Northwestern

Implementation Science 201

Overview of Experimental Designs for Implementation Research with Applications to HIV

PRESENTERS

C. Hendricks Brown, Ph.D. hendricks.brown@northwestern.edu
J.D. Smith, Ph.D. jd.smith@northwestern.edu
Nanette Benbow, M.A.S. nanette.benbow1@northwestern.edu

Center for Prevention Implementation Methodology FOR DRUG ABUSE AND HIV

Northwestern

Institute for Sexual and Gender Minority Health and Wellbeing

Northwestern University Feinberg School of Medicine
Institute for Public Health and Medicine

THE UNIVERSITY OF CHICAGO

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NIMH: PrEP Implementation Science Research to Inform an Integrated Public Health Model for Biomedical HIV Prevention (Supplement to TC-CFAR, Greene PI, Brown & Smith Co-Is)

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NIMH: Implementation Research Institute (IRI; R25MH080916, Proctor PI)

ODP: Prevention Science & Methodology Group (P30DA027828-07S1, Brown PI)

Contributors

Brian Mustanski	Northwestern	Ce-PIM Co-Director
Juan Villamar	Northwestern	Ce-PIM Coordinator
Carlos Gallo	Northwestern	Ce-PIM Co-I
Larry Palinkas	USC	Ce-PIM Co-I
John Schneider	U of Chicago	Ce-PIM Co-I
Sean Young	UCLA	Ce-PIM Co-I
Patrick Sullivan	Emory	Ce-PIM Co-I
Judy Moskowitz	Northwestern	TC-CFAR BSIS Co-Dir
Alida Bouris	U of Chicago	TC-CFAR BSIS Co-Dir

Goals

- Defining characteristics of trials testing implementation
- Basic understanding of various implementation study designs
- Appreciation of key challenges in designing and conducting an implementation trial
- Part 2 of an ongoing series of workshops in implementation science for HIV

Outline

- Terminology
- Implementation Research Questions
- Implementation Strategies
- Measuring Implementation Outcomes
- Implementation Research Designs
  - Within-Site Designs
  - Between-Site Designs
  - Within- and Between-Site Designs: Roll-Out Designs
  - Hybrid Effectiveness-Implementation Trials
  - Additional Considerations
- Summary

Terminology

- **Implementation** is the use of strategies to adopt and integrate evidence-based health interventions and change practice patterns within and across specific systems
- **Implementation research** evaluates of the use of strategies to integrate interventions into real-world settings to improve patient outcomes
- **Implementation science** is the study of methods to promote the integration of research findings and evidence into healthcare policy and practice
- **PrEP** Pre-Exposure Prophylaxis
- **LHD** Local Health Department

Brown, Smith, Benbow, & Villamar, 2016; Brown et al. 2017; NIH, 2008; NIH, 2013

Implementation Science 101

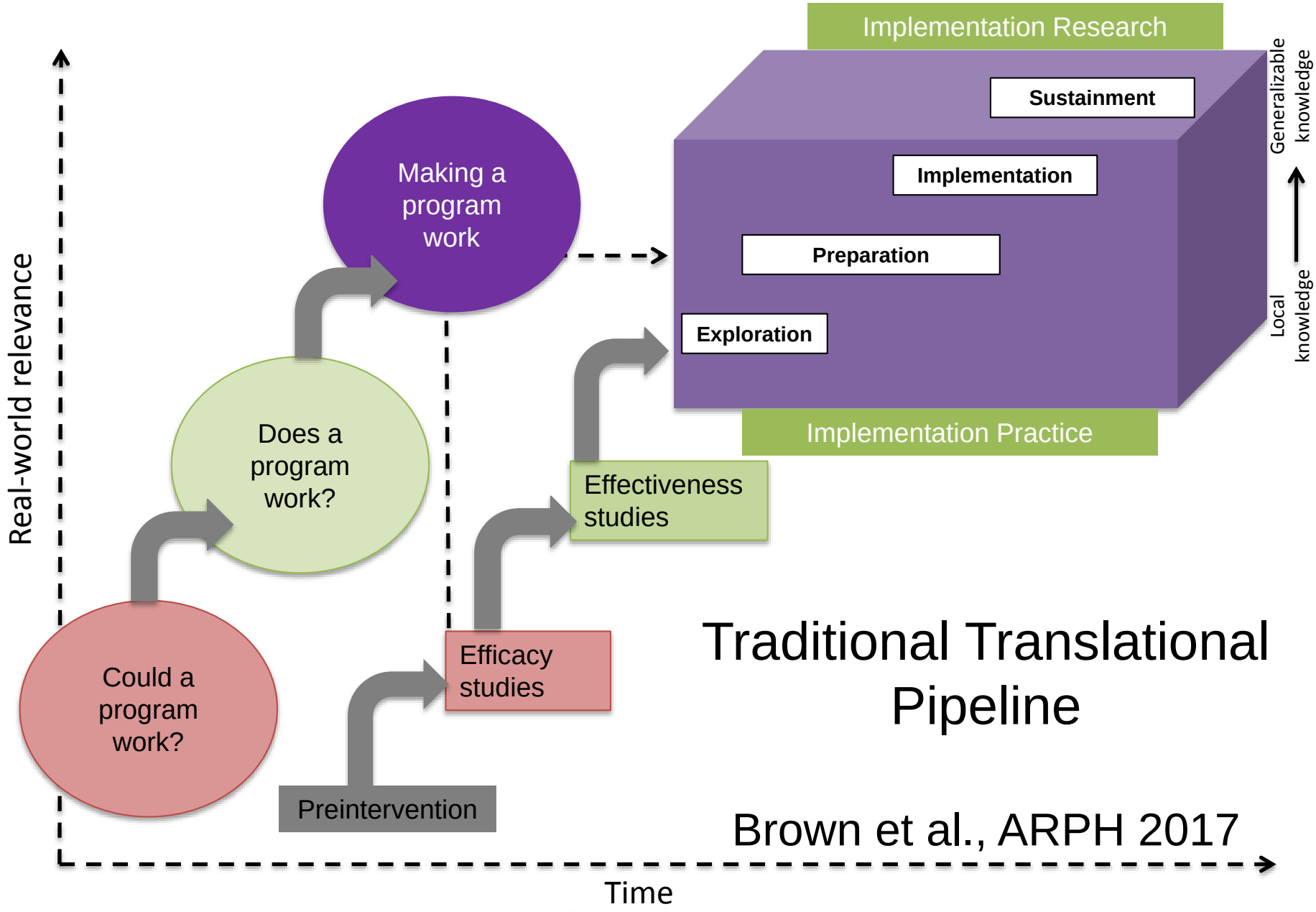
Brown, Smith, Benbow, & Villamar (December, 2016)

Basics of Implementation Science methodology with an example of its use to support diverse sexual transmitted infection (STI) clinics around the country in delivering PrEP to prevent spread of HIV infections.

