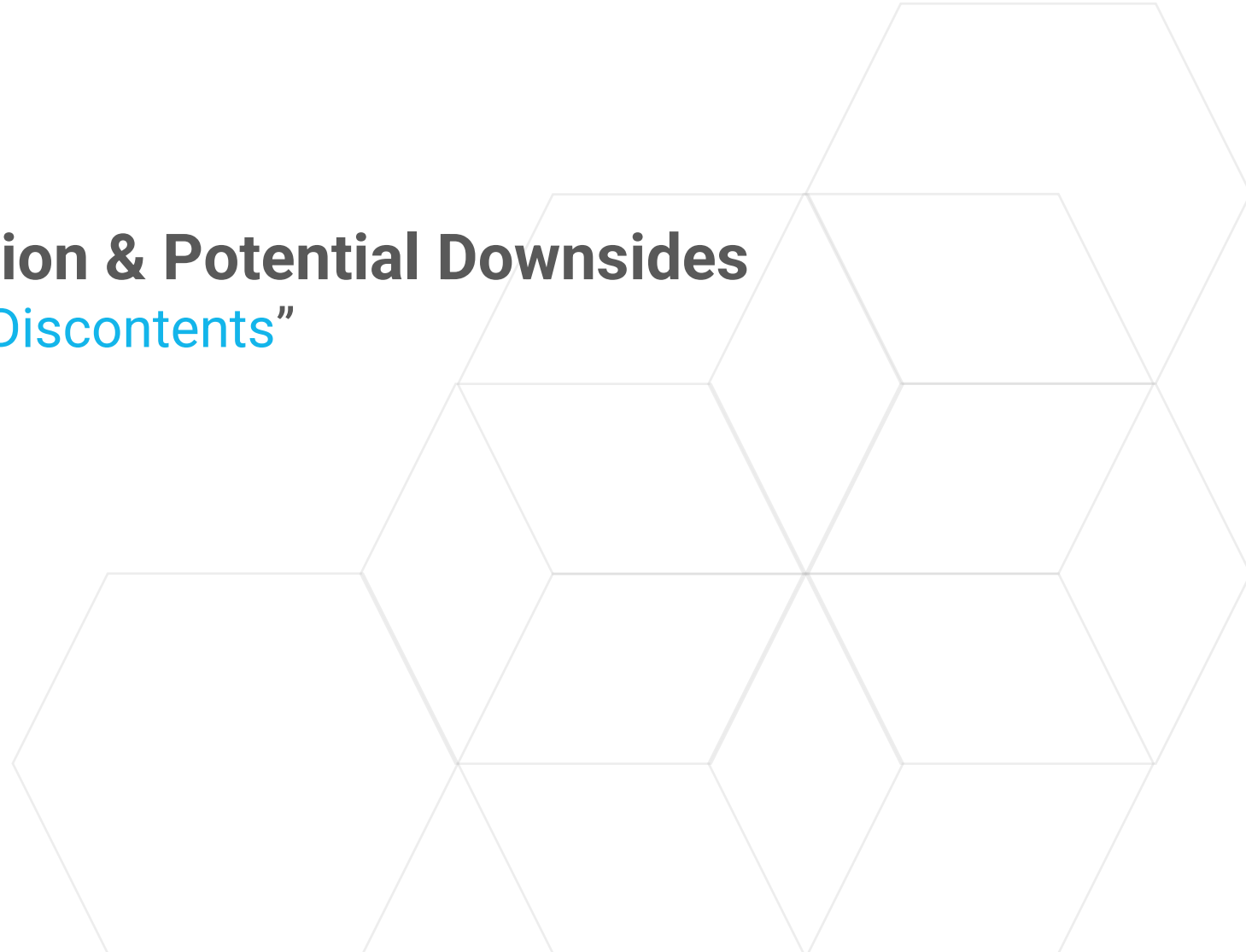




Consolidation, Industrialization & Potential Downsides or “CNS Drug Development & Its Discontents”

Mark G. Opler, PhD, MPH
WCG MedAvante-ProPhase

Changing Site Landscape
ISCTM Annual Meeting, 2022
Washington, DC



Disclosure:

Dr. Opler is an employee and shareholder of WCG Clinical Inc.

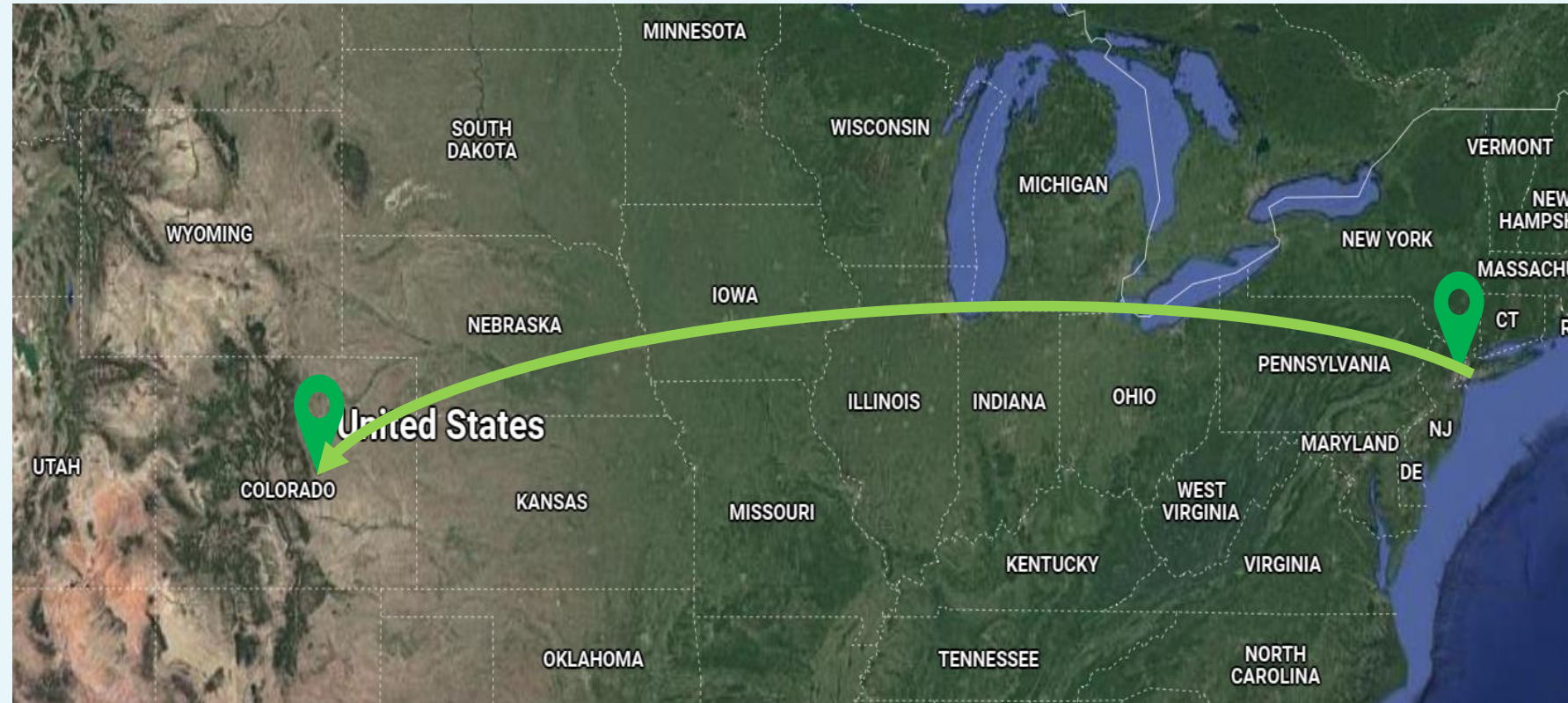
JFK to COS (1 stop, MSP)

