Clinical Drug Development
with a
Bayesian Lens

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Advanced Analytics
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Lilly

Acknowledgements

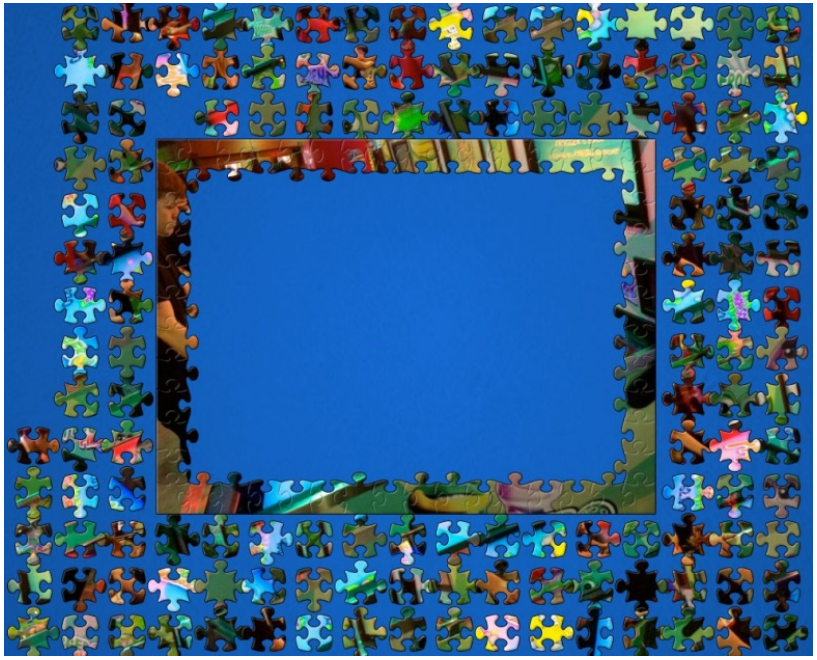
Meg Gamalo

Karen Price

Scott Berry

John Seaman

The Beginning is Always the Hardest



APPROVAL

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Key Question

What would it look like if

SUBSTANTIAL EVIDENCE

was based on a

Bayesian posterior probability

rather than

p-value(s)?

Substantial Evidence

Pr (drug works) > threshold

Substantial Evidence

Drug – Placebo > 0

Pr (drug works) > threshold

Substantial Evidence

Drug – Placebo > CM

Pr (drug works) > threshold

Substantial Evidence

Drug – Placebo > Benefit-Risk

Pr (drug works) > threshold

Approval

Pr (drug works) > threshold

Disease

Common

Life-threatening

Rare disease

Unmet need

Approval

Pr (drug works) > threshold

Endpoints

Hard

Surrogate

Objective

Subjective

Approval

Hypothetical Examples

Pr (cure for pancreatic cancer) > 0.50

Pr (weight loss of 5kg) > 0.95

Pr (increased survival by 9 months) > 0.85

Approval

"FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards."