http://cepim.northwestern.edu/trainings/

Implementation Research Questions

Addressing Gaps



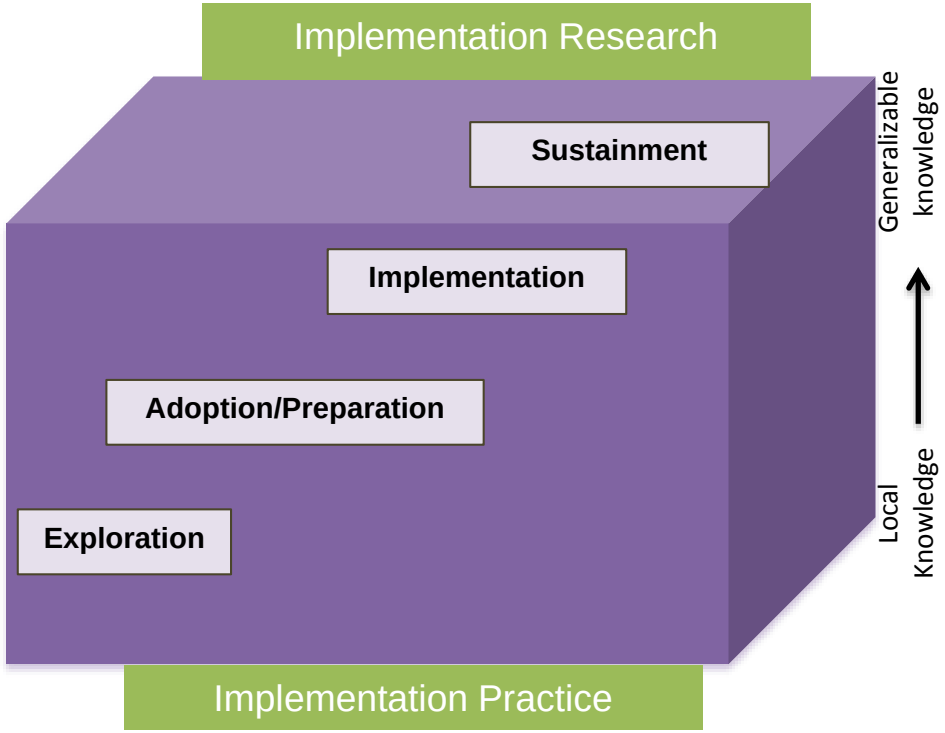
Traditional Translational Pipeline

Brown et al., ARPH 2017

Implementation Research Studies

4 Phases of Implementation: Aarons et al., 2011

Making a program work



System Related Research Questions: Do organizations adopt; is it delivered with fidelity; is it sustained over time?

As Yet Few Implementation Research Studies in HIV

Classification of Published Biomedical Intervention Trials for HIV Testing, PrEP, or ART Involving Efficacy/ Effectiveness and/or Implementation Questions

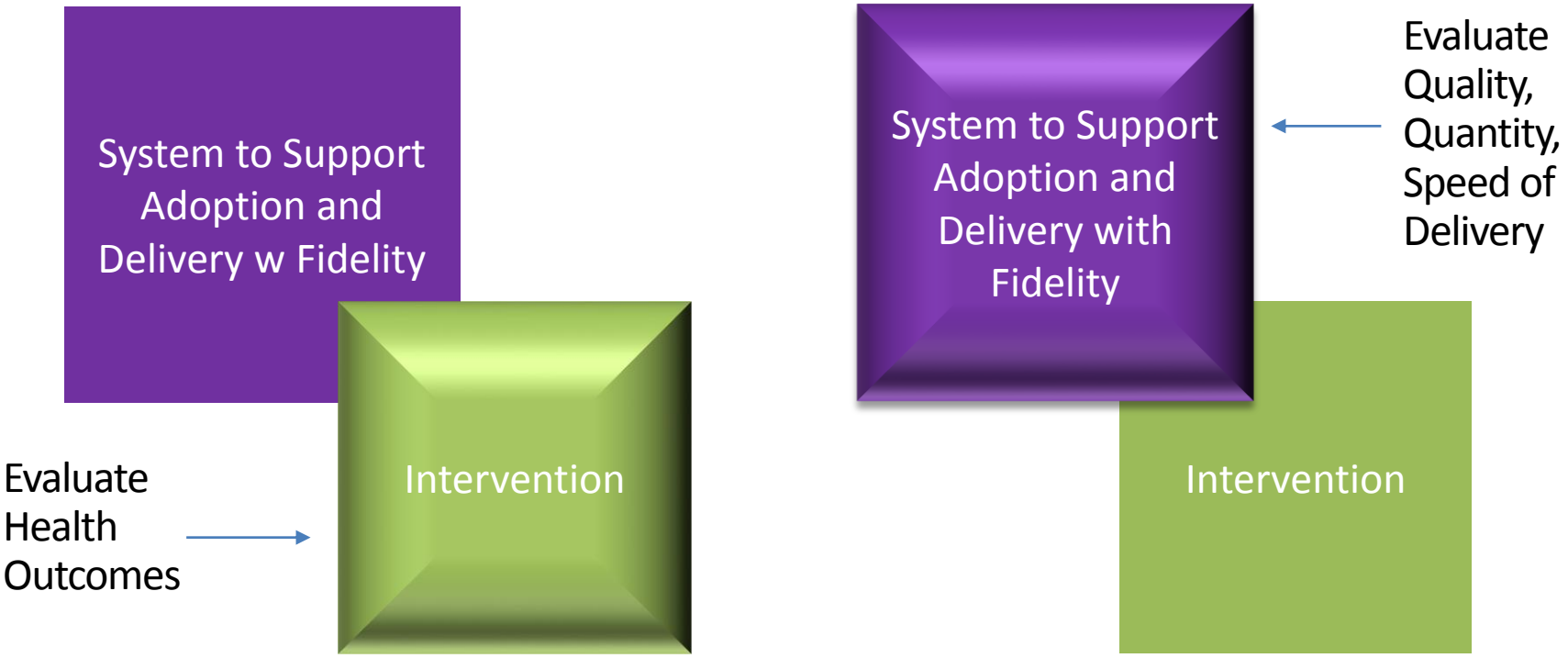
***N* = 107**

	Efficacy	Effectiveness	Implementation
N	79	18	Implementation = 5 Hybrid = 1
	74%	17%	Implementation = 5% Hybrid = 1%

Ce-PIM (2015, unpublished)

Implementation Research Has a Different Emphasis Than Other Types of Research

Effectiveness **vs.** **Implementation**



Influences what to measure, what to model, and what and how to test or evaluate

Implementation Research Can be as Rigorous as Effectiveness

- Frameworks guide the implementation and help inform the selection of outcomes to measure
- Strategies are manipulations to the system for the implementation of new innovations
- Processes and outcomes of implementation are multilevel, dynamic, and systems oriented
- Implementation can be measured, modeled, and tested
- The success of implementation research can be tracked by using appropriate outcome measures
- Implementation research can be rigorously evaluated and contribute to generalizable knowledge through use of rigorous research designs

PrEP as an Illustration

- Pre-Exposure Prophylaxis (PrEP)
- Extends the example from Implementation Science 101 Workshop
- Wide-ranging considerations for implementing PrEP in real-world settings

PrEP for HIV Prevention

Who should take PrEP?