My questions:

“Why are studies so difficult now?”

“Why is placebo effect increasing year-over-year?”

“Why is signal disappearing?”



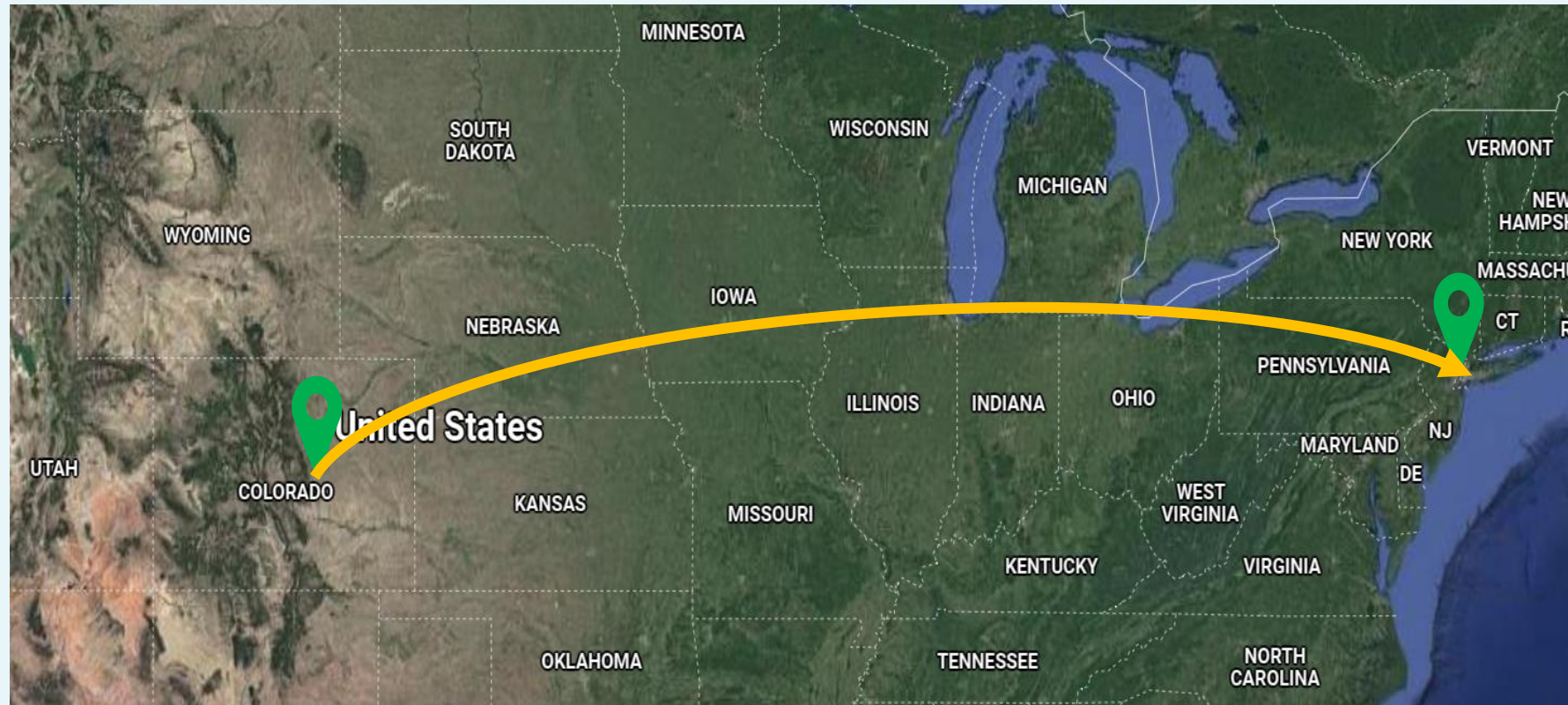
COS to JFK (1 stop, MSP)

His answers:

“I don’t know...”

“Studies are much, MUCH bigger now and investigators are asked to do a lot more at a much faster pace.”

“It may be harder to be a PI when you have to work at industrial scale.”



