# Two trials rules versus pooled trials rule

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# Disclaimer

- I am an employee of J&J
- Slides don’t necessarily reflect view of J&J

# Terminology

## Two trials rule

- Twin trials analyzed according to frequentist paradigm
- One-sided test of primary null hypothesis at 0.025 in each trial
- If two positive trials are required, risk of approving non-efficacious drug is $0.025^2$=1/1600
- Oncology, rare diseases and large cardiovascular trials are common exceptions
- However, two trials rule is still the norm within many therapeutic areas

## Pooled trials rule

- Single trial where primary endpoint is assed vs one-sided $0.025^2$
- Risk of approving non-efficacious drug is $0.025^2$=1/1600
- Suppose we conduct a single trial with 2N observations instead of two trials with N each
- Senn* and others have shown this pooled trials rule to be more powerful

*Reference: Stephen Senn, Statistical Issues in Drug Development, 2021.

# Potential pros and cons

## Potential advantages

- Moderate power gains (for total sample size of 2N)
- Facilitates early stopping and other interim adaptations
- Potential operational advantages of conducting a single trial
- Relevant information synthesized into a single primary analysis to facilitate decision-making

## Potential caveats

- Concern if pooled trials rule is used to motivate smaller programs
- Could be mitigated by holding total sample size fixed at 2N
- Independent replication from two trials rule is lacking

# Proposal and question

1. Suppose that two trials, each with sample size N, are deemed adequate to support approval
2. As an alternative, a single trial with sample size 2N could form the basis for regulatory decision-making

Question: In which situations would it be appropriate to replace 1 with 2?