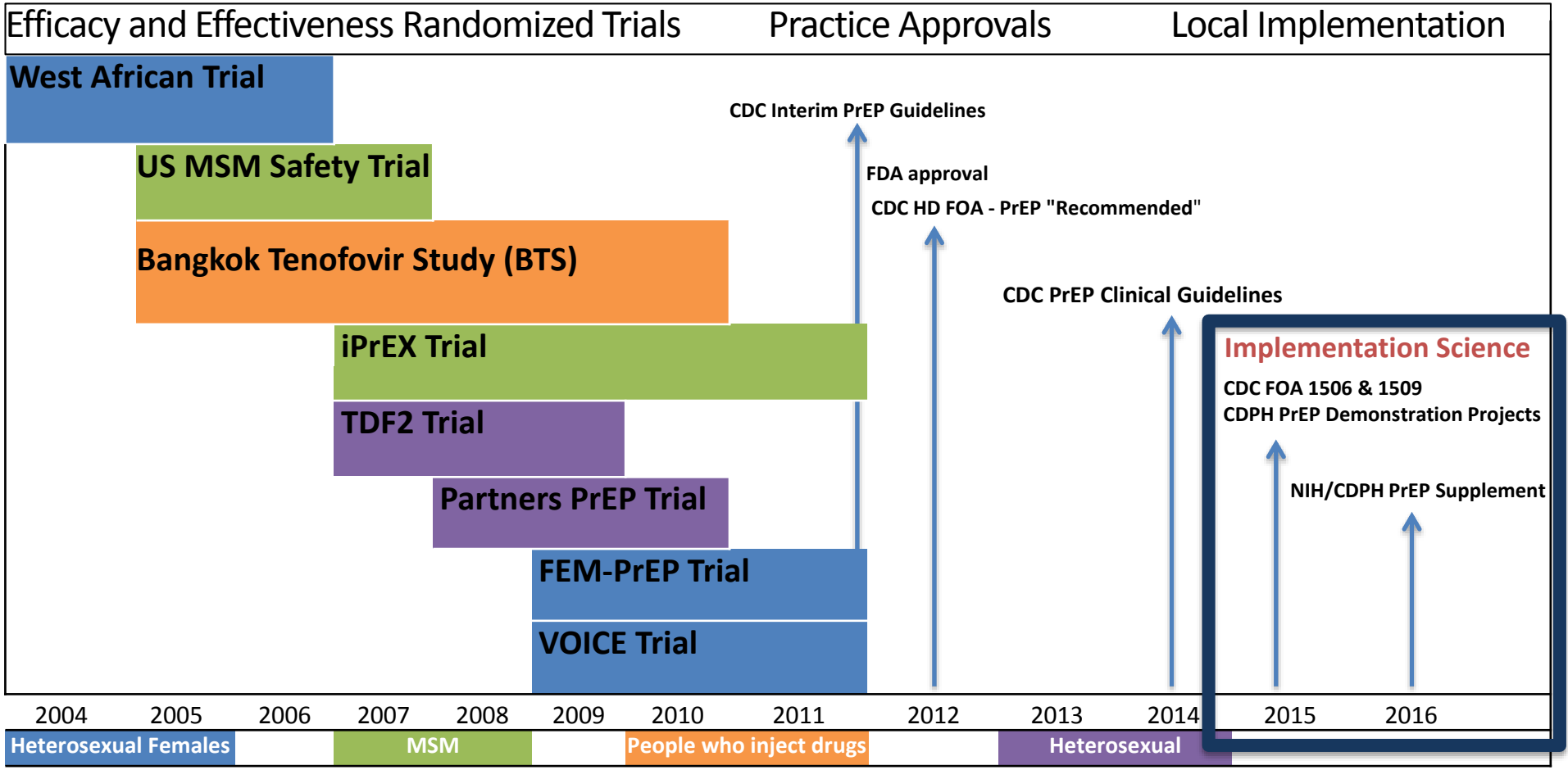
HIV-uninfected individuals who engage in behaviors that place them at substantial risk of HIV acquisition:

- **Sexually active adult men who have sex with men (MSM)**
  - 1 in 4 MSM
- **Adult heterosexually active men and women**
  - 1 in 200
- **Adult injection drug users (IDU)**
  - 1 in 5 IDU

Note: When 2014 CDC Comprehensive Clinical Practice Guidelines were released, data on efficacy and safety of PrEP among adolescents were insufficient and thus did not make a recommendation for this population

https://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf

PrEP
Research-> Practice Timeline 2004 - 2016



As of November 2016, there are currently 45 on-going (N=30) and planned (N=15) Open Label Demonstration and Implementation Projects (a total of 6 are in the U.S.). The populations of focus include: MSM (18 projects); Adolescents (13), female sex workers (6); transgender women (5); and heterosexuals (4).

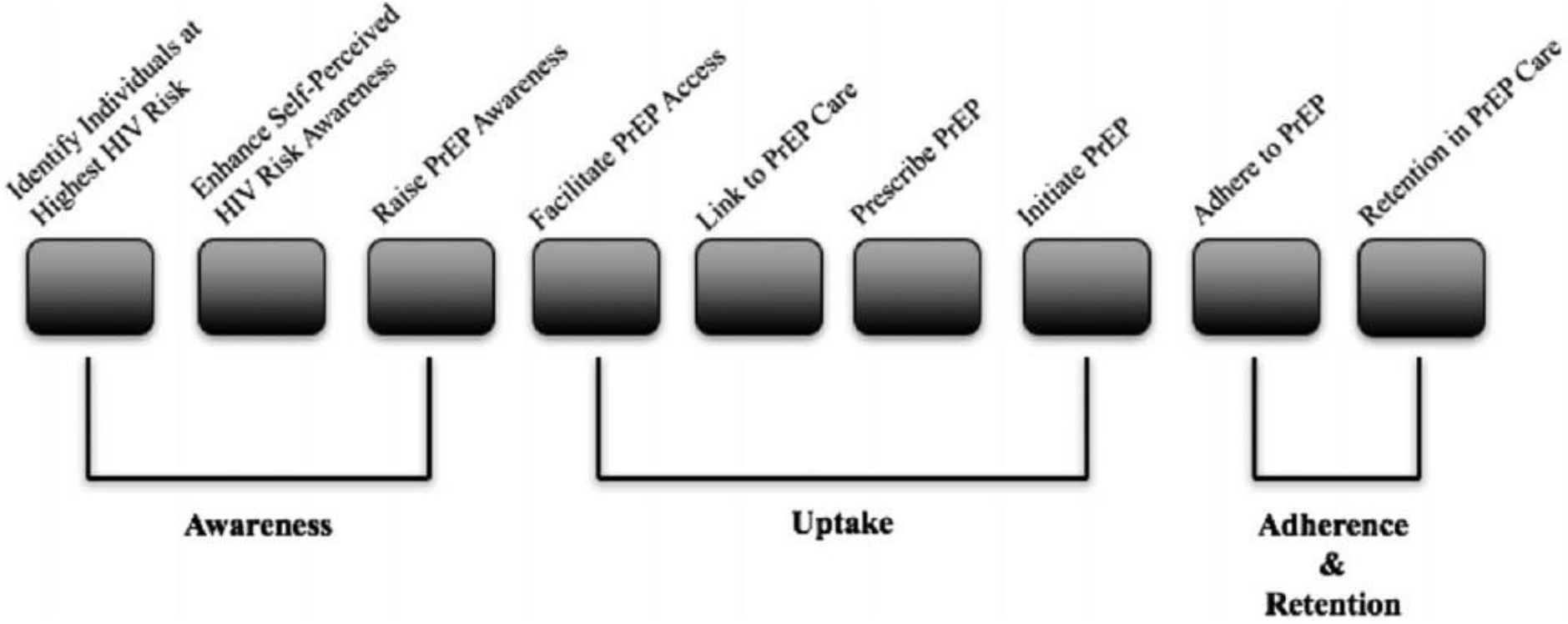
Source: AVAC, www.avac.org/pxrd.