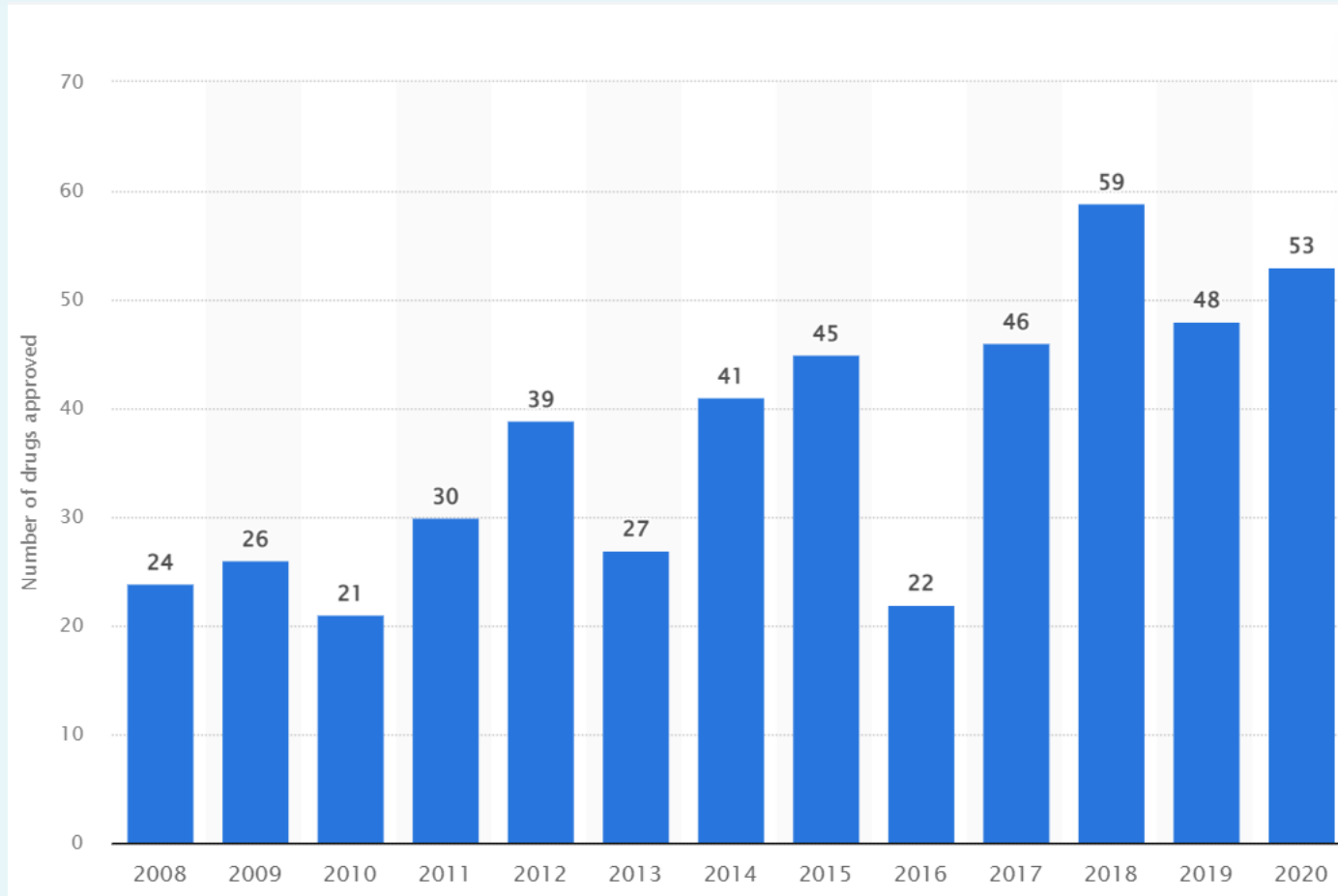
Have we thought meaningfully about the impact of industrialization on sites and patients?

“The process of industrialization is necessarily painful. It must involve the erosion of traditional patterns of life...

“...for the field labourer, the loss of his common rights and the vestiges of village democracy; for the artisan, the loss of his craftsman’s status; for the weaver, the loss of livelihood and of independence; for the child, the loss of work and play in the home; for many groups of workers whose real earnings improved, the loss of security, leisure and the deterioration of the urban environment.”

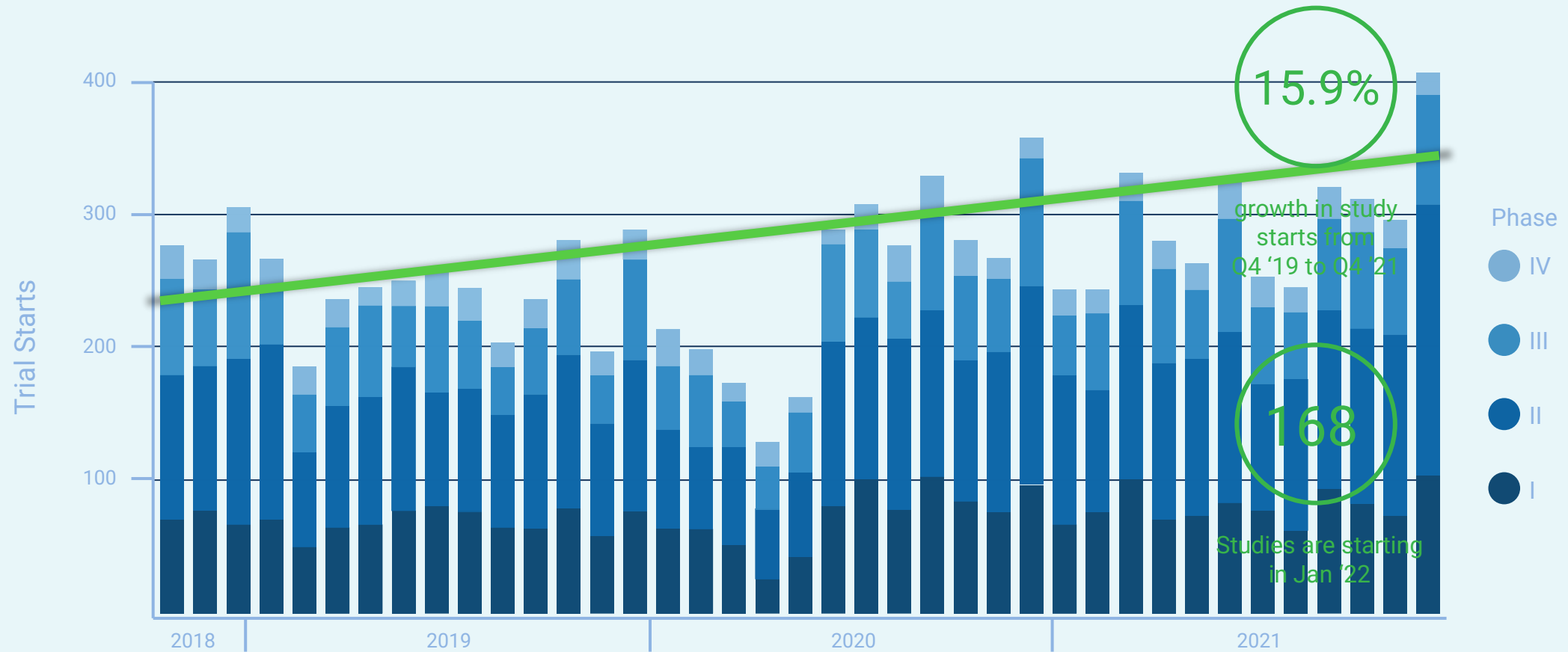
— E.P. Thompson, *The Making of the English Working Class* (1963)

