Minutes and transcripts of meeting, including how each expert voted
  - Whether an expert disclosed a COI but received a waiver
- Not disclosed:
  - What drugs the FDA rejects without referring the case to AC
  - Details of reported COIs

COI policy

- Experts are required to disclose potential conflicts on Form 3410
  - "involvement or financial link with the meeting/task issues (including competing companies)"
  - Current or recent investments, employment, advising/consulting, research support, patents, expert witness, speaking fees
- If a disclosed conflict exceeded a threshold:
  - Either the expert is excluded from the meeting
  - Or the committee chair requests a waiver from the FDA to allow the expert to participate
- Until 2008, many waivers were granted
  - Unclear how many were requested
  - Unclear what threshold was applied

COI and FDA scandals

- In 2004, Merck withdrew its painkiller Vioxx from the market
  - Evidence that Vioxx increased the risk of heart attack and stroke
  - Merck was accused of hiding this evidence for 5 years
- Scrutiny of the experts who voted on Vioxx and similar drugs
  - 1/3 of the AC members had some financial tie to the firms concerned
- The experts had disclosed their ties to the FDA, but were allowed to participate
- In 2005, the FDA began posting COI waivers granted online
- In 2008, Congress drastically reduced the number of COI waivers permitted

Prevalence of COI

- 2001-2004 Lurie et al. [2006] study:
  - Freedom of Information Act Request to obtain COIs
  - At least 1 COI in 81% of AC meetings discussing a product
  - In 22% of meetings, more than 50% of the experts had a COI
  - Recusals were very rare (1%)
  - 23% of COIs involving research support exceeded $100K
  - 44% of COIs involving lecturing/honoraria exceeded $10K
- They conclude that excluding experts with COIs would have resulted in less favorable vote totals, but not by enough to change the outcome

Waivers are now rare

Percent of advisory committee members participating in meetings in the month who were granted waivers

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FY 2010 Target: Less than 13.04%

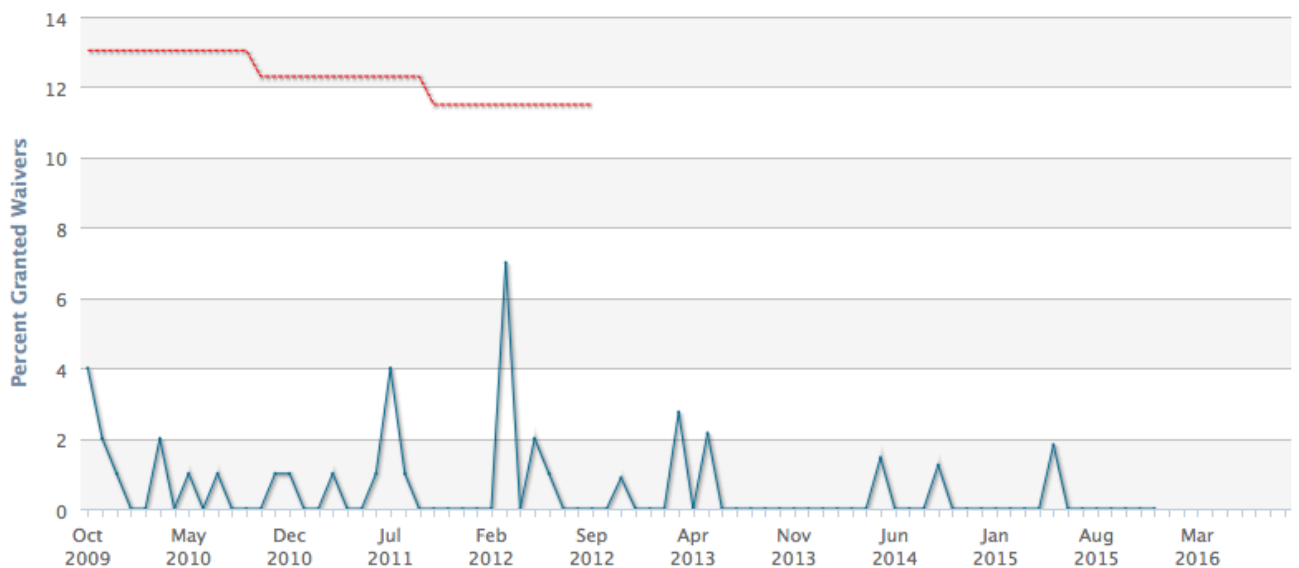
Dictionary: When FDA determines that an advisory committee member has a financial conflict of interest, the agency may grant a waiver that allows the member to participate in an advisory committee meeting if certain criteria and policies are met. In general, FDA may grant a waiver if the requirements set forth by 18 U.S.C. 208 are met. FDA searches for experts who have the necessary expertise without conflicts of interest; yet, in some cases, the top authorities in specialized scientific fields may have a conflict of interest. When FDA grants a waiver, the financial interests associated with the waiver are posted on FDA's website along with the reasons for granting the waiver.