PrEP can be Effective

- Studies have shown that PrEP reduces the risk of getting HIV from sex by more than 90% when used consistently.
- Among people who inject drugs, PrEP reduces the risk of getting HIV by more than 70% when used consistently.

https://www.cdc.gov/hiv/basics/prep.html

PrEP Continuum of Care



Nunn, Amy S., Lauren Brinkley-Rubinstein, Catherine E. Oldenburg, Kenneth H. Mayer, Matthew Mimiaga, Rupa Patel, and Philip A. Chan. Defining the HIV pre-exposure prophylaxis care continuum. 2017 AIDS

PrEP Awareness and Uptake

- Currently **3%** of an eligible 1.2 million are taking PrEP
- ~60% of those eligible know about PrEP
- Beliefs and stereotypes
  - PrEP users are HIV+, promiscuous

(Golub et al. 2017)

  - Conspiracy beliefs and lack of trust

(Eaton et al. 2017)

Settings for PrEP Implementation

- PrEP implementation can take place at various levels:
  - Nationally through partnerships between national funders, state and LHDs, associations, advocacy groups, and policy experts
  - City or statewide partnerships between LHDs, community advocates, CBOs, and providers
  - Clinic-based (e.g., **STD clinics**, family planning clinics, HIV specialty care, primary care, FQHCs)

PrEP Implementation Readiness in Local Health Departments (LHD)

Assessment of LHD Engagement in PrEP

- 500 LHDs sampled in 2015; 284 respondents
- 109 LHDs (**38%**) currently engaged in PrEP implementation
  - 53% anticipate that the LHD will expand its level of engagement in PrEP
- Among LHDs not currently engaged in PrEP implementation (62%):
  - **18%** expect to become engaged over the next 4 years
  - **36%** report that it is unlikely they will become engaged
  - **46%** are undecided

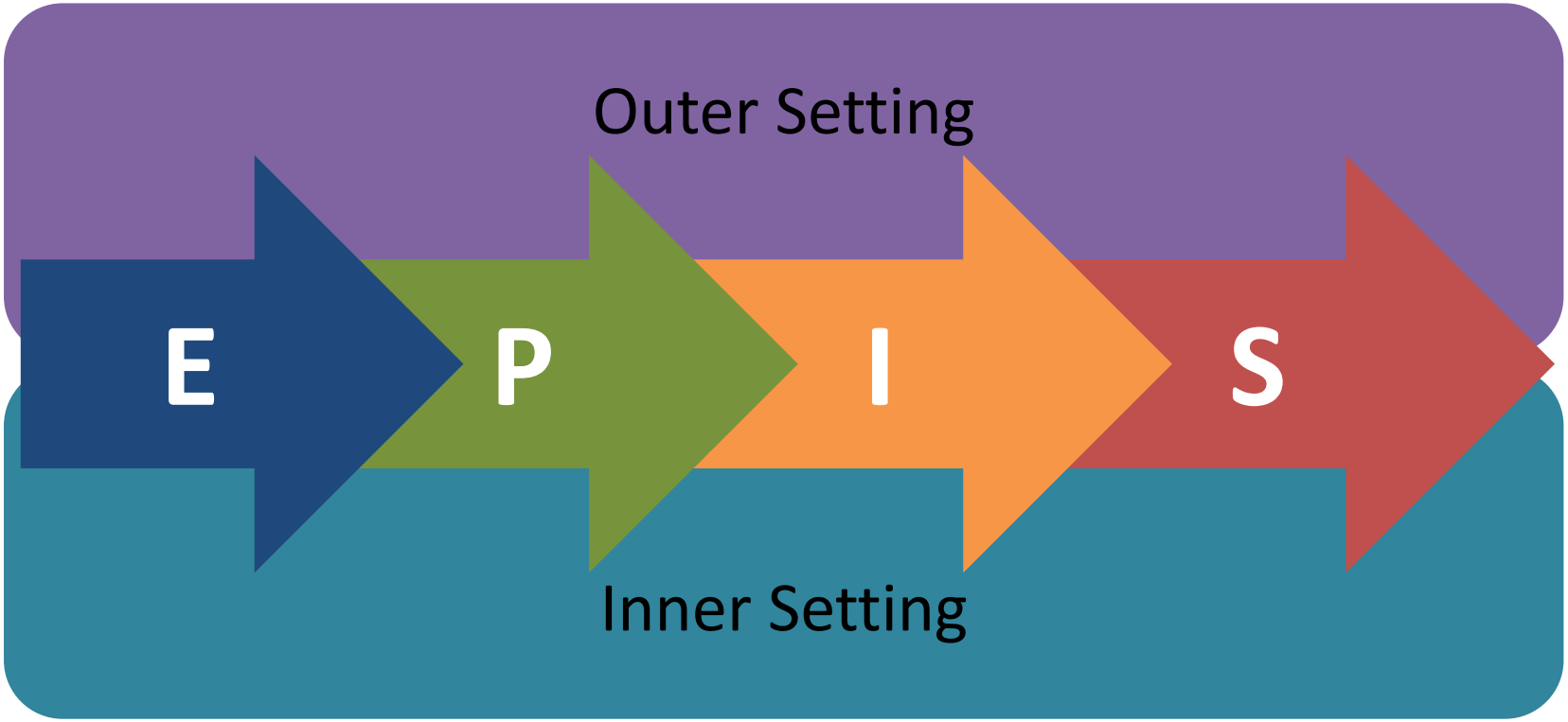
Weiss, 2015 and 2016

NACCHO
National Association of County & City Health Officials

Illustrations of Implementation Research Questions

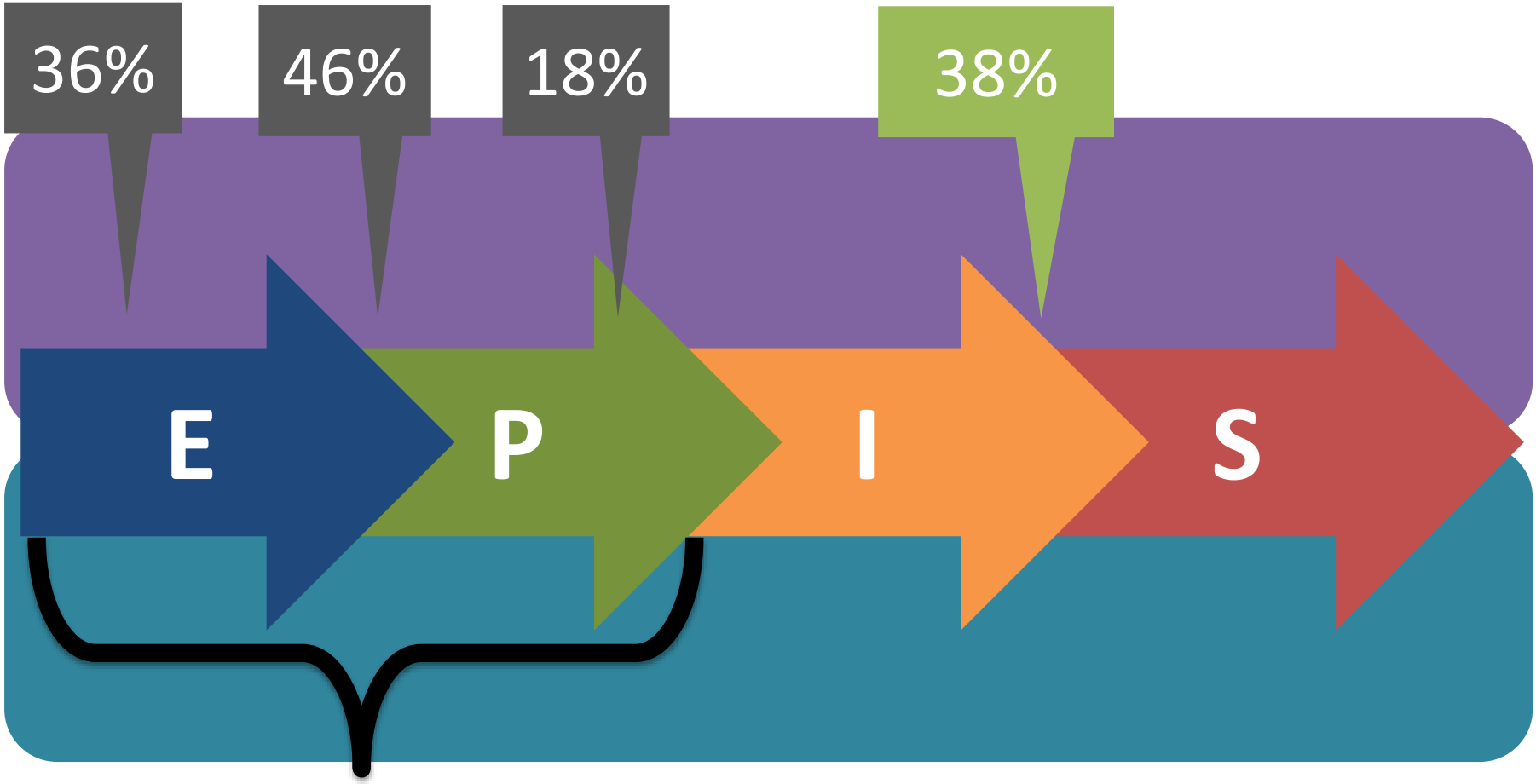
- **Implementation research should allow us to answer questions like:**
  - Is delivery of PrEP more effective when PrEP is provided within the clinic versus referring to a PrEP provider outside the clinic?
  - Under what conditions does implementation Strategy A work better, faster, more efficiently than Strategy B for getting patients on PrEP and maintaining adherence over time?

