Discounting the Results of "Positive" Phase 2 Trials: What is the Probability of Phase 3 Success?

Mark J. Ratain, M.D.
University of Chicago

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Essay

Why Most Published Research Findings Are False

PLOS Med, 2005

John P. A. Ioannidis

- **Probability of a true positive depends on**
  - **Power (1-β) of prior study**
  - **α of prior study**
  - **Pre-study probability of success (≤0.5)**
  - **Bias (10-80%)**
- **Best-case scenario is 85% "truth"**

Estimating Base Case

- $(1-\beta)/[(1-\beta)+\alpha]$
  - 0.94 (α=0.05, 1-β=0.8)
  - 0.89 (α=0.1, 1-β=0.8)
  - 0.75 (α=0.2, 1-β=0.6)

Discounting Phase 3 Success from Base Case

- **Bias**
  - **10-40% (based on sponsor and flexibility of Phase 2 trial)**
- **Historical controls**
  - **15-100% (multiply α by at least 2; many studies do not even have a formal historical control)**
- **Subset analyses**
  - **≥67% (at least 3 analyses)**
- **Pre-study skepticism**
  - **?75% (if 20% success rate prior to start of Phase 2)**

Table 4. PPV of Research Findings for Various Combinations of Power (1 – β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

1 – β	*R*	*u*	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17