Information is current as of December 31, 2015.

Change Fiscal Year All

Fiscal Year - All

Change chart type:



And finding experts is hard

Percent of FDA advisory committee member positions vacant at the end of the month

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Dictionary: Access to state-of-the-art, scientific expert advice to support agency decision making processes is imperative to the FDA advisory committee process. Having the fewest vacancies on our committees allows the agency to have ready access to those experts and supports the ability of FDA to meet its public health mission. For more information about FDA advisory committees, please visit http://www.fda.gov/AdvisoryCommittees/default.htm

Information is current as of December 31, 2015.

Change Fiscal Year All

Fiscal Year - All

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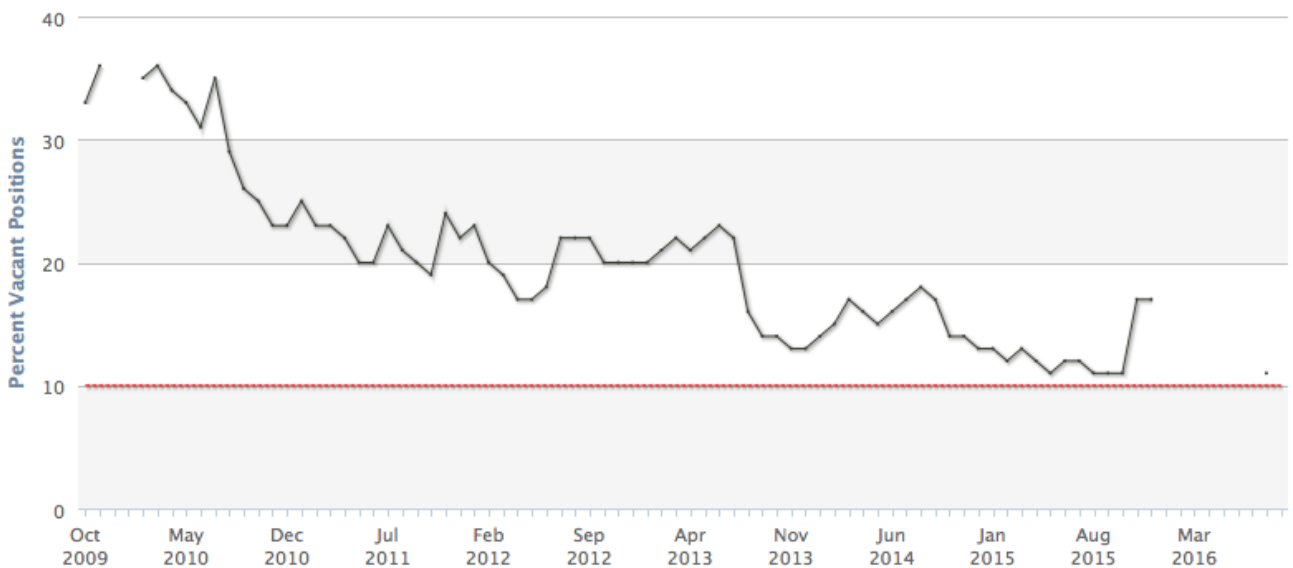