EPIS Process Model



Exploration, **P**reparation, **I**mplementation, **S**ustainment

Aarons et al. 2011



Among the 62% of LHDs NOT implementing PrEP:

- Motivate the 36% not currently interested
- Help the 46% contemplating
- Support the 18% who have decided

Among the 38% LHDs implementing PrEP

- Data monitoring and feedback system improve delivery and/or sustainment of PrEP

Implementation Strategies

Changing the System

Interventions vs. Implementation Strategies

- Evidence-Based **Clinical or Preventive Intervention: 7 P's**
  - **Pill (PrEP)**
  - Program (PROMISE)
  - Practice (routine HIV screening in clinical settings)
  - Principle (HIV Treatment as Prevention)
  - Product (condom)
  - Policy (housing for people at high risk for HIV)
  - Procedures (male circumcision)

Brown et al., 2017

Interventions vs. Implementation Strategies

- Implementation Strategies are an intervention on the system to increase adoption of evidence-based innovations into usual care
  - 9 categories derived from 75 discrete evidence-informed strategies

Powell et al. 2015

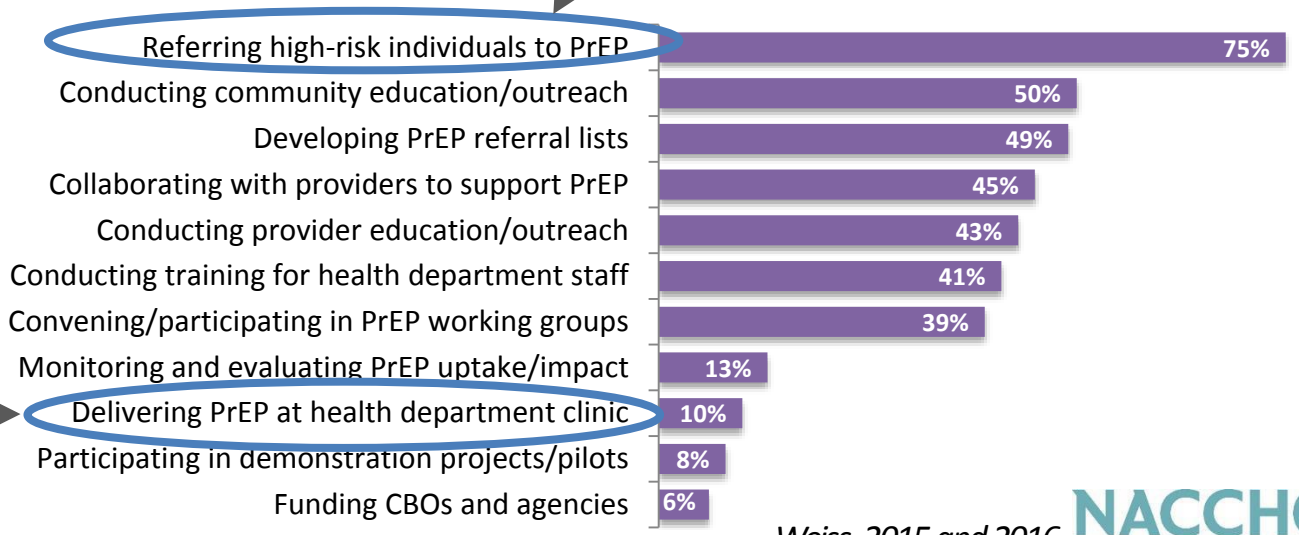
Potential Strategies Along the PrEP Continuum

- Awareness
  - Social marketing
  - Outreach strategies to potential users through PrEP ambassadors
  - Community campaigns to raise PrEP awareness and interest
- Uptake
  - Co-location of PrEP services in HIV testing sites
  - Client/patient navigation, benefits eligibility and active follow-up
  - Provider education to increase provision of PrEP
  - Partner services actively identify PrEP candidates and refer
  - Active referral to PrEP services
- Adherence & Retention
  - Appointment reminders
  - Consistent contact with clinic through staff / peers
  - Interactive reminder messaging

PrEP Implementation Readiness in LHDs

Among LHDs currently engaged in PrEP implementation

Can adding an automated EHR trigger improve providers' referral rates?



Can integrating PrEP into clinic improve uptake and adherence?

Weiss, 2015 and 2016

Measuring Implementation Outcomes

Showing that Strategies are having an Impact

Taxonomy of Implementation Outcomes

Definition: Implementation outcomes are the effects of deliberate and purposive actions (strategies) to embed new treatments, practices, and services into real-world systems of care.

Proctor et al. 2011

Implementation Measurement

- Questionnaire
  - Implementation Leadership Scale (ILS)
  - Implementation Climate Scale (ICS)
- Observation
  - Stages of Implementation Completion (SIC)
  - Fidelity/Adaptation Coding (implementation strategy[ies])
- Health Economic (Cost Benefit/Budget Impact)
  - Cost Capture Templates
  - Administrative/Insurance Data
  - Service Records/EHR
- Reach/Penetration rates
- Qualitative Data

Implementation Research Designs

Evaluating the Impact of Implementation Strategies

Design Terminology

- As used here, **design** refers to the planned set of procedures to
  - select subjects or larger units for study
  - assign these to or measure their naturally chosen conditions
  - assess measures before, during, and after assignment in the conduct of a study.

Designs for Implementation Research

- Examine how EBPs are adopted, scaled up, and sustained in community or service delivery systems

- Evaluate the impact of implementation strategies to improve the adoption, adaptation, scale-up, and sustainability of interventions (NIH, 2016 in PAR 16-236, 237, 238)

  - Randomized and non-randomized designs
  - Hybrid effectiveness-implementation trials
  - Quality improvement designs for local knowledge
  - Simulation modeling

Brown et al. 2017; Landsverk, Brown, Smith, et al. 2017; NIH, 2016

Characteristics and Challenges of Implementation Research Trials

- External validity > internal validity
- Minimize disruptions to and burden on the systems
- Randomization occurs at “higher levels” of the service system (e.g., provider, clinic, county, etc.)
  - Small number of “units”
  - Nesting within multiple levels of the system(s)
  - Interactions between
- Researcher manipulates and controls the implementation strategy/strategies
- Context, context, context!

