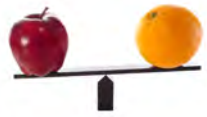
Comparative Efficacy and Effectiveness Research for Clinical Decision-Making

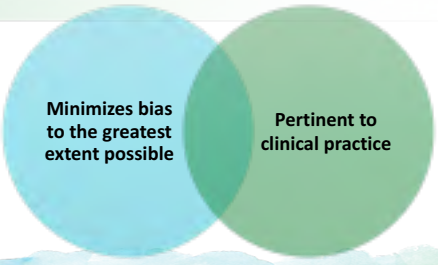
April W. Armstrong, MD MPH
Associate Dean for Clinical Research
Vice Chair and Associate Professor of Dermatology
University of Southern California



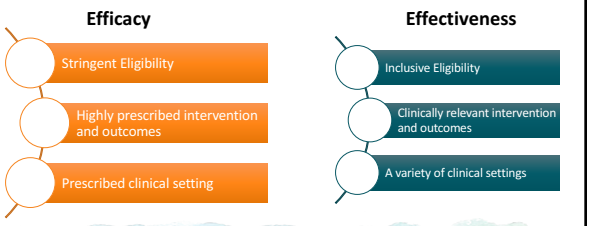
Outline

- Framework for Comparative Efficacy Research
- Indirect comparison methods
- Framework for Comparative Effectiveness Research

What is "best evidence"?



Efficacy and effectiveness are not the same



Gartlehner et al J Clin Epid 2006

Efficacy and effectiveness studies optimize different aspects of validity

Experimental (RCTs)

Pragmatic trials
Quasi-experimental study designs
Observational designs

Adapted from: Winstein & Lewthwaite, Eugene Michels Forum: CSM, Nashville TN, February 7, 2004

Head-to-head studies are the gold standard in comparative efficacy trials.

Head-to-head trials between different treatments are often not available.

Indirect comparison methods create opportunities for comparative efficacy evaluation.

Head-to-head

- Patients are randomized to Drug A versus Drug B *in the same trial*.

Indirect Comparison

- Results for Drug A from one trial is compared to results for Drug B from a *different* trial.

Patient-Level versus Aggregate Data

- Patient-Level Data:
  - Data for *individual* patients

- Aggregate data
  - Summary for a *group* of patients

Comparative Efficacy Evidence Level

Data from the same trial

Head to Head: Drug A versus Drug B in the same trial

Data from different trials

Indirect Comparison: **Patient-level** Drug A versus **Patient-level** Drug B

Indirect Comparison: **Patient-level** Drug A versus **Aggregate** Drug B

Indirect Comparison: **Aggregate** Drug A versus **Aggregate** Drug B

Comparative Efficacy Evidence Level

Head to Head: Drug A versus Drug B in the same trial

Indirect Comparison: **Patient-level** Drug A versus **Patient-level** Drug B

Indirect Comparison: **Patient-level** Drug A versus **Aggregate** Drug B

Indirect Comparison: **Aggregate** Drug A versus **Aggregate** Drug B

Head-to-head RCTs answer efficacy question with high internal validity.

	Greater Short-Term Efficacy
Ustekinumab vs etanercept	Ustekinumab
Secukinumab vs etanercept	Secukinumab
Secukinumab vs ustekinumab	Secukinumab
Ixekizumab vs etanercept	Ixekizumab
Ixekizumab vs ustekinumab	Ixekizumab
Brodalumab vs ustekinumab	Brodalumab
Guselkumab vs Adalimumab	Guselkumab

Etanercept dose is the high-dose 50 mg twice weekly for the first 3 months.