Other changes over time

- Voting procedures
  - Prior to 2008, votes were oral and sequential
  - Gradual shift to simultaneous electronic votes over 2007-2008 in response to concerns about "groupthink"
  - Votes are public throughout
- Concerns about financial relationships in medicine generally
  - Ghostwriting of articles -> increased disclosure requirements at medical journals
- 2010 "Sunshine Act" mandated the creation of a database of all payments from industry to doctors
  - In effect as of late 2013

Prevalence of COI

- Subsequent work (Golec & Cooper [2015]) has extended the time period
- General claims:
  - Conflicted advisors are not pivotal
  - Advisors sometimes vote against their interests (e.g., to approve a competing product)
  - Advisors with conflicts are more likely to agree with the FDA's ultimate decision, and with stock market analysts
- Some drawbacks:
  - Omitted variables
  - Agreement with FDA or stock market analysts is not necessarily proof of superior expertise
  - Narrow definition of financial ties

Committee and meeting data

- Started with data used in Lurie et al. [2006], updated in Ackerley et al. [2009]
  - 2001-2007
  - Only questions related to product recorded (approval, withdrawal, new indication, labelling change)
  - Many other data quality issues
- We collected 2008-2013 ourselves
  - Fewer COIs due to rule changes
  - Electronic simultaneous voting
  - All questions: separate votes on safety, efficacy, risk/benefit

Expert data

- Committee rosters -> names, degrees, current affiliation
- MDs:
  - Scrape of healthgrades.com for age, gender, medical school, year of graduation, board certifications
  - Medicare database for medical school, gender, hospital affiliations
- PhDs:
  - ProQuest Theses & Dissertations for year of degree, subject area

Expert data

- NIH grant information -> funding by year
- clinicaltrials.gov -> number of trials for which advisor was lead investigator, by year
- Pubmed data on publications
  - Number of publications by year
  - Measure of author status (distance from center of the list of co-authors)

Ties to industry

- Option 1:
  - Information from FDA waivers
  - Only covers prior 12 months
  - Only available when conflict exceeded some threshold
  - Only available for financial ties to sponsor or direct competitor
- Option 2:
  - Propublica + Sunshine Act data
  - Only for MDs; voluntary disclosures by industry pre-2013
- Option 3:
  - clinicaltrials.gov data
  - Ties to industry defined by leading industry-sponsored trials

Our new measure

- Most medical journals require authors to disclose funding sources, particularly since 2005
- Authors are also supposed to disclose other financial ties if the article concerns a specific drug
- We create a measure of financial ties as follows:
  - We find the electronic version of each article authored by an expert
  - We parse the text for disclosure information
  - We create indicator variables for support for sponsor, competing firm, other drug firm
  - We can construct "second degree" ties to industry via co-authors

Example

- Cardiovascular and Renal Drugs AC met on 23 February 2012 to discuss NORTHERA (droxidopa capsules) of Chelsea Therapeutics International, Ltd.
- "Should droxidopa be approved for the treatment of symptomatic neurogenic orthostatic hypotension in patients with primary autonomic failure, Dopamine Beta Hydroxylase Deficiency, and Non-Diabetic Autonomic Neuropathy?"
- No COI waivers granted
- 7 votes for approval, 4 against, 1 abstention
- FDA did not immediately approve, but asked for another study
- AC voted again on 14 Jan 2014, 16-1 to approve
- FDA approved 1 month later

Example

Based on the agenda for today's meeting and all financial interests reported by the committee's members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

Example

DR. LEWIS: I voted no. And I spent a lot of time trying to go through the design and the details of how all these were conducted. And in the end, I couldn't find a comforting anything other than a hypothesis, and my own confirmation bias that I want to believe it will help these people that need help, to choose to believe the 301 and ignore the 302 or 303, or interpret it in a positive way.