An Overview of Research and Evaluation Designs for Dissemination and Implementation

Annual Review of Public Health
Vol. 38:1-22 (Volume publication date March 2017)
DOI: 10.1146/annurev-publhealth-031816-044215

C. Hendricks Brown,[1] Geoffrey Curran,[2] Lawrence A. Palinkas,[3] Gregory A. Aarons,[4] Kenneth B. Wells,[5] Loretta Jones,[6] Linda M. Collins,[7] Naihua Duan,[8] Brian S. Mittman,[9] Andrea Wallace,[10] Rachel G. Tabak,[11] Lori Ducharme,[12] David A. Chambers,[13] Gila Neta,[13] Tisha Wiley,[14] John Landsverk,[15] Ken Cheung,[16] and Gracelyn Cruden[1,17]

- Within-Site Designs
- Between-Site Designs
- Within- and Between-Site Designs

Within-Site Designs

Evaluating Change in a Single Site

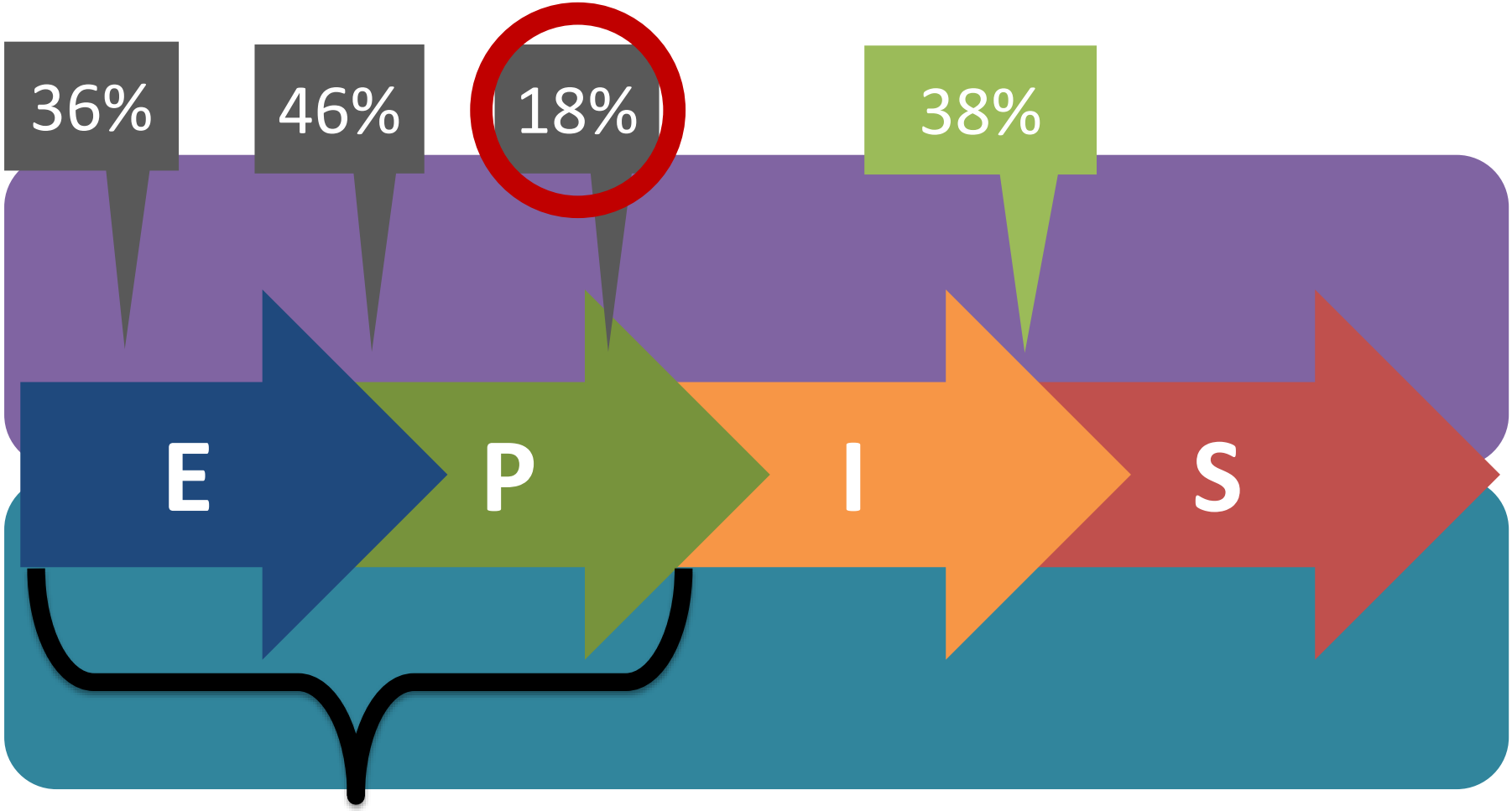
Design Types and Definitions

- Post Design
  - Only measure implementation outputs after a new EBP is adopted
  - Common in quality improvement
- Pre-Post Design
  - Compare implementation outputs before and after a new strategy is used to deliver an EBP
- Interrupted Time-Series
  - Single unit experiments with multiple baselines

Post Design Example

- Can using PrEP active referral model between LHD STD Clinic and the PrEP clinic lead to completed appointments with a PrEP provider?
  - Target population: Patients with negative HIV test in combination and selected risk factors/STD results
  - Strategy: Active referral where STD clinic provider receives consent from client to provide contact information to PrEP clinic who then contacts client to schedule appointment with a PrEP provider
  - Comparison: No such services at baseline

Mikati et al. 2015



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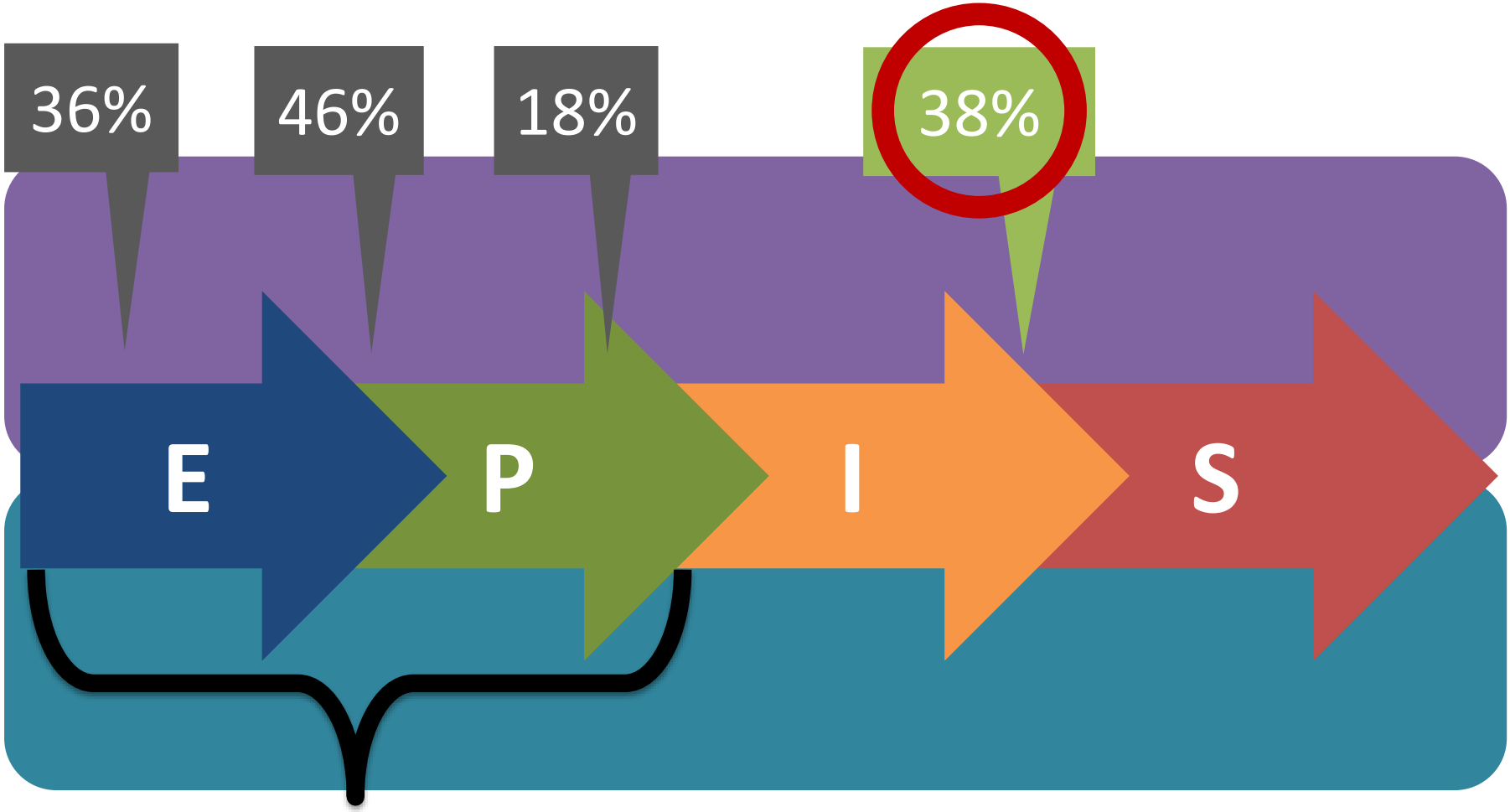
Among the 38% LHDs implementing PrEP