Increasing pace of research, reflected in new drug approvals



Year-wise new drug approvals

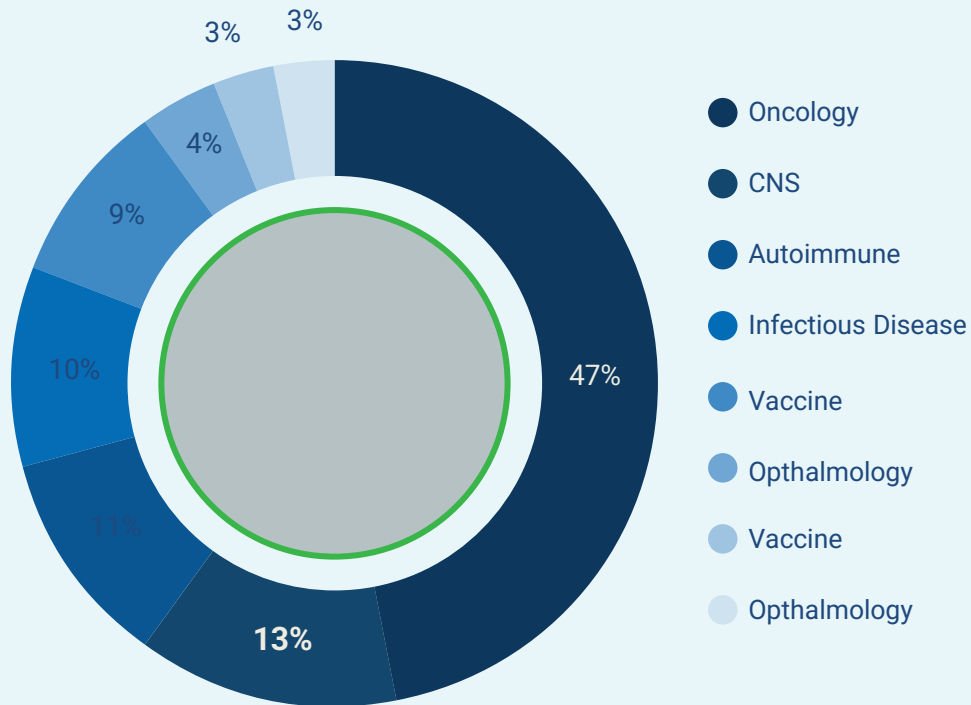
How is the pace of industrialization changing?



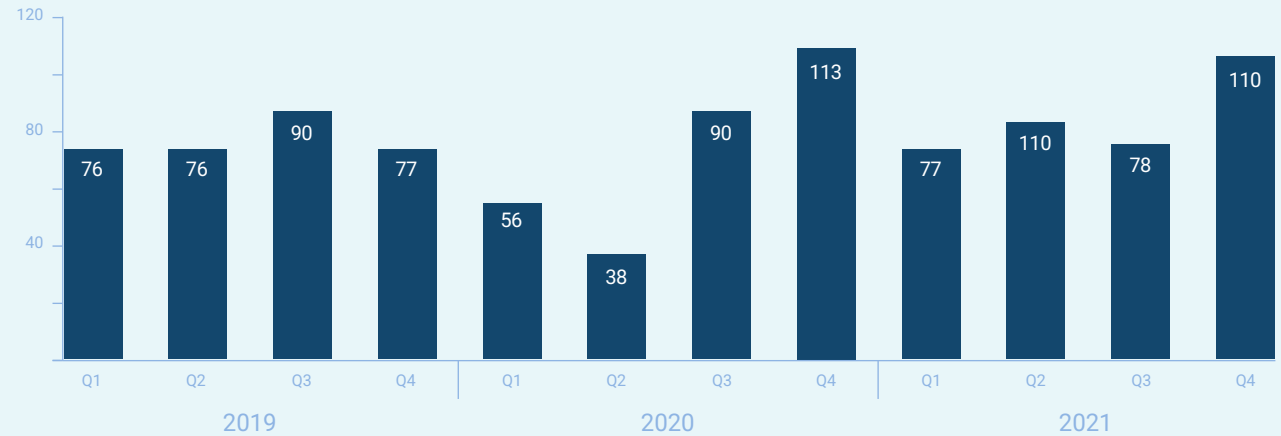
Source: WCG Knowledge Base

How is the pace of industrialization changing?