21 C.F.R. § 314.105(c).

Phase 3

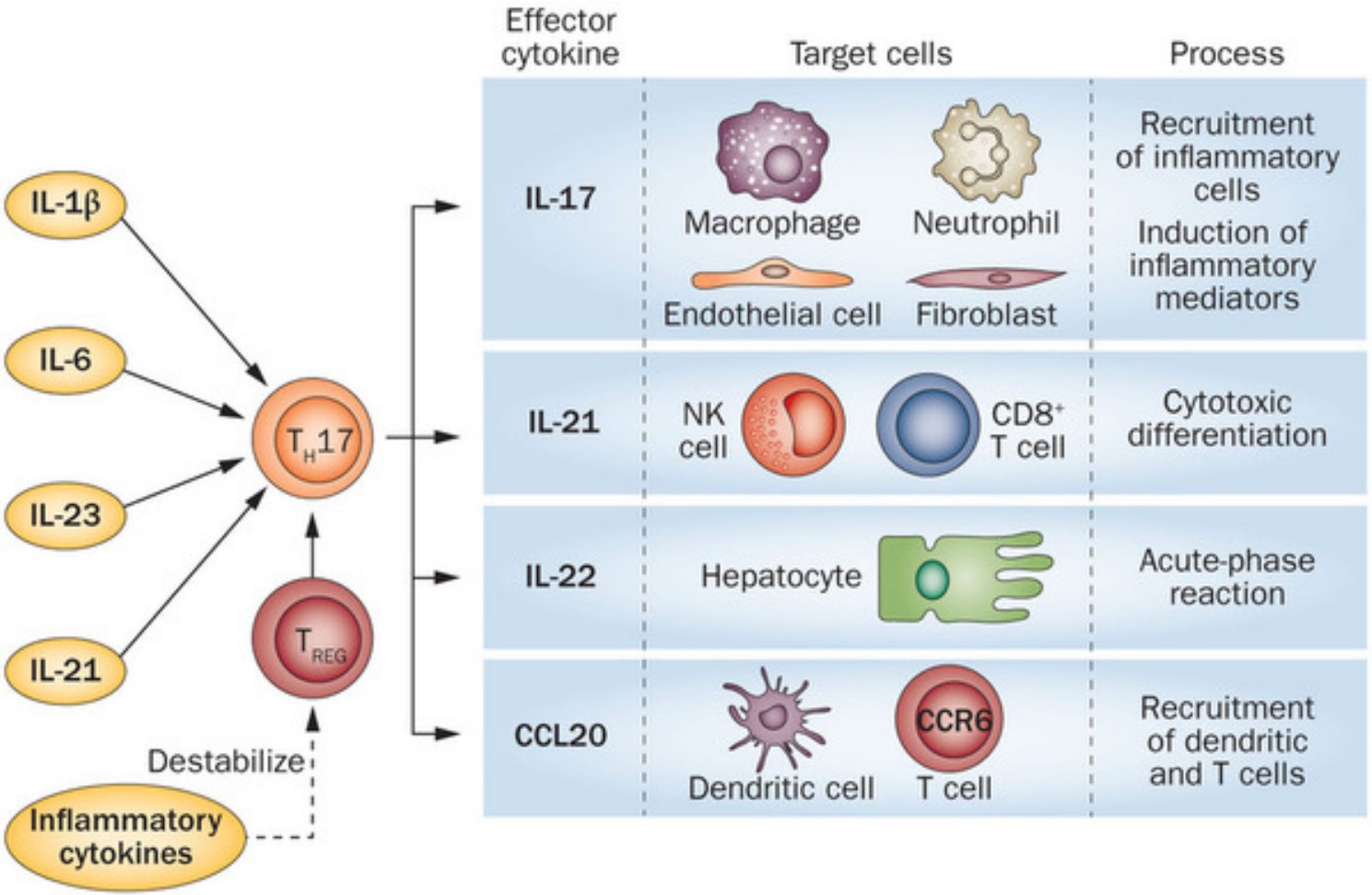
How much data?