Example

Cardiorenal Med. Feb 2012; 2(1): 1–10.
Published online Oct 26, 2011. doi: 10.1159/000333249
PMCID: PMC3318932

Renal Dysfunction in the Presence of Normoalbuminuria in Type 2 Diabetes: Results from the DEMAND Study

Jamie P. Dwyer,[a,*] Hans-Henrik Parving,[b,c] Lawrence G. Hunsicker,[d] Moti Ravid,[e] Giuseppe Remuzzi,[f] and Julia B. Lewis[a], for the DEMAND Investigators

Example

Disclosure Statement Go to:

J.P.D. reports research and travel support from Keryx Biopharmaceuticals, Inc, and Eli Lilly, Inc., and H.-H.P consultancy and speaker's fees from Sanofi-Aventis, Merck, Bristol-Myers-Squibb, and Novartis. L.G.H received research support from Bristol-Myers-Squibb, Sanofi-Aventis, and Eli Lilly. G.R. obtained speaker's fees from Astra-Zeneca and Novartis, and has acted as a consultant to Pharmanet. M.R. reports speaker's fees from Sanofi-Aventis and has acted as consultant for Novo-Nordisk. J.B.L. confirmed research and travel support from Bristol-Myers-Squibb, Sanofi-Aventis, Nephrogenix, Keryx Biopharmaceuticals, and Eli Lilly.

The sponsors of the study (Bristol-Myers Squibb and Sanofi-Aventis) contributed to the study design, data collection, and reviewed and commented on drafts of the original DEMAND report, but had no role in data analysis (performed by J.P.D. and L.G.H.), interpretation or writing the report, or reviewing drafts of this current study. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Drug data (in progress)

- For each drug:
  - All competing drugs within same disease area, and their sponsors
  - Size, severity of disease
  - Quantity of scientific information available: number of scientific publications mentioning it, number of clinical trials, size of trials
  - Novelty and importance
- For each sponsor (drug firm):
  - Number of previously approved drugs
  - Number of previously withdrawn drugs
  - Measures of financial support to teaching hospitals, academic institutions, and individuals

Advisor characteristics

Variable	Mean	Std. Dev.	Min.	Max.	N
Has academic affiliation	0.64	0.48	0	1	983
MD	0.75	0.43	0	1	1090
PhD	0.23	0.42	0	1	1090
PharmD	0.04	0.19	0	1	1090
MPH	0.07	0.26	0	1	1090
Female	0.33	0.47	0	1	1090
Age	54.2	9.72	26	87	854

Advisor characteristics

Variable	Mean	Std. Dev.	Min.	Max.	N
Total publications (as of 2014)	62.43	73.19	0	566	1090
Percentage of papers as last author	0.13	0.13	0	1	1090
Percentage of papers as first author	0.20	0.19	0	1	1090
Ever received NIH grant	0.55	0.50	0	1	1090
Number of clinical trials	1.48	3.18	0	32	1090

Financial ties of advisors

Variable	Mean	Std. Dev.	Min.	Max.	N
Any payment disclosed in 2013 under Sunshine Act	0.21	0.41	0	1	1090
Number of industry-sponsored clinical trials	0.30	0.92	0	14	1090
Ever received a waiver for COI	0.17	0.38	0	1	1090
Advisor ever reported financial support from industry in publication	0.14	0.35	0	1	1090
Number of firms advisor reported financial support from in publications	0.34	1.6	0	23	1090

Quality and financial ties

	No Tie	Any Tie	Difference
Number of previous meetings attended	6.11	8.03	-1.92***
Years since completing MD or PhD	26.20	27.87	-1.67***
Number of years serving as expert	2.46	3.61	-1.15***
Cumulative publications	25.87	41.34	-15.47***
Ever received NIH grant	0.45	0.66	-0.21***
Average status in publications	0.26	0.30	-0.04***
Number of clinical trials	0.64	2.08	-1.44***
Number of board certifications	0.41	0.70	-0.29***
Number of advanced degrees	1.09	1.22	-0.13***

