Background: Evidence-based medicine and comparative effectiveness research movements have increased interest and activity in relative effectiveness of interventions.

- There is an expressed need for innovative approaches to clinical trials to be conducted under conditions of actual practice, enabling estimates of real-world effectiveness.
- There is an expressed need for statistical and epidemiological methods to predict patient responses to interventions.
- Key Requirements: **Transparency** so studies, data, conclusions can be assessed. Sufficient detail regarding methods, PICOTS (patients, interventions, comparators, outcomes, timing setting).

RCTs

Good internal validity if well designed and conducted; however, are time consuming, expensive and may lack external validity.

Pragmatic or Practical Trials

Danger of "buzz term."

Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in 6 therapeutical trials. J Chronic Dis 1967;20:637-48. PMID 4860352

- Referred to as "explanatory" trials if investigators attempted to establish causality.
- Referred to as "pragmatic" trials if designed to help choose options for clinical care.
- Pragmatic trials were NOT introduced as **a new trial design**, but rather an **"attitude"** to clinical trial design.

❖	Explanatory Trials	Pragmatic Trials
1	Efficacy	Effectiveness
2	Ideal conditions	Normal practice conditions
3	Highly selected (compliant, likely to benefit) subjects	Minimal selection criteria beyond clinical condition
4	Enforced, monitored interventions	Flexibility in interventions to reflect normal practice
5	Outcomes: short-term, intermediate	Outcomes relevant to end-users

- Need to critically appraise trials for validity first.
- The term "pragmatic" should not be assumed to be more valid or more useful.
- Explanatory trials may have good external validity.
- Pragmatic trials may have serious threats to internal validity.

Other Designs with Control Groups

- Interrupted time series or delayed treatment design: several units are studied with before/after intervention and progressively delayed starting times.
- Propensity scores
  - Start with observational study and assume equal groups using propensity scores (note—assumption likely to be wrong)
  - Then perform regression analysis providing estimate of effect
  - Scores can only account for the factors measured and only as well as the instruments can measure them (selection bias). Problems with differing dosages and other care experiences (performance bias). Requires modeling (assessment bias)
- Network meta-analyses
  - Assess the comparative effects of more than two alternative interventions for the same condition that have not been studied in head-to-head trials--they must have one intervention in common
  - Include both direct and indirect evidence (mixed comparisons)
  - Indirect evidence is derived from statistical inference—not direct comparisons—which requires multiple complex assumptions and complex statistical models to adjust for the inclusion of both direct and indirect evidence and multiple clinical and methodological differences in the included trials
  - The combination of direct and indirect evidence may be more likely to result in distorted estimates of effect size if there is inconsistency in effect sizes between direct and indirect comparisons
  - Network meta-analyses rank different treatments according to the probability of being the best treatment—rankings may be misleading because differences may be quite small or inaccurate if the quality of the meta-analysis is not high

Observational & Administrative Claims Data, Surveys, Medical Records

Can use these sources to (examples)—

- Identify populations for further study
- Evaluate implementation of intervention
- Generate hypotheses
- Current condition scenarios (e.g., who, what, where in QI projects)
- Safety signals
- Extend findings from RCTs, meta-analyses (e.g., registry data)
- Economic projections (e.g., balance sheets, models)

Need for more information on costs and benefits of data collection, transparency, skills in modeling

Positive Predictive Value by Study Type

Well-done RCT	0.85
Meta-analysis of well-done RCTs	0.85
Meta-analysis of small, inconclusive RCTs	0.41
Well-done epidemiological (observational) study	0.20
Epidemiologic study with threats to validity	0.12
Discovery-oriented exploratory research	0.0010

Ioannidis JPA. Why Most Published Research Findings are False. PLoS Med 2005; 2(8):696-701 PMID: 16060722