Study Design


PRIOR

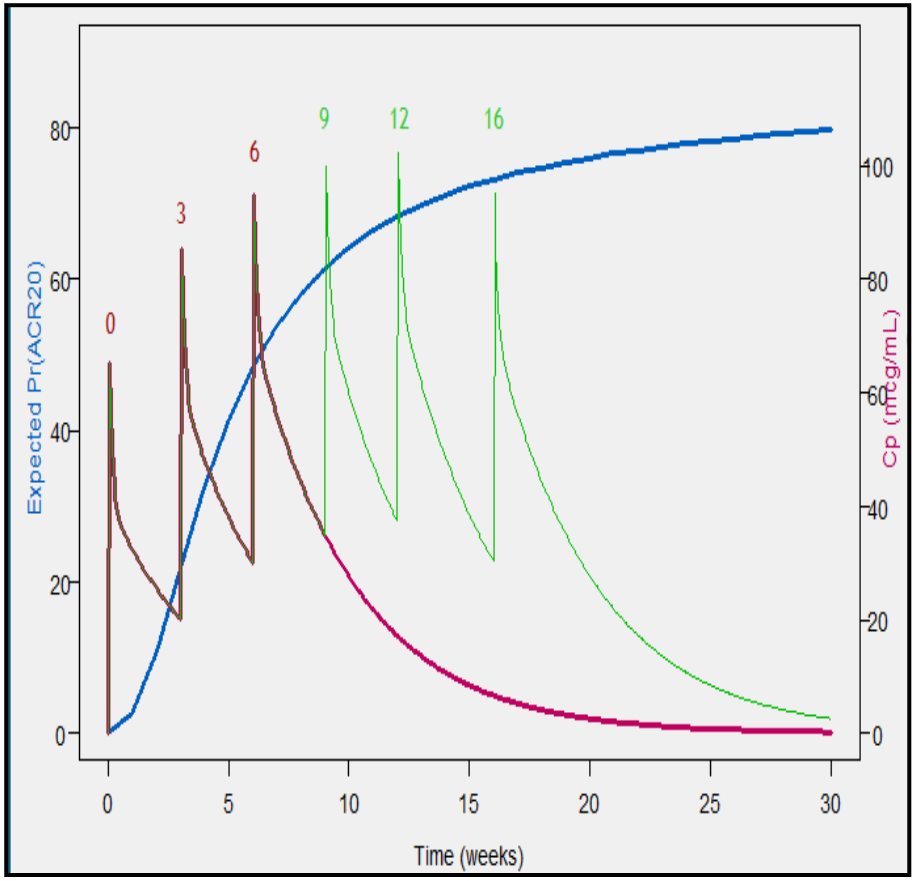
EoPh2 Meeting

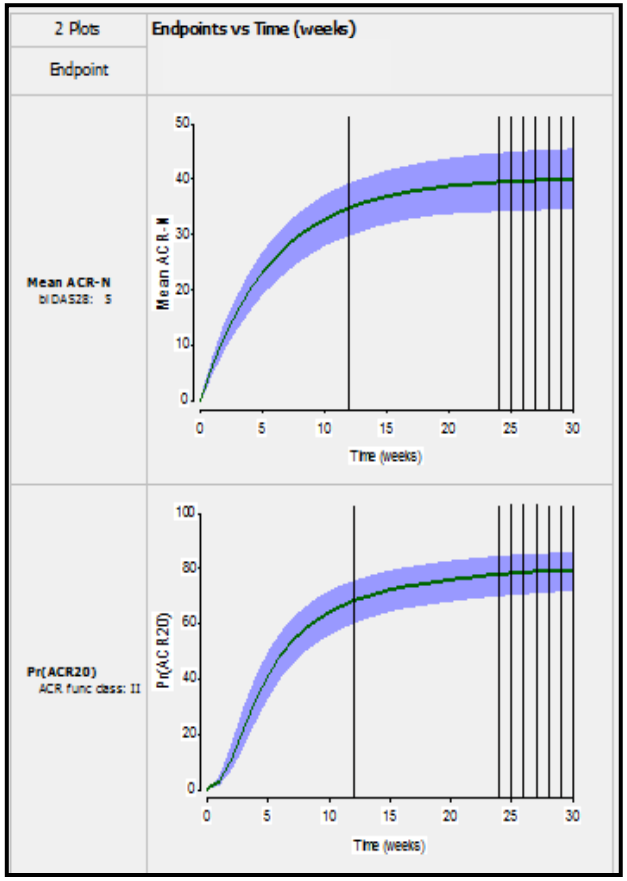
Mechanistic Research



PK / PD Models

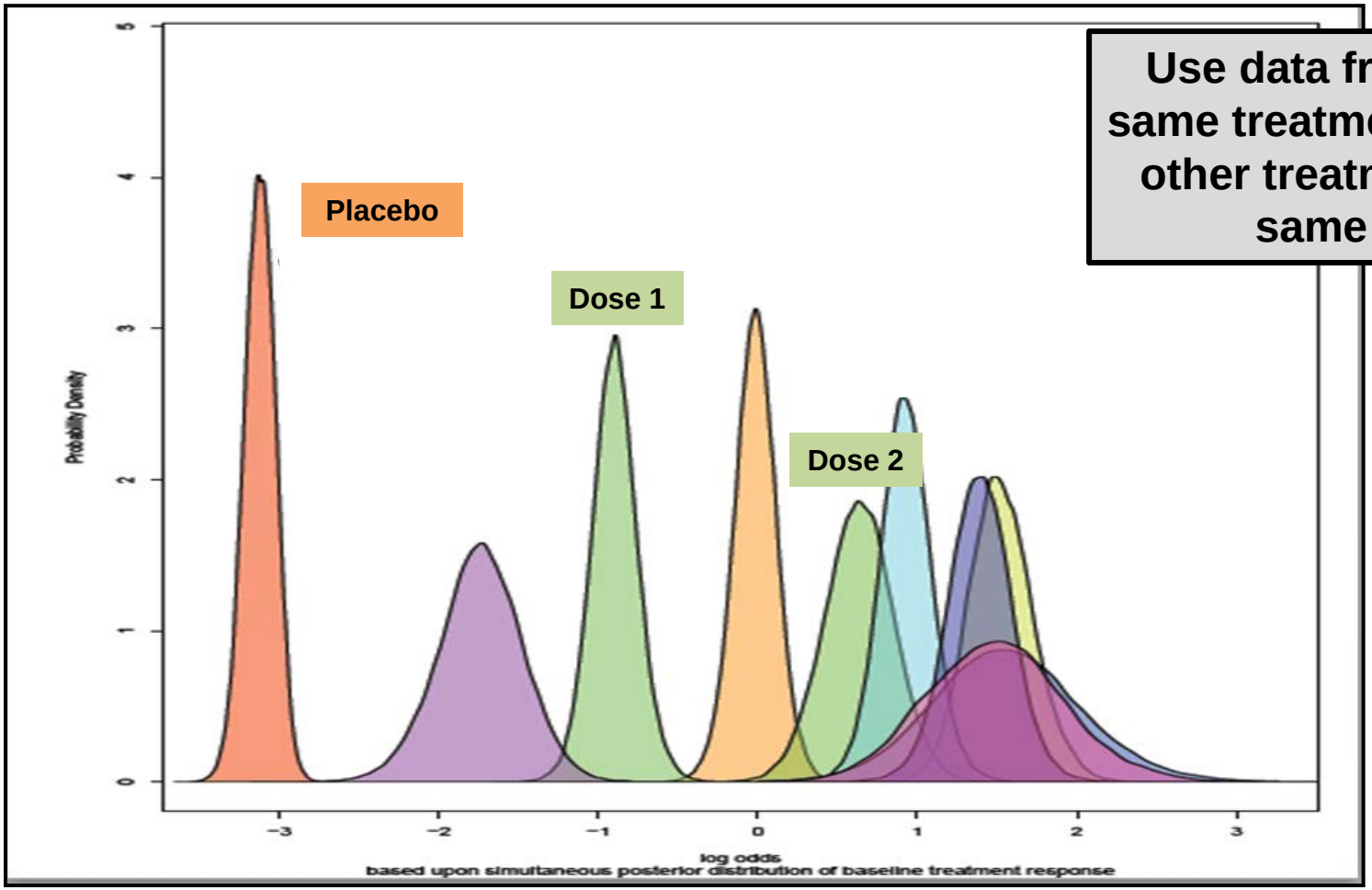
$$ACR20 = \text{logit.inv}(BL + (Amplitude * time_{wks}) / (et50 + time_{wks}), upper = 100, lower = 0)$$





Phase 2 Data

(or Phase 1 in some cases)



Use data from trials of same treatment as well as other treatments in the same class.

Robust Bayes

- Usual approach: for unknown parameter(s), $\boldsymbol{\theta}$, specify 'informative prior' $\boldsymbol{\theta} \sim \pi_I(\boldsymbol{\theta}|\boldsymbol{\eta})$
- A 'robust' approach (just use a prior mixture):

$$\boldsymbol{\theta} \sim \epsilon \cdot \pi_I(\boldsymbol{\theta}|\boldsymbol{\eta}_1) + (1-\epsilon) \cdot \pi_R(\boldsymbol{\theta}|\boldsymbol{\eta}_2)$$

'Your informative prior'

'Your **what-if-I'm-really-wrong** prior'