- Data monitoring and feedback system improve delivery and/or
- Sustainment of PrEP

Example: Timeline for Post Design to Evaluate Impact

	Implementation Strategy	**Impacts**
No PrEP service (no referrals)	STD clinic partners with PrEP provider	1. Referrals to PrEP provider (adoption) 2. Completion of appointment with PrEP provider



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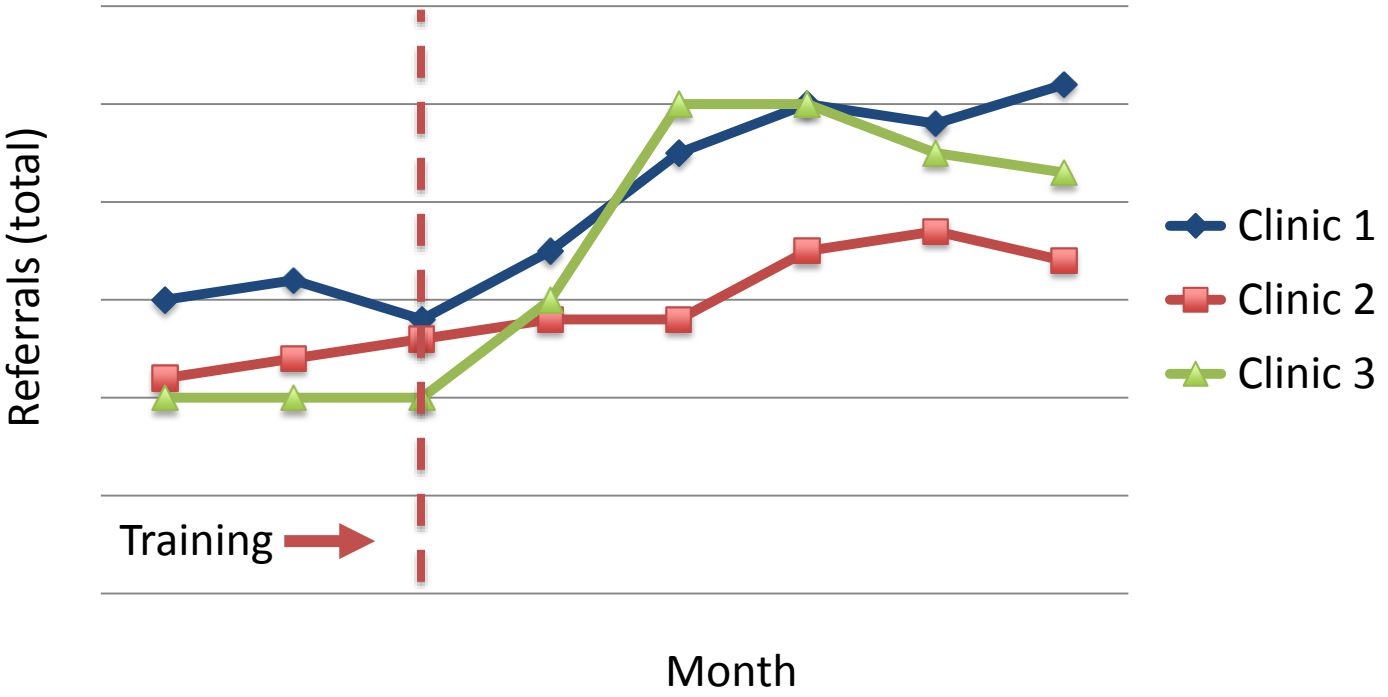
Weiss, 2015; 2016

Pre-Post Design

- Pre-Post Design testing the impact of an implementation strategy to sustain PrEP usage in LHD STD clinics
  - Example 1: Can the 38% of LHDs using PrEP increase long-term PreP usage?
  - Example 2: Can we improve linkage by adding a PrEP coordinator at the STD clinic who is responsible for identifying, counseling, and referring to PrEP clinic?

Interrupted Time-Series Design

- Does providing formal training to STD clinic staff on identification and referral practices impact referral rates for PrEP over time?



Smith, 2012

Summary of Within Site Designs

- Post, Pre-Post, Interrupted Time-Series Designs for novel interventions
  - Single site can demonstrate feasibility and initial impact
  - Multiple sites for full evaluation
- Rarely, if ever, randomized
- Simple and useful
- Local knowledge