Meeting characteristics

Variable	Mean	Std. Dev.	Min.	Max.	N
N of committee members present	15.43	4.71	4	35	217
N of standing members present	7.50	2.78	2	15	217
N of temporary members present	7.92	4.39	0	25	217
N of with MD	11.19	4.22	0	26	217
N of with PhD	4.45	2.57	0	15	217
N of with industry tie	10.57	5.41	0	35	217
Orphan drug	0.31	0.46	0	1	164
Important drug	0.38	0.49	0	1	217
Novel drug	0.32	0.47	0	1	164

Votes and outcomes

	Outcome for drug			
Category	For	Against	Tie	Total
Safety	56	25	4	85
Efficacy	86	32	4	122
Safety+efficacy or risk/benefit	59	30	1	90
Approval	75	35	0	110
Withdrawal	1	3	0	4
Restriction	5	2	0	7
Relabeling	3	7	0	10
OTC switch	1	0	0	1
Other	36	56	2	94
Total	322	190	11	523

Reduced-form results

	Model 1 b/se	Model 2 b/se	Model 3 b/se	Model 4 b/se
Financial tie	0.002			
	(0.011)			
Ever received a waiver for COI		−0.011		
		(0.014)		
Sunshine Act payment			0.040∗	
			(0.013)	
Advisor ever reported financial support from industry in publication				−0.015
				(0.017)
N	8036	8036	8036	5718
R^2	0.0000	0.0001	0.0012	0.0001
Adj. R^2	−0.0001	−0.0000	0.0011	−0.0000

Reduced-form results

	Model 1 b/se	Model 2 b/se	Model 3 b/se	Model 4 b/se
Financial tie	0.025	0.032+		
	(0.015)	(0.015)		
Any tie (publication)				0.026
				(0.027)
Any sponsor tie			0.039	0.180
			(0.026)	(0.163)
Any competitor tie				−0.155
				(0.163)
N previous meetings attended	−0.004∗	−0.003∗	−0.003∗	−0.004∗
	(0.001)	(0.001)	(0.001)	(0.001)
Age	0.001+	0.002+	0.002+	0.002
	(0.001)	(0.001)	(0.001)	(0.001)
Cumulative publications	−0.000	−0.000+	−0.000+	−0.000+
	(0.000)	(0.000)	(0.000)	(0.000)
Cumulative trials led	−0.000	0.001	0.002	−0.000
	(0.003)	(0.003)	(0.003)	(0.003)
Ever received NIH grant	−0.005	−0.003	−0.002	−0.001
	(0.015)	(0.015)	(0.015)	(0.018)
MD	0.006	0.032	0.036	0.080∗
	(0.024)	(0.024)	(0.024)	(0.028)
PhD	−0.023	−0.001	−0.002	0.040
	(0.019)	(0.019)	(0.019)	(0.023)
Female	−0.014	−0.006	−0.005	−0.006
	(0.015)	(0.015)	(0.015)	(0.018)
Patient representative	−0.101∗	−0.078+	−0.078+	−0.062
	(0.039)	(0.039)	(0.039)	(0.043)
Standing member	0.009	0.001	−0.001	−0.030
	(0.014)	(0.014)	(0.014)	(0.016)
Orphan drug	−0.042+	−0.020	−0.017	−0.038
	(0.017)	(0.018)	(0.018)	(0.022)
Important drug	0.013	−0.047∗	−0.049∗	−0.050+
	(0.014)	(0.016)	(0.016)	(0.019)
Novel drug	0.077∗	0.066∗	0.067∗	0.058∗
	(0.014)	(0.016)	(0.016)	(0.019)
Intercept	0.533∗	0.156+	0.161∗	0.062
	(0.048)	(0.062)	(0.062)	(0.076)
Year fixed effects	No	Yes	Yes	Yes
Committee fixed effects	No	Yes	Yes	Yes
N	5606	5606	5606	4076
R^2	0.0171	0.0573	0.0569	0.0725
Adj. R^2	0.0146	0.0517	0.0513	0.0647