- Example:

$$\boldsymbol{\theta} \sim .85 \cdot N(.52, .1) + .15 \cdot U(.1,2)$$

Used with permission
Zach Thomas, Eli Lilly

Limitations

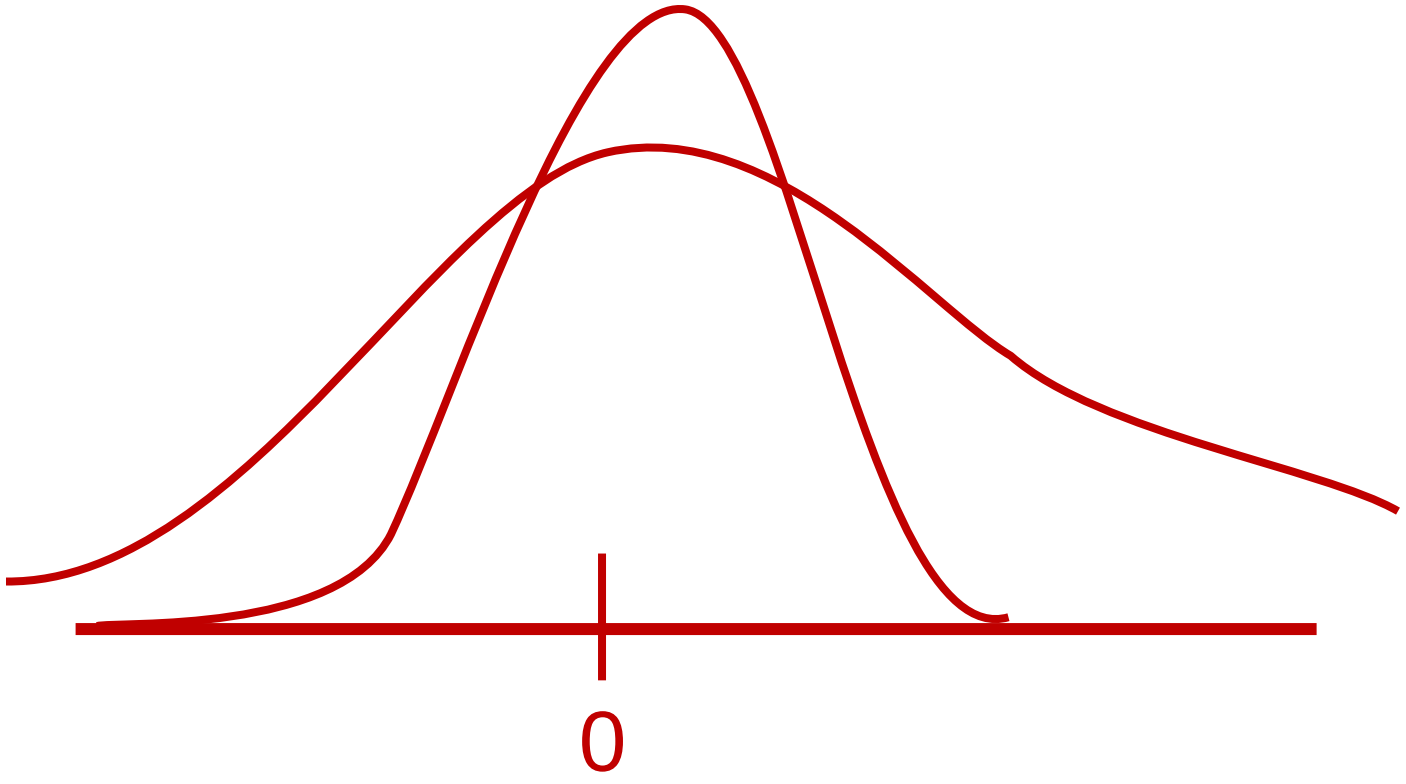
- Shrinkage of Ph 2 results
- Network meta-analysis
  - How much data to include
  - How far back to go
- Changes in patient populations, geographies, doses, duration of treatment
- Changing endpoints (actual measure and the time of measurement)