Trial Starts by TA Initiated in 2021



CNS Trial Starts



Study starts per quarter as 2019 median

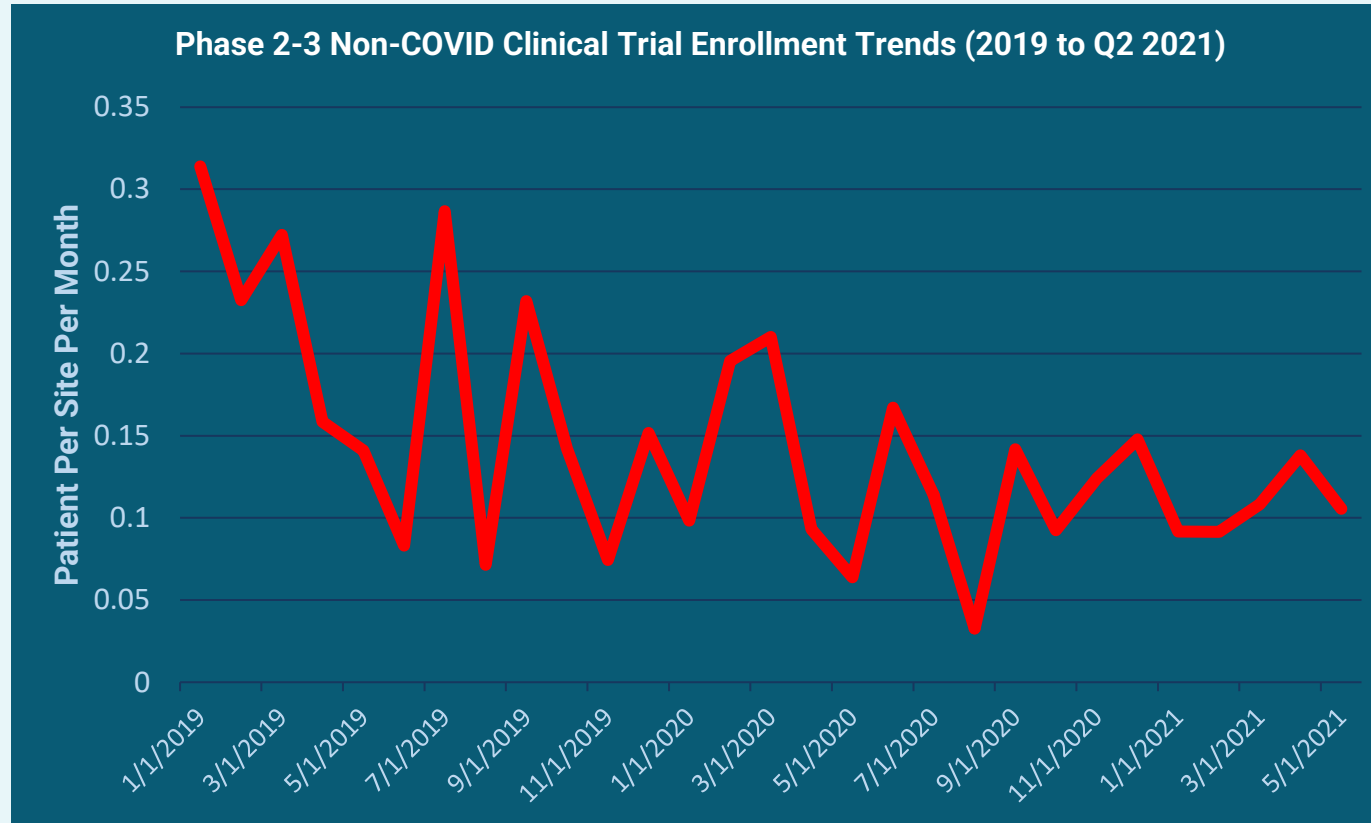


Increase from 2019 to 2021



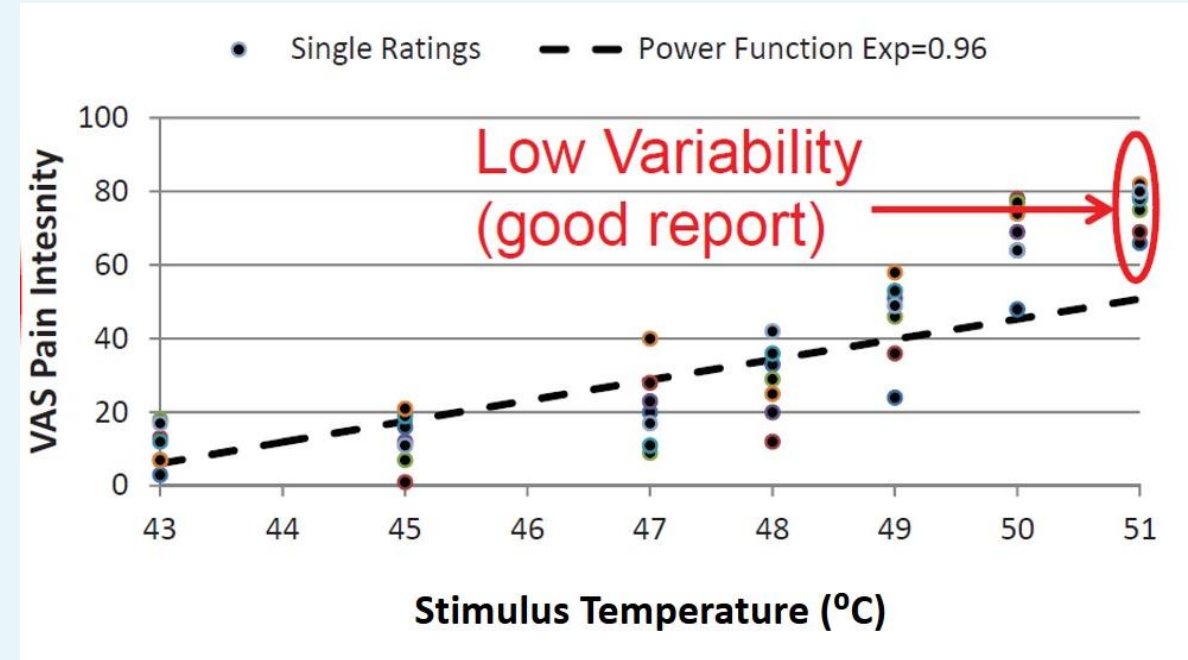
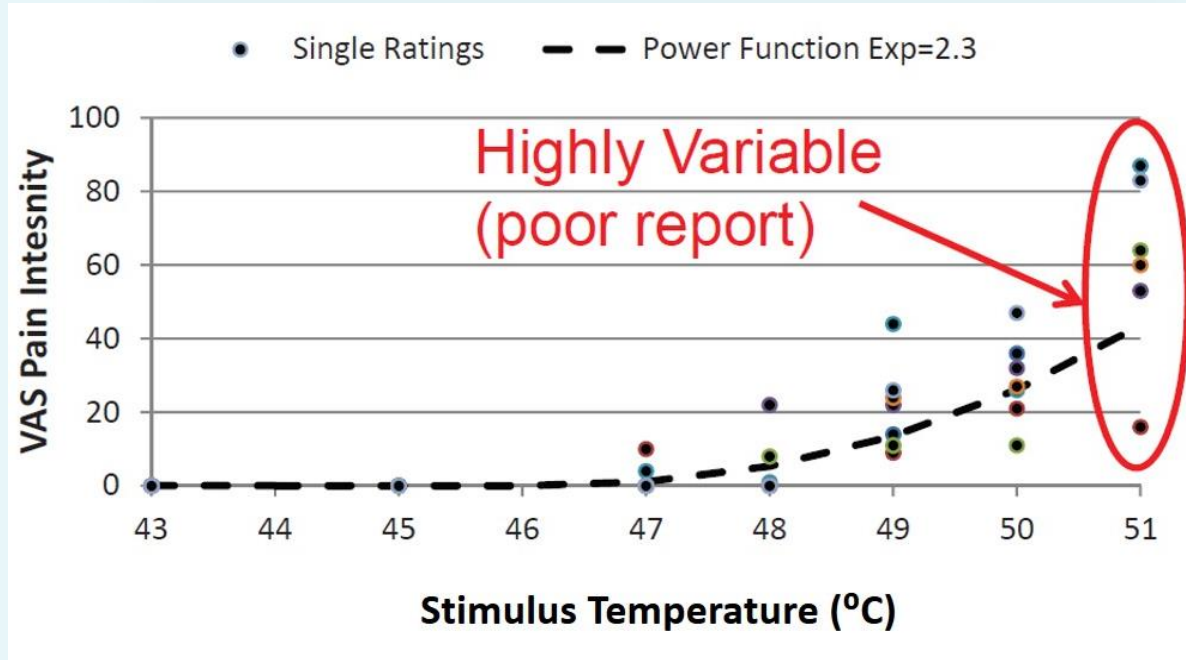
Study starts per quarter as 2021 median

