Speed vs. Robustness of the Data

How the pressure to be first, faster, puts pressure on us all and what we can do about it

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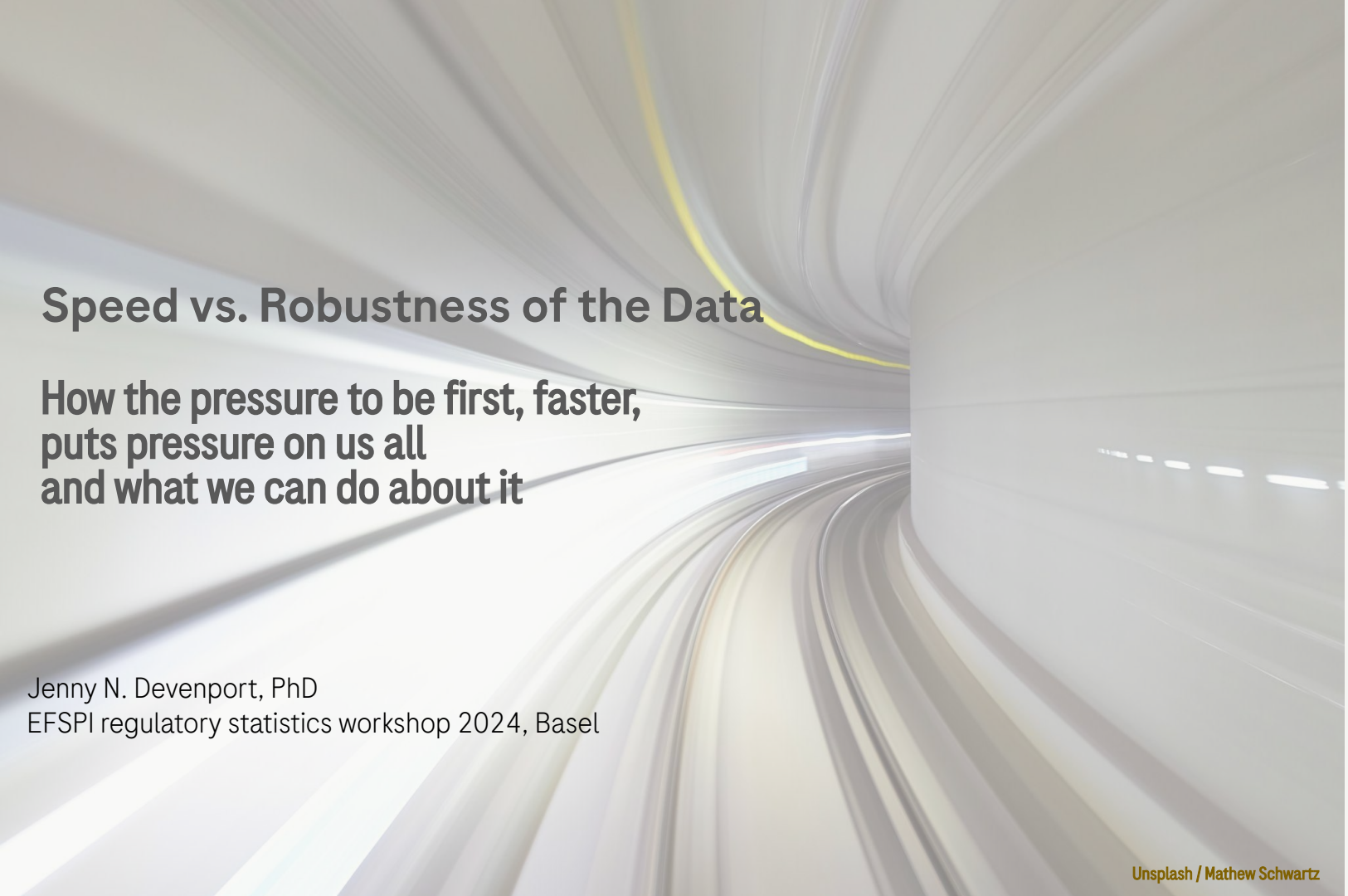


Unsplash / Mathew Schwartz

Disclaimers & Acknowledgements

This work represents the research of the presenter and not necessarily the views of her employer.