Blauvelt A et al. *J Am Acad Dermatol* 2017;76:60-69. Gordon KB et al. *N Engl J Med*. 2015; 373:136-144. Griffiths CE et al. *N Engl J Med*. 2010;362:118-128. Griffiths CEM et al. *Lancet*. 2015;386:541-551. Langley RG et al. *N Engl J Med*. 2014;371: 326-338. Leonardi M et al. *N Engl J Med*. 2015;373:1318-1328. New head-to-head data. 2017. https://investor.lilly.com/releasedetail.cfm?ReleaseID=1015859

Comparative Efficacy Evidence Level

Head to Head: Drug A versus Drug B in the same trial

Data from different trials

Indirect Comparison: **Patient-level Drug A** versus **Patient-level Drug B**

Rare

Indirect Comparison: **Patient-level** Drug A versus **Aggregate** Drug B

Indirect Comparison: **Aggregate** Drug A versus **Aggregate** Drug B

Comparative Efficacy Evidence Level

Head to Head: Drug A versus Drug B in the same trial

Data from different trials

Indirect Comparison: **Patient-level** Drug A versus **Patient-level** Drug B

Indirect Comparison: **Patient-level Drug A** versus **Aggregate Drug B**

Indirect Comparison: **Aggregate** Drug A versus **Aggregate** Drug B

How does short-term efficacy compare between apremilast and methotrexate in adults with moderate-to-severe psoriasis?

PASI-75 response in methotrexate and apremilast from different trials at week 16

- Methotrexate
- Patient-level data
- **36.4% methotrexate**, 18.9% placebo (CHAMPION)

- Apremilast
- Aggregate data
- **38.7% apremilast**, 7.6% placebo (ESTEEM-1)
- **33.3% apremilast**, 3.6% placebo (ESTEEM-2)

**645 patients from the ESTEEM trials and 163 patients from CHAMPION were used for the indirect comparison; All methotrexate naïve population.

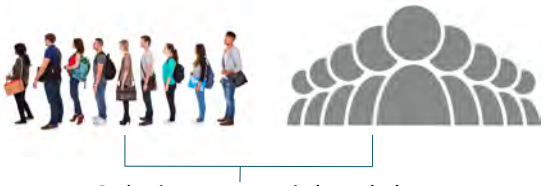
Armstrong et al, J Am Acad Dermatol. 2016 Oct;75(4):740-746.

Indirect comparison

- $Difference\ in\ rate\ difference = (R_{APR} - R_{PBO}) - (R_{MTX} - R_{PBO})$

Armstrong et al, J Am Acad Dermatol. 2016 Oct;75(4):740-746. 18

To account for differences between trials, we **pool the variances** from treatment arms



Pool variance to create a single standard error "Anchor-based" indirect comparison

Armstrong et al, J Am Acad Dermatol. 2016 Oct;75(4):740-746. 19

- The difference in PASI-75 response rate differences between apremilast vs. methotrexate was not statistically significantly different at 16 weeks (p-value 0.086)

No significant Difference in PASI 75 Response

Rate difference=13% (95% CI -1.8%,28%), (p-value 0.086)

Armstrong et al, J Am Acad Dermatol. 2016 Oct;75(4):740-746.

Number Needed to Treat (NNT)

- The number of patients that would need to be treated with the intervention A instead of intervention B to gain one additional responder
- Which drug is more effective:
  - Drug A: NNT to gain one additional responder=4 patients
  - Drug B: NNT to gain one additional responder=2 patients
- A therapy is **more effective** if it has a **small NNT** to gain one additional responder.

How many patients needed to be treated with apremilast instead of methotrexate to gain one additional PASI 75 responder?

Use reciprocal of the rate difference to calculate NNT

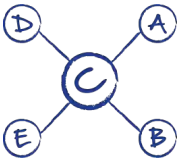
- 7.6 patients would need to be treated with apremilast instead of methorexate to gain 1 additional PASI-75 responder

How much does it cost to gain one additional responder by using apremilast instead of methotrexate?