Summary

- Consistent with earlier studies' (non-)findings, even with additional variables
  - Most advisor observables are not systematically related to voting
  - Which suggests that committee selection is rather good
- Important omitted variable: unobserved drug quality
  - Which suggests that the experts serve a purpose
  - Motivates our use of a structural model

Set-up (derived from Iaryczower and Shum [2012])

- N experts, $i = 1...N$; T independent applications, $t = 1...T$
- $\omega_t \in \{0, 1\}$ is the unobserved state indicating whether a drug "should" be approved, or true quality
- Each i votes for/against in each t, $\nu_i^t \in \{0, 1\}$
  - Prior to voting, each i observes a private signal $s_{it} = \omega_t + \sigma_{it}\epsilon_t$
  - $\epsilon \sim \mathcal{N}(0, 1)$
  - $\theta_{it} = 1/\sigma_{it}$ parameterizes the informativeness of i's signals, satisfying MLRP
- $\rho_t \equiv \Pr(\omega_t = 1)$ is the common prior for ω_t
- Committee aggregates decisions using majority rule to make a recommendation to the FDA

Payoffs

- i receives payoffs that depend on the truth (ω_t) and his vote (ν_t):
  - $-\pi_i \in (0, 1)$ if $\nu_t = 1$ but $\omega_t = 0$ (cost of recommending a bad drug)
  - $-(1 - \pi_i)$ if $\nu_t = 0$ but $\omega_t = 1$ (cost of blocking a good drug)
- i may also a financial tie that affects his payoff:
  - Financial ties can enter into π
  - Other assumptions about how ties enter payoffs are also possible
- Here, we normalize payoffs to 0 when $\nu_t = \omega_t$

Payoffs

	$\omega_t = 0$	$\omega_t = 1$
$v_{it} = 0$	0	$-(1 - \pi_{it})$
$v_{it} = 1$	$-\pi_{it}$	0

- If $\forall i, \pi_i = 1/2 \rightarrow$ pure common values model
- If $\pi_i \approx 1 \rightarrow$ expert is more willing to reject a good drug than to approve a bad one, or prefers type I error
- If $\pi_i \approx 0 \rightarrow$ expert is more willing to approve a bad one than to reject a good drug, or prefers type II error

Voting rule

Vote $\nu_i^t = 1$ given information E if the payoff from iff

$$-\pi_{it} \Pr(\omega_t = 0|E) \quad \geq \quad -(1-\pi_{it}) \Pr(\omega_t = 1|E)$$

Equivalently, expert i votes yes if the likelihood ratio exceeds a threshold:

$$\frac{\Pr(E \mid \omega_t = 1)}{\Pr(E \mid \omega_t = 0)} \geq \frac{\pi_{it}}{1-\pi_{it}} \frac{1-\rho_t}{\rho_t}$$

Equilibrium (sincere or expressive model)

i votes 1 if i receives a signal $s_{it} > s_{it}^{\exp}$, where $s_{it}^{\exp}$ is a cutoff point that solves

$$\begin{aligned} \frac{\Pr^i(s_{it}|\omega_t = 1)}{\Pr^i(s_{it}|\omega_t = 0)} &= \frac{\phi(\theta_{it}[s_{it} - 1])}{\phi(\theta_{it} s_{it})} \\ &\geq \frac{\pi_{it}}{(1 - \pi_{it})} \frac{1 - \rho_t}{\rho_t} \end{aligned} \tag{1}$$