Every day I get work with brilliant people who inspire me. Many of you are here 😇

I also get to collaborate across companies, academics, and regulators
who have enhanced my perspective

Let’s define some terms…

In statistics:

Robustness - the ability of the estimates to remain consistent in the presence of violations of assumptions (eg., distributional assumptions like proportional hazards; model misspecification; protocol violations, missing data, outliers, etc.)

Uncertainty - refers to the variability in the estimates (eg., from sampling variability, measurement error, etc)

Let’s define some terms…

More broadly [non statisticians] may also think of

Robustness - validity of the results under different conditions (eg., relatively impervious to variations in patient populations or clinical settings)

Uncertainty - variability due to genetic, environmental or other patient factors

When do we have enough of the right data to call it substantial evidence?

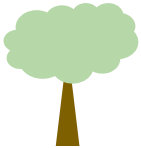
Speed has never killed anyone.
Suddenly becoming stationary, that’s what gets you.

-Jeremy Clarkson

Pressure to Increase the Speed of Drug Development

Patients are waiting

Healthcare systems need effective treatments to reduce burden of disease



Sustainable innovation in the Pharmaceutical Industry

Patient Pressure to Increase the Speed of Drug Development[1]

"The "classic" drug development model relegates the role of patients and patient advocacy groups to that of ***grateful recipients of new treatments that seem to fall from a clear blue sky.***

...

There is little sense of a shared endeavor."

Photo by J. Devenport 17 Feb 2024 - 10:23 am

1 House T, et al. (2019)

Patient Pressure to Increase the Speed of Drug Development[2]

Compassionate use programs to allow access to new drugs prior to formal regulatory approval

Patient advocacy groups are more engaged in drug development with the goals of:

- Increasing the number of therapies in the development by working with multiple sponsors
- Engaging patients to improve enrollment timelines and retention rates
- Influencing patient-relevant endpoint selection
- Testifying at regulatory or advisory committee meetings
- More effective post-marketing safety

2 CTTI (2015)

HC System Pressure to Increase the Speed of Drug Development[3]

A well functioning health system responds in a balanced way to a population's needs by:

- improving the health status of individuals, families and communities
- defending the population against what threatens its health
- protecting people against the financial consequences of ill-health
- providing equitable access to people-centered care
- making it possible for people to participate in decisions affecting their health and health system.

3 WHO

Industry Pressure to Increase the Speed of Drug Development[4,5,6]

According to financial analyses, being first to market ensures more market share.

- First to market products: on average…40% market share and still lead followers by 6% after 10 years
- Advantage is larger for specialty care (12%) and having multiple indications (13%)

4 Schulze et al (2013)
5 Cha et al (2014)
6 Spring et al (2023)

Pressure to Increase the Speed of Drug Development[4,6]

Being first has substantial advantages.

- Unless your drug **stinks**!
  - Or your competitor(s) **follow fast**,
    - have differentiated performance (**value-add**)

Faster approval means more revenue over a longer period of the patent term

4 Schultze et al (2013)
6 Spring et al (2023)

Examples: Fast to Market vs. Best in Class[6]

a) **BTKi ibrutinib had a 4 year lead on competitor launches, captured 77% of class.**

b) **Pembrolizumab launched 3 months before next follower. Fended off competition with superior efficacy and broader label (monotherapy in 1st line NSCLC).**

6 Spring et al. (2023)

Drug development is expensive, and increasingly inefficient[7]

Eroom's Law: R&D efficiency has declined steadily for decades (approvals / 1 bil USD spent)

There are lots of great medicines.

New ones must be "Better than the Beatles"

- Higher sample sizes to demonstrate incremental improvements
- Larger / more complex programs to differentiate performance
- Lower access / price with poor differentiation

7 Scannell et al. (2012)

But of course, being fast doesn’t guarantee success

Speed is irrelevant if you are going in the wrong direction.
Mahatma Gandhi

Speed on the bench doesn't always translate to bedside

The scientific advances made in the last few decades were expected to dramatically accelerate target identification.