Simultaneous Challenge of Low Enrollment

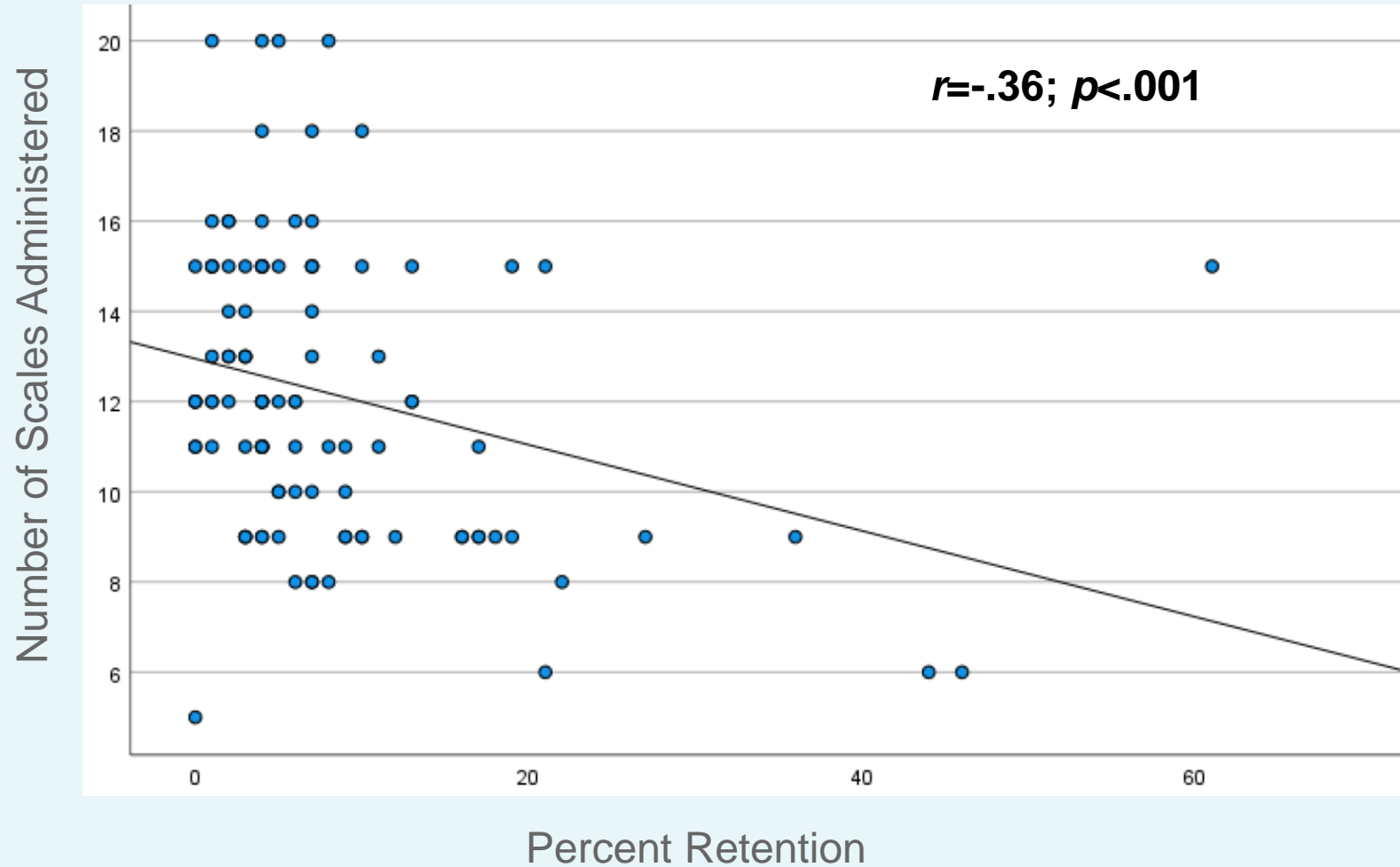


Recruitment as Patients per Site Per Month (Non-COVID)

What is the impact of scaling on quality for patients?