Incremental Cost Per Responder (ICPR)

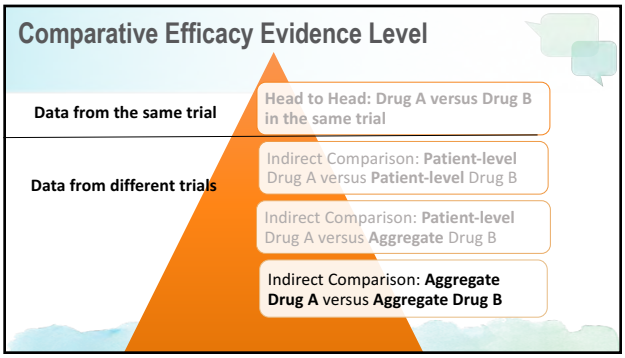
$$ICPR = \left(\frac{Annual\ Cost_{APR} - Annual\ Cost_{MTX}}{Difference\ in\ Rate\ Difference}\right)$$

Incremental Cost Per Responder (annual, US$)



What happens when you only have published aggregate data and no patient-level data?

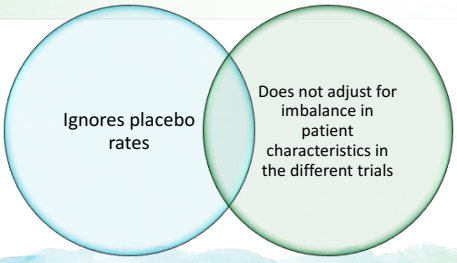
Comparative Efficacy Evidence Level



Naïve comparison of response rates is flawed and not recommended

	Drug A Trial		Drug B Trial	
	Drug A	Placebo	Drug B	Placebo
Response Rate	37%	1.4%	22%	0.6%

Why is naïve comparison not recommended?



Below are results for two separate trials--one trial for Drug A versus placebo, and another trial for Drug B versus placebo. **Which drug performs better?**

	Response Rate (%)	
Trial	Active Drug	Placebo
Drug A	68%	4%
Drug B	51%	2%

- A. Drug A performs better than drug B
- B. Drug B performs better than drug A
- C. It's a tie between drug A and drug B

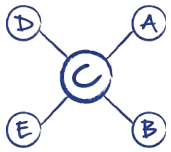
Different relative effect measures can lead to conflicting conclusions about which treatment is better.

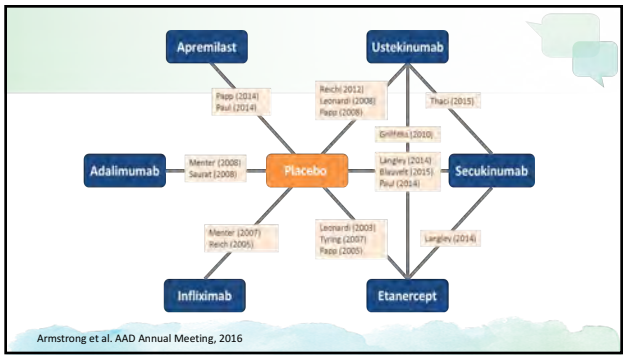
Trial	Response Rate (%) Active Drug [x]	Placebo [y]	Treatment Effect (Active vs. Placebo) Rate Difference [x]-[y]	Relative Rate [x]/[y]	Odds Ratio* o[x]/o[y]
Drug A	68	4	64	17	51
Drug B	51	2	49	26	51
Placebo-Adjusted Indirect Comparison of Drug A vs. Drug B			15.0 **Favors A**	0.67 **Favors B**	1.00 **Tie**

*o[x] = [x]/(100% - [x])
x=response rate in active drug
y=response in placebo

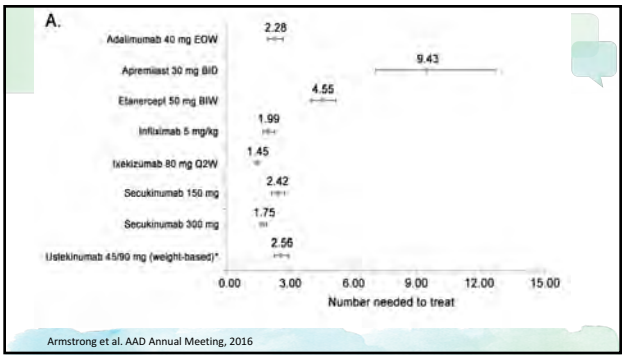
Network meta-analysis provides relative efficacies among therapies