Identification: intuition

- Two critical assumptions:
  - Common prior $\rightarrow$ correlation of votes.
  - Everyone is more likely to vote for a good drug than a bad drug.
- With no bias ($\pi \approx 1/2$), an uninformative prior ($\rho \approx 1/2$), good information (θ large):
  - Unanimous decisions, evenly split between approval/rejection
- If an expert has low quality of information:
  - Variable voting and more often in the minority
- If an expert is biased:
  - Low variability in votes; i will more consistently vote for (or against)

Parameterization

Prior ρ as function of application (sponsor, drug) characteristics:

$$\rho(\mathbf{X}_t; \beta) \equiv \frac{\exp(\mathbf{X}_t'\beta)}{1 + \exp(\mathbf{X}_t'\beta)} \in [0, 1]$$

Bias and skill as functions of application and advisor characteristics:

$$\pi(\mathbf{X}_t; \mathbf{Z}_{it}; \mu, \xi) \equiv \frac{\exp(\mathbf{Z}_{it}'\mu + \mathbf{X}_t'\xi)}{1 + \exp(\mathbf{Z}_{it}'\mu + \mathbf{X}_t'\xi)} \in [0, 1]$$

$$\sigma(\mathbf{X}_t; \mathbf{Z}_{it}; \zeta, \eta) \equiv \exp(\mathbf{Z}_{it}'\zeta + \mathbf{X}_t'\eta)$$

Likelihood

Using $\theta = 1/\sigma$ and $s_{it} = \omega_t + (1/\theta_i)\epsilon_{it}$:

$$\begin{aligned}
\gamma_{it,1} &\equiv \Pr(\nu_{it} = 1 | \omega_t = 1) \\
&= 1 - \Pr(1 + (1/\theta_i)\epsilon_{it} > s_i^*) \\
&= 1 - \Pr(\epsilon_{it} > \theta(s_i^* - 1)) \\
&= 1 - \Phi(\theta(s_i^* - 1)) \\
\gamma_{it,0} &= 1 - \Phi(\theta_i s_i^*)
\end{aligned}$$

$$\max_{\beta,\mu,\xi,\zeta,\eta} \sum_t \log \rho \prod_{i=1}^{n} (\gamma_{i,1})^{\nu_{it}} (1 - \gamma_{i,1})^{1-\nu_{it}} + (1 - \rho) \prod_{i=1}^{n} (\gamma_{i,0})^{\nu_{it}} (1 - \gamma_{i,0})^{1-\nu_{it}}$$

Estimates of ρ

(Positive coefficients indicate more favorable prior for drug quality.)

Variable	ρ
Intercept	0.2744
Safety	0.0434
Efficacy	0.0931
Approval	0.3129
Important	0.0458

Estimates of $\sigma = 1/\theta$

(Negative coefficients indicate greater precision or ability.)

	σ
Intercept	-0.4746
Safety	0.0870
Efficacy	0.1154
Approval	-0.0152
Important	-0.0272
MD	-0.1560
PhD	-0.1179
Patient rep	0.0419
Financial tie	-0.1016
Experience	0.0006
Standing	0.0024

Table: Determinants of σ

Estimates of π

(Negative coefficients are more favorable to pro-industry votes.)

	π
Intercept	0.2680
Safety	0.2188
Efficacy	-0.2661
Approval	-0.2080
Important	-0.3560
MD	0.0505
PhD	0.1599
Patient rep	0.3910
Financial tie	-0.2298
Experience	0.0359
Standing	0.1780

Table: Determinants of π

Summary of results (very preliminary!)

- Very parsimonious structural specification yields reasonable results
- Specifically:
  - Estimates of advisor "quality" make sense: those with scientific backgrounds have more precise signals
  - Financial ties are associated with a tendency to vote in favor of the industry, but are also linked to higher quality
- But we haven't verified the robustness or economic importance yet

Counterfactuals to consider

- Banning all industry ties
- Removing restrictions on COIs

- Eventually, we would like to integrate the FDA's delegation decision and use of AC recommendations

Conclusion

TBD.

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