Participant Retention and Number of Scales Administered Across All CNS Indications



What Sponsors Want from Raters

Key visits to be audio / video recorded & reviewed

All raters to have significant years experience using instruments

Same rater at every visit

Same rater conducting CGI and primary endpoint

All raters to have MD/PhD degree

Some Evidence



Mixed Evidence



No Evidence



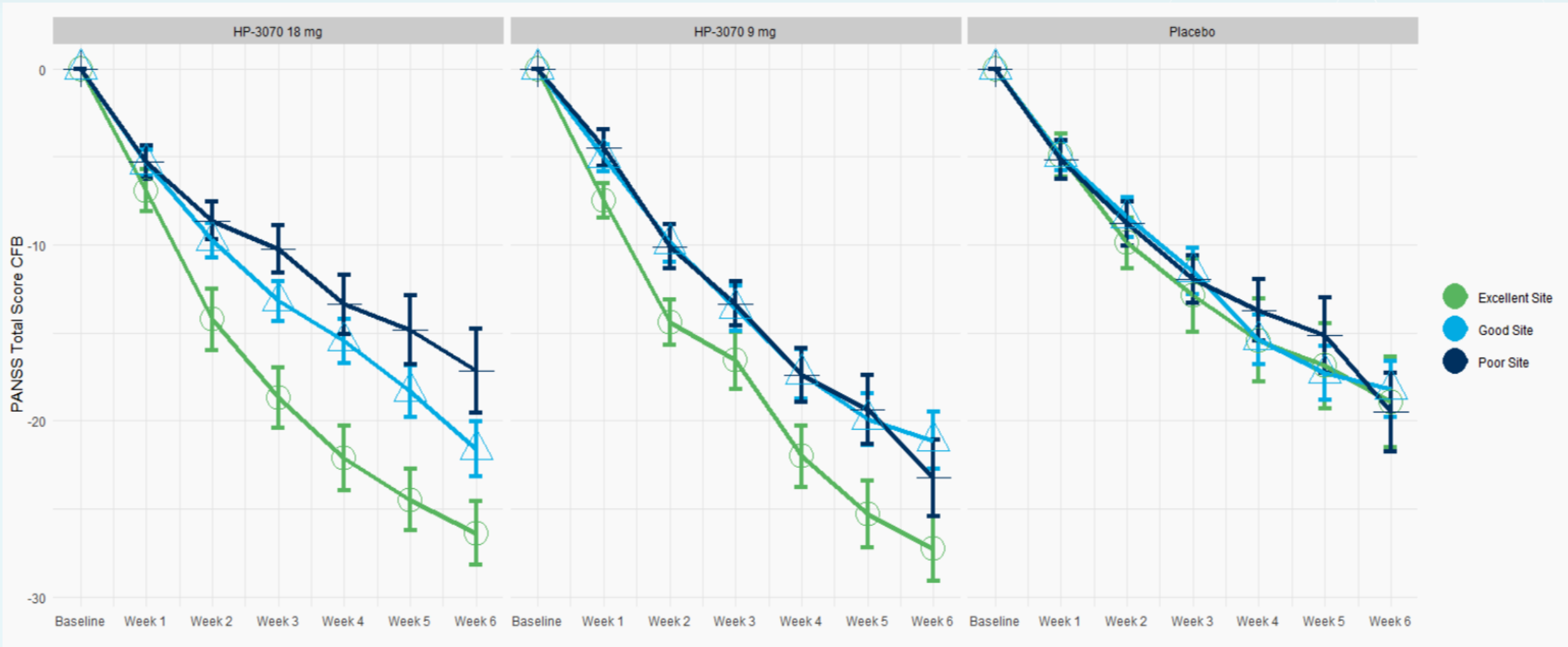
Negative Evidence



Have our responses to sustain data quality in the face of increasing industrialization been:

- **Effective?**
- **Rational?**
- **Equitable?**

What is the impact of scaling on quality on sites?



Rater Burden Model

CDR and SIGMA primary outcome



Model: Total Scale Score; Numbers of Assessments Day; ≥ 2 Discrepancies; ≥ 1 Discrepancy; Rate of Score Failures; Rate of Quality Failures; Rate of Flagged Assessments; Duration (Too Short); Duration (Too Long).



Screening & Baseline visits

CDR $R^2=0.822$, SIGMA $R^2=0.744$

Assessments/Day: $p < 0.05$



Non-Screening/Baseline visits

$R^2=0.574$ for SIGMA, < 0.2 for CDR

Assessments/Day: $p > 0.05$



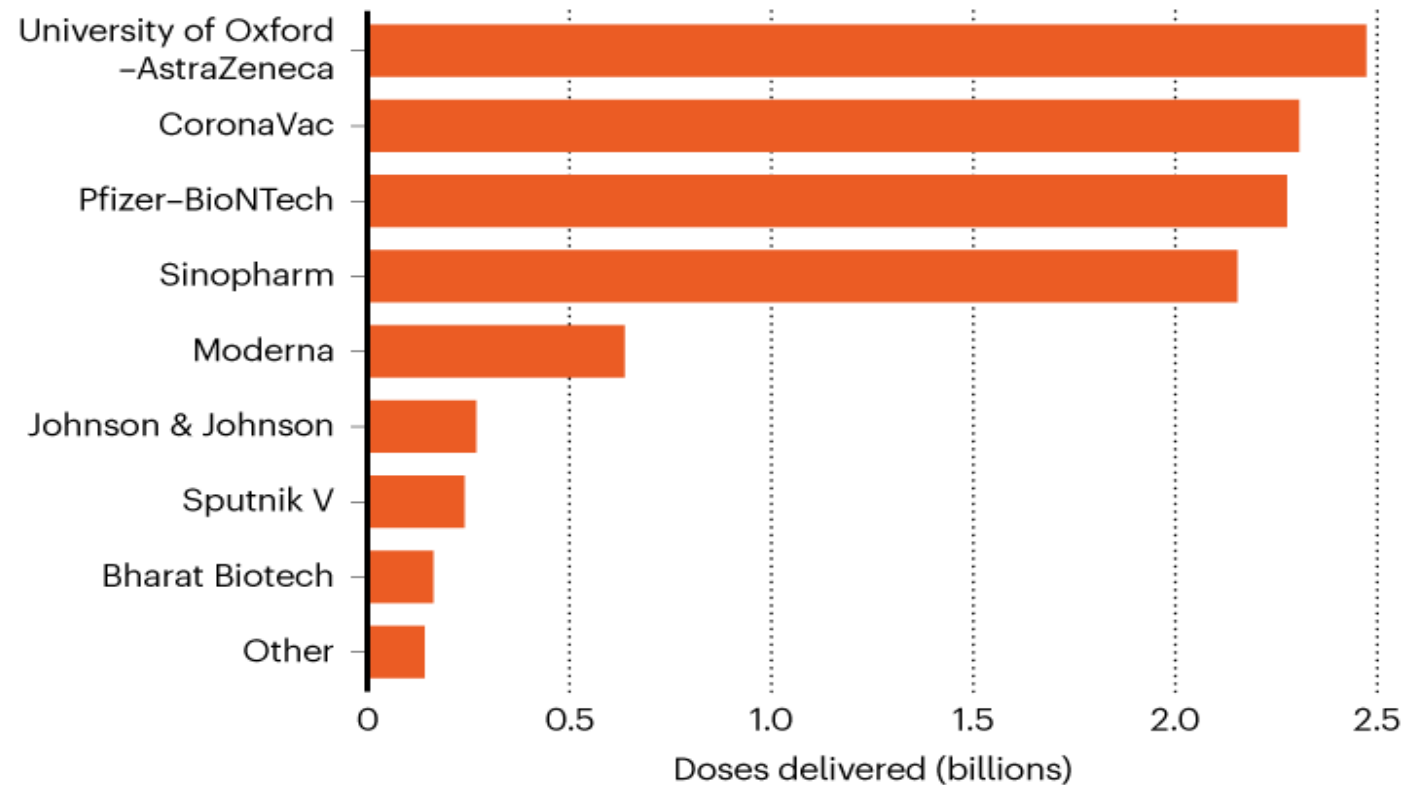
Conclusion:

Rater burden, based on number of assessments per day, the level of pathology in patients under evaluation, and other factors may be associated with poor quality and higher likelihood of discrepancies. This appears to be more likely at screening/baseline, but less so at subsequent visits in both mood and dementia studies.

So Now What?

THE RACE TO VACCINATE

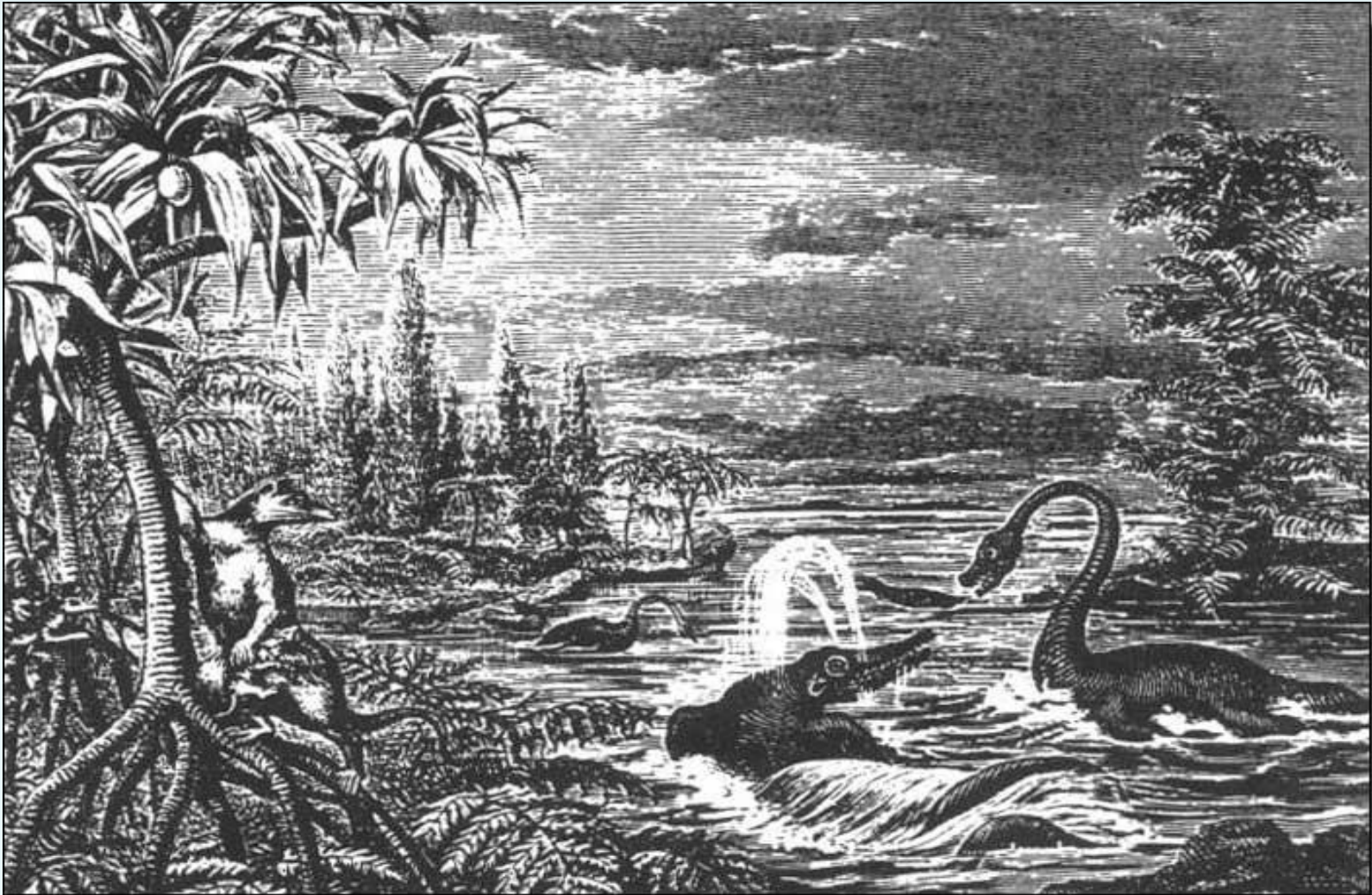
Nearly 10 billion doses of COVID-19 vaccine have been delivered around the world since mid-2020, 8.5 billion of which had been administered by late 2021. Eight different vaccines make up the vast majority of doses*.



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*Data as of 14 December 2021.

So Now What?



Thank you!