- Uses **direct comparisons** of treatments within RCT and **indirect comparisons** across trials based on a **common comparator**
- Commonly adjusts for observable differences at trial level (with meta regression)





Armstrong et al. AAD Annual Meeting, 2016



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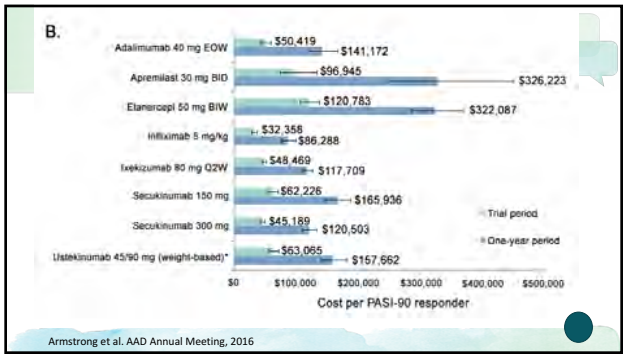


Armstrong et al. AAD Annual Meeting, 2016

Framework for Comparative Effectiveness Research

Key Features of Comparative Effectiveness Research

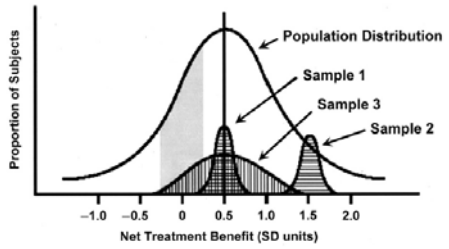
- The objective is to inform decisions
- Compares at least 2 alternatives, each with potential to be best practice
- Analysis at the individual and group levels
- Measure outcomes important to patients (both benefits AND harms)
- Conducted in real world settings

Committee on Comparative Effectiveness Research Prioritization – Institute of Medicine. *Initial National Priorities for Comparative Effectiveness Research*. The National Academies Press, 2009.

Drug vs. drug **Screening vs. usual care**

Lifestyle vs. drug **Drug vs. device**

Comparative effectiveness research assesses treatment effects at population-level



Reprinted from Kravitz et al. *Milbank Q. 2004;82:661– 687*

Comparative effectiveness studies often use pragmatic trial and observational study design.

Characteristic	RCT	Pragmatic	Observational
Focus	Efficacy and safety; assess mechanistic effect; Can it work	Effectiveness and safety; assess / inform decision-making; Does it work under usual care conditions?	Effectiveness and safety; Does it work in actual practice?
Setting	Ideal / artificial	Real-world routine care (with potential minor departures)	Real-world routine care
Population	Strictly defined; homogenous	Typically broad; heterogeneous	Broad; heterogeneous
Randomization	Yes	Typically yes	No
Blinding	Typically yes	No	No
Interventions	Fully interventional	Minimally interventional (e.g., rand.)	Non-interventional
Outcomes	Clinical surrogates; short term	Longer term outcomes; PROs	Long term outcomes; PROs
Sample Size	Typically small	Typically larger	Typically large
Validity	High internal (↓ bias); low external (↓ generalizability)	Moderate internal; moderate to high external	Low internal; high external
Prospective/Retro	Prospective	Prospective	Prospective or retrospective
Comparable cost	Higher	Moderate	Lower

Putting it all together

- Consider all *scientifically valid* data from **broad ranges** of data sources and study designs
- **Innovate** research methodology to reduce bias
- Know **limitations** associated with study design and analyses
- Comparative efficacy and comparative effectiveness research must **not be used as a blunt policy instrument** for cost control.

Thank You!

April W. Armstrong, MD MPH
Associate Dean for Clinical Research
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Keck School of Medicine
University of Southern California