DAILY ENGLISH READING

10 September 2026 - C1 - 30 minutes

If one pivotal trial may be enough, what has to become stronger?

Pivotal evidence - statistical robustness - confirmatory evidence - TFL transparency

WHY THIS READING

If one pivotal trial carries most of the efficacy burden, more weight sits on one protocol, one SAP, one set of operational decisions, and one integrated TFL package. The key distinction is not simply one trial versus two trials, but how much credible, independent and internally robust evidence the full package contains.

READING ORDER

0-3	Preview	One pivotal trial vs one piece of evidence
3-14	Main article	Replication, chance, bias, generalizability
14-20	FDA 2026	Strength of evidence and credibility factors
20-25	Confirmatory evidence	Independent support vs within-trial robustness
25-30	Output	Build a single-trial evidence map

SOURCES

MAIN - JAMA HEALTH FORUM - 4 SEP 2026 - OPEN ACCESS

Opportunities and Risks of a Single-Trial Default for FDA Drug Approval

SUPPORT - FDA - REVISED 2026 DRAFT

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

SUPPORT - FDA

One Adequate and Well-Controlled Investigation and Confirmatory Evidence

BRIEF BACKGROUND

Replication and robustness answer different questions.

Independent pivotal trials test whether a result survives a new group of participants, sites, operations and random variation. Multiple analyses of one trial can test robustness, but they cannot recreate independent replication.

FDA's evidentiary framework is context-specific. One adequate and well-controlled investigation plus confirmatory evidence can sometimes satisfy the substantial-evidence standard. That flexibility increases the importance of design credibility, statistical persuasiveness and the total evidence package.

For statistical programming, the high-stakes areas are estimand traceability, multiplicity, missing-data assumptions, sensitivity analyses, subgroup stability, protocol deviations and transparent TFL design.

A useful mental model

> less replication -> more pressure on design credibility -> more pressure on analysis robustness -> more pressure on transparent reporting

KEY VOCABULARY

Term	中文解释	Meaning / use
pivotal trial	关键性试验	A study intended to provide the primary evidence supporting a regulatory decision on efficacy and safety.
substantial evidence	充分有效性证据	The statutory evidentiary standard FDA applies when deciding whether a drug's effectiveness has been demonstrated.
adequate and well-controlled investigation	充分且良好对照的研究	A clinical investigation with design, conduct, controls, endpoints, and analyses capable of supporting a credible causal conclusion.
confirmatory evidence	确证性证据	Additional evidence that supports the findings of one adequate and well-controlled clinical investigation.
replication	重复验证	Obtaining compatible evidence from an independent study or source.
generalizability	可推广性	The extent to which results apply beyond the exact participants, sites, conditions, or settings studied.
statistical power	统计效能	The probability that a study detects a real effect of a specified size.
type I error	第一类错误	The probability of falsely concluding that an effect exists when the null hypothesis is true.
multiplicity	多重性	The inflation of false-positive risk when many hypotheses, endpoints, subgroups, or analyses are tested.
robustness	稳健性	The degree to which a conclusion remains stable under reasonable alternative assumptions or analyses.
sensitivity analysis	敏感性分析	An analysis used to examine whether conclusions change under alternative assumptions or handling rules.
intercurrent event	伴随事件	An event occurring after treatment initiation that affects how an endpoint is interpreted or whether it is observed.
missing-data assumption	缺失数据假设	An assumption about how unobserved outcomes relate to observed data and treatment assignment.
external validity	外部效度	The credibility of applying study findings to populations or settings outside the trial.
evidentiary package	证据组合	The complete body of trial, supportive, mechanistic, external, and other evidence used for a regulatory conclusion.

USEFUL PHRASES

1. a single trial places more weight on design credibility
A single trial places more weight on design credibility.

2. replication protects against chance and study-specific bias
Replication protects against chance and study-specific bias.

3. confirmatory evidence should strengthen rather than merely decorate the pivotal result
Confirmatory evidence should strengthen rather than merely decorate the pivotal result.

4. the analysis plan must anticipate fragile conclusions
The analysis plan must anticipate fragile conclusions.

5. sensitivity analyses should target the assumptions that matter most
Sensitivity analyses should target the assumptions that matter most.

6. generalizability cannot be inferred from statistical significance alone
Generalizability cannot be inferred from statistical significance alone.

7. a marginal primary result leaves little redundancy in the evidence package
A marginal primary result leaves little redundancy in the evidence package.

8. the TFL package should make uncertainty visible
The TFL package should make uncertainty visible.

9. independent confirmation and internal consistency are different forms of reassurance
Independent confirmation and internal consistency are different forms of reassurance.

10. efficiency gains should not be confused with reduced evidentiary burden
Efficiency gains should not be confused with reduced evidentiary burden.

COMPREHENSION

1. Why can two independent pivotal trials provide information that multiple analyses of one trial cannot fully replace?

2. Why is one pivotal trial plus confirmatory evidence different from simply lowering the standard of evidence?

3. Which SAP and TFL elements become especially important when one trial carries most of the efficacy burden?

4. Why are sensitivity analyses useful but not equivalent to replication?

5. How can an SP make uncertainty visible without editorially overstating weakness?

RETELLING

30 seconds - Explain replication versus robustness.

45 seconds - Fewer independent trials -> higher design burden -> stronger analysis transparency -> stronger TFL traceability.

60 seconds - Explain why statistical significance can still be unpersuasive when the surrounding evidence is fragile.

5-MINUTE SPEAKING / OUTPUT TASK

Minute 1: State endpoint, estimand, population and treatment-effect measure.

Minutes 2-3: Identify five failure points and the analysis/TFL that exposes each one.

Minute 4: Separate primary statistical strength, within-trial robustness and independent confirmation.

Minute 5: Give a 90-second recommendation on whether the package is persuasive.

ONE SENTENCE TO KEEP

> When one pivotal trial carries most of the efficacy burden, the statistical package has less room for hidden ambiguity: estimands, multiplicity, missingness, sensitivity analyses, traceability, and uncertainty all have to be unusually clear.