Regulatory Considerations

- It’s different for everyone, but …
- Reward more robust Phase 2 programs

Phase 2


PRIOR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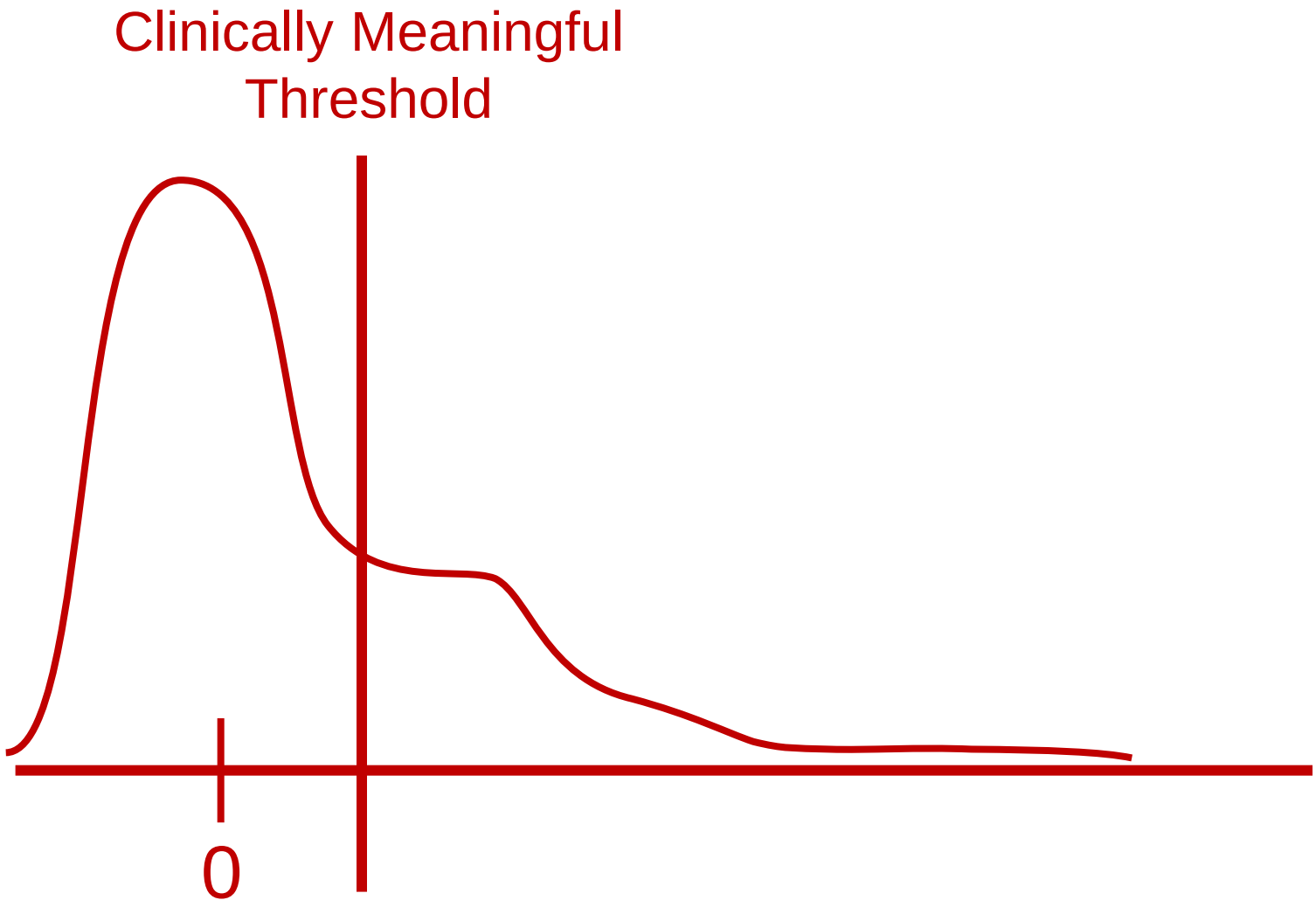
Clinically Meaningful
Threshold
0

Nature Biotechnology
January, 2014

Clinical development success rates for investigational drugs

Michael Hay, David W Thomas, John L Craighead, Celia Economides & Jesse Rosenthal

The most comprehensive survey of clinical success rates across the drug industry to date shows productivity may be even lower than previous estimates.