- Combinatorial chemistry increased molecule synthesis per chemist by approx 800 fold during 1980s and 1990s,
- DNA sequencing is over 1 billion times faster (aiding identification of new targets),
- High-throughput screening (HTS) has resulted in a tenfold reduction in the cost of testing compound libraries against protein targets since the mid-1990s

7 Scannell et al. (2012)

And what of AI / ML?

“Like carpenters they want to know *which tools*.
They never ask *why build*.” *–Anne Sexton*

We [statisticians] will always be presented with questions about “new” tools.

Of course we love tools. We must ask, WHY BUILD?

Speed may not ensure patient benefit, access, and sustainability

Reviews show a number of post marketing withdrawals of expedited approvals [8]

Reviews of HTA for medicines with Conditional Marketing Authorization suggest scientific uncertainty, with only limited positive opinions [9]

If all companies pursued all possible indications / combinations, drug development resources would quickly be exhausted (eg., CIT space where 1000 trials were ongoing in 2017) [10]

8 Koole SN et al. (2024)
9 Vreman et al (2019)
10 Chen et al (2018)

There are regulatory avenues and well established statistical tools intended to accelerate time to approval while mitigating risks.

Regulatory pathways to speed up drug development[11]

EU

PRIME, Accelerated Assessment and Conditional Marketing Authorisation

UK

Licencing under Exceptional Circumstances, Early Access to Medicines Scheme (EAMS), Innovative Licensing and Access Pathway (ILAP), Conditional Marketing Authorisations

US FDA

Priority Review, Accelerated Approval, Fast Track, and Breakthrough Therapy Programs
Real-time Oncology Review (RTOR)

Cross-jurisdiction

Project ORBIS, ACCESS Consortium… and many, many more

11 Hotaki et al (2023)

So how can statisticians help?

A statistician's role in drug development involves

- structuring the problem / asking good questions
- making a series of good decisions
- designing & running appropriate trials to answer questions (and inform more decisions)
- interpreting evidence properly

Lather, rinse, repeat…

Structure the problem

Every step of drug development is intended to address a specific question.

Be clear about those questions. When you already have data to know the answers, perhaps there are opportunities for efficiency?

When you aren't clear about the questions, it is harder to find or generate the right data. Put all of your assumptions on the table.

NO is still an important answer, even if we don't like it!

Facilitate Data-Driven Decision Making

Statisticians have long had the tools to help with this.

- For every decision you make you run the risk of being wrong. (false positives, false negatives)
- Quantify risks, uncertainty, and understand the range you are playing in

Specific tools in the statistician's kit for SPEED

Focus on time to approval

Don't have a STATS only mindset…Think like a drug developer!

Well established tools in the statistician's kit for SPEED

Focus on time to approval

Don't have a STATS only mindset…Think like a drug developer!

- Merge or skip steps in the drug development cycle (eg., adaptive designs, interim analyses, seamless II/III)
- Test multiple products / combinations at once for operational and statistical gains (eg., platform trials)
- Improve precision or reduce the required sample size
  - SAT, with augmented or external / virtual controls;
  - Covariate adjustment (improve estimation precision)
  - Patient enrichment
- Use surrogate endpoints (that can be observed sooner)

Risk mitigation in accelerated programs

Futility analyses…with meaningful boundaries

Adaptive designs with pre-specified criteria

DSMBs / IDMCs

Close collaboration with health authorities and other stakeholders

Punchlines

All stakeholders in drug development feel some pressure to be fast.

Being fast doesn't guarantee success.

Drug development gets increasingly expensive and inefficient.

There are regulatory avenues and well established statistical tools intended to accelerate time to approval while mitigating risks.

We can work better together as statisticians, regulators, and drug developers to help with speed AND robustness of the data.

Photo by J. Devenport 10 Feb 2024 - 15:42 pm

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