Table 4 Phase success and LOA by drug class

	Phase 1 to phase 2				Phase 2 to phase 3				Phase 3 to NDA/BLA				NDA/BLA to approval			
	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]
FDA classification[e]																
All indications	2,541	1,918	64.5%	10.4%	3,743	2,268	32.4%	16.2%	1,554	975	60.1%	50.0%	908	659	83.2%	83.2%
NMEs	1,585	1,218	64.2%	7.5%	2,375	1,470	28.6%	11.6%	831	515	53.2%	40.7%	425	293	76.5%	76.5%
Biologics	572	411	68.4%	14.6%	819	464	37.9%	21.3%	320	182	63.2%	56.1%	159	116	88.8%	88.8%
Non-NMEs	218	168	66.7%	20.0%	355	226	45.1%	29.9%	321	234	75.6%	66.3%	293	227	87.7%	87.7%
Lead indications	1,770	1,336	66.5%	15.3%	2,070	1,247	39.5%	23.1%	1,009	633	67.6%	58.4%	664	472	86.4%	86.4%
NMEs	1094	848	65.2%	12.0%	1,275	791	36.4%	18.3%	497	300	61.7%	50.3%	283	185	81.6%	81.6%
Biologics	362	257	75.1%	20.8%	403	216	44.0%	27.7%	182	106	71.7%	63.1%	106	75	88.0%	88.0%
Non-NMEs	167	124	66.9%	23.2%	232	153	49.0%	34.6%	254	186	79.0%	70.7%	246	189	89.4%	89.4%
Biomedtracker product category[f]																
Small molecule NMEs	1,335	1,033	65.4%	7.6%	2,053	1,283	29.0%	11.6%	725	449	52.3%	39.8%	369	264	76.1%	76.1%
Large molecules	912	658	65.8%	13.2%	1,279	714	37.7%	20.1%	511	296	60.1%	53.3%	244	166	88.6%	88.6%
mAbs	329	234	70.1%	14.1%	458	268	38.1%	20.1%	147	84	60.7%	52.7%	65	53	86.8%	86.8%
non-mAb proteins	192	151	58.9%	13.1%	280	170	35.3%	22.3%	150	87	69.0%	63.1%	93	59	91.5%	91.5%
Vaccines	121	57	67.1%	14.9%	160	79	44.3%	22.2%	67	34	50.0%	50.0%	23	20	100.0%	100.0%

[a]Number of indications identified. [b]Total number of transitions used to calculate the success rate, the *n* value noted in the text. The difference between 'Total in phase' and 'Advanced or suspended' is the number of indications that remain in development. [c]Probability of successfully advancing to the next phase. [d]Probability of FDA approval for drugs in this phase of development. [e]FDA NME, biologic and non-NME classifications as defined in the results section. Data are presented for all and lead indication development paths. [f]BioMedTracker classification of small-molecule NMEs and large-molecule drugs. Large molecules are further stratified by biochemical profile.

Table 5 Phase success and LOA by disease[a]

	Phase 1 to phase 2				Phase 2 to phase 3				Phase 3 to NDA/BLA				NDA/BLA to approval			
	Total in phase[b]	Advanced or suspended[c]	Phase success[d]	Phase LOA[a]	Total in phase[b]	Advanced or suspended[c]	Phase success[d]	Phase LOA[a]	Total in phase[b]	Advanced or suspended[c]	Phase success[c]	Phase LOA[a]	Total in phase[b]	Advanced or suspended[c]	Phase success[d]	Phase LOA[a]
All indications																
Other[f]	254	198	72.2%	18.2%	419	251	44.2%	25.3%	252	159	71.1%	57.1%	169	112	80.4%	80.4%
Infectious disease	247	196	65.8%	16.7%	288	157	45.9%	25.4%	159	98	65.3%	55.4%	115	86	84.9%	84.9%
Autoimmune	241	178	68.0%	12.7%	350	215	34.0%	18.7%	149	95	68.4%	55.0%	88	61	80.3%	80.3%
Endocrine	223	180	58.3%	11.6%	293	198	33.8%	19.8%	147	95	67.4%	58.5%	91	61	86.9%	86.9%
Respiratory	110	90	66.7%	11.1%	193	120	27.5%	16.7%	58	30	63.3%	60.8%	33	25	96.0%	96.0%
Neurology	389	298	62.4%	9.4%	520	348	30.2%	15.0%	285	188	60.6%	49.9%	192	152	82.2%	82.2%
Cardiovascular	158	127	60.6%	7.1%	229	152	26.3%	11.7%	121	89	52.8%	44.6%	78	58	84.5%	84.5%
Oncology	919	651	63.9%	6.7%	1,451	827	28.3%	10.5%	383	221	45.2%	37.0%	142	104	81.7%	81.7%
Total	2,541	1,918	64.5%	10.4%	3,743	2,268	32.4%	16.2%	1,554	975	60.1%	50.0%	908	659	83.2%	83.2%
Lead indications																
Other[f]	193	146	75.3%	24.5%	273	157	50.3%	32.5%	174	115	74.8%	64.6%	122	81	86.4%	86.4%
Infectious disease	228	181	66.9%	19.3%	248	135	45.9%	28.8%	127	76	69.7%	62.8%	94	70	90.0%	90.0%
Respiratory	79	66	63.6%	16.3%	120	76	31.6%	25.6%	40	20	85.0%	81.0%	29	21	95.2%	95.2%
Autoimmune	165	127	67.7%	15.4%	178	102	37.3%	22.8%	77	52	80.8%	61.1%	56	37	75.7%	75.7%
Endocrine	188	152	61.2%	14.5%	226	155	38.1%	23.8%	122	78	69.2%	62.4%	78	51	90.2%	90.2%
Oncology	489	334	68.9%	13.2%	527	298	42.3%	19.1%	193	106	54.7%	45.3%	85	58	82.8%	82.8%
Neurology	301	228	62.7%	12.3%	339	218	34.4%	19.6%	191	124	66.9%	56.8%	137	106	84.9%	84.9%
Cardiovascular	127	102	62.7%	8.7%	159	106	27.4%	13.8%	85	62	56.5%	50.6%	63	48	89.6%	89.6%
Total	1,770	1,336	66.5%	15.3%	2,070	1,247	39.5%	23.1%	1,009	633	67.6%	58.4%	664	472	86.4%	86.4%

[a]Categories are listed from highest to lowest LOA from phase 1 for all indications (lead and nonlead). [b]Number of indications identified. [c]Total number of transitions used to calculate the success rate, the *n* value noted in the text. The difference between 'Total in phase' and 'Advanced or suspended' is the number of indications that remain in development. [d]Probability of successfully advancing to the next phase. [e]Probability of FDA approval for drugs in this phase of development. [f]Includes allergy, gastroenterology, ophthalmology, dermatology, obstetrics/gynecology and urology.

BEGIN

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Regulatory Input or Not?

How many studies?

Reproducibility

Interim Analysis

Multiplicity

See Brad Carlin's presentation

Summary

From Comments on ASA Statement on p-values

(1) What does the data say?

- P-values attempt to answer Q1, but they are not the best answer.

(2) What should I believe?

- A likelihood function gives a richer depiction of evidence, and Bayesian methods formally answer Q2 with prior probability distribution to represent pre-data information or belief.

(3) What should I decide?

- Q3 requires a loss function in addition to data.

Summary

Do simulations to assess characteristics of this system

See Scott Berry's and Telba Irony's presentations

Summary

Nowhere did I say
“Alpha is …”

Summary

Making probability assessments (intuition, judgments) more explicit/quantifiable

Summary

ICH-E9

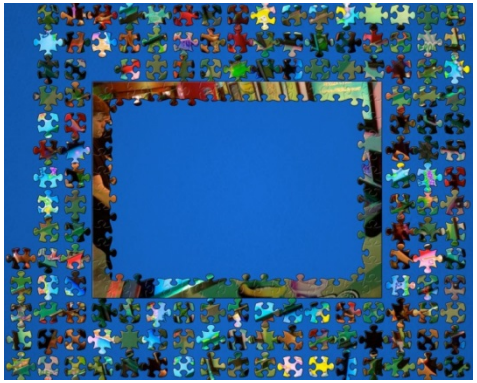
Pre-specification

- Bring objectivity, good science
- Minimize post hoc assessments

Conclusion

Where to start?

- Non-inferiority
- Pediatrics
- Anti-infectives
- Orphan drugs
- Breakthrough



See Telba Irony's presentation

Conclusion

Fundamentally change the way we do business

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