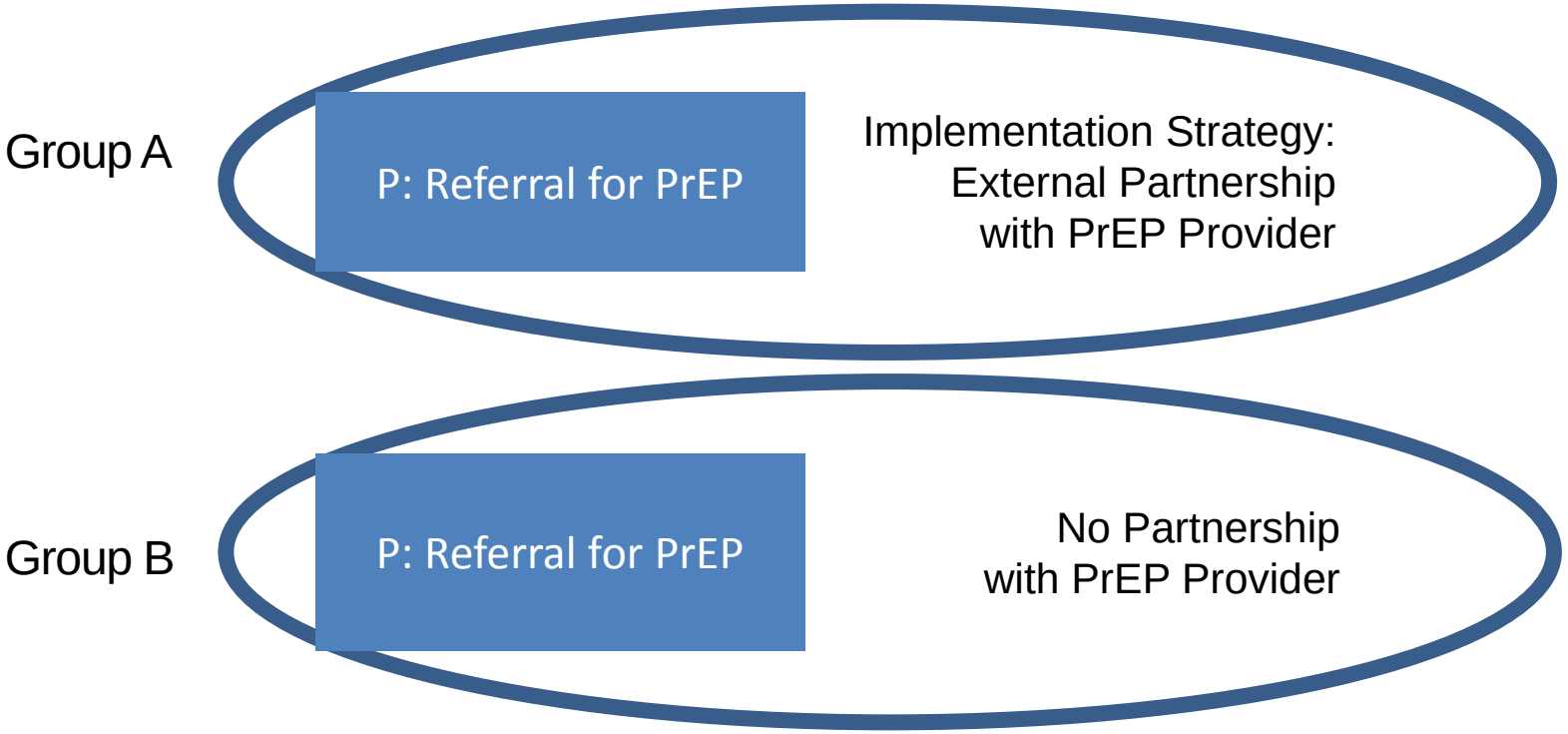
Between-Site Designs

Compares Outcomes Between Two or More Sites

Design Types and Definitions

- Novel implementation strategy vs routine practice
  - Non-Randomized or Randomized
- Head-to-Head Randomized Implementation Trial
  - Two novel implementation strategies for the same clinical/preventive intervention (7 Ps)

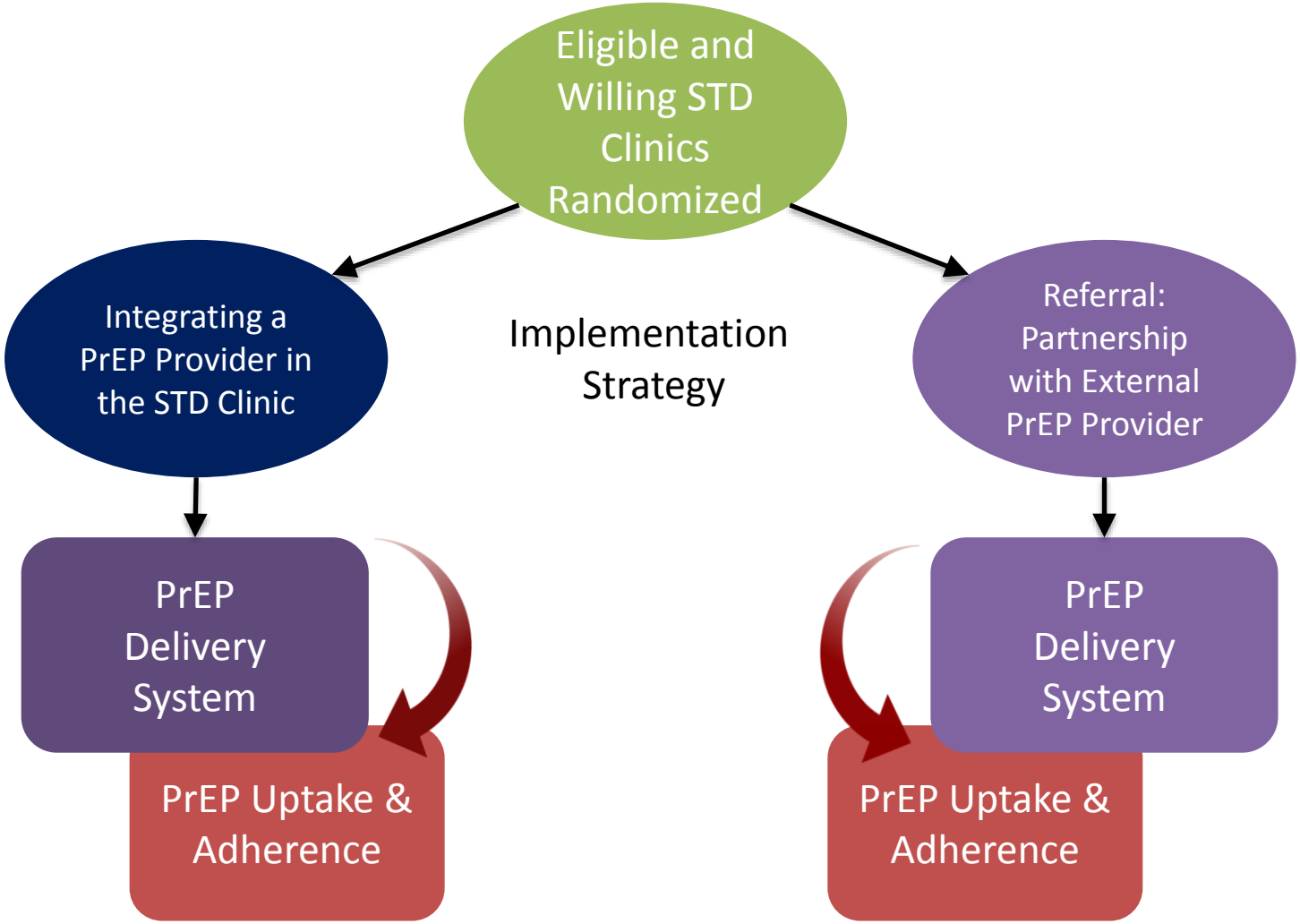
Novel Implementation Strategy vs Routine Practice using a Non-Randomized Implementation Design



Group A determined through self-selection, selective invitation, RFA process

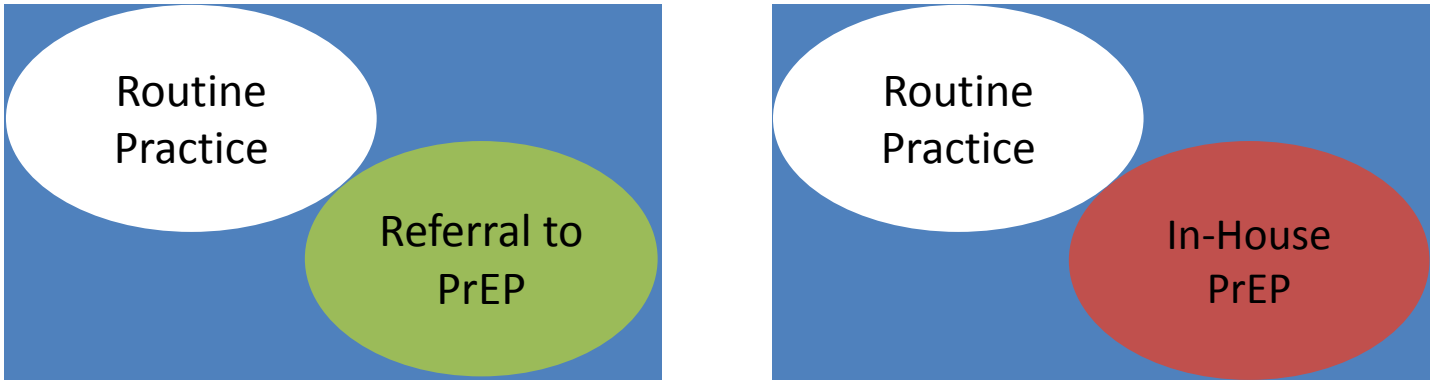
- High potential for introduction bias due to capacity/readiness

Design for a Head-to-Head Randomized Implementation Trial involving Delivery of PrEP



Incomplete Block Designs for Indirect Comparison of Two Strategies

- Blocking within one experimental unit's (e.g., LHDs) subunits (e.g., STD Clinics) are assigned to different implementation strategies
- Incomplete blocking: Not possible to test all



No direct comparison of Referral versus In-House – Requires indirect comparison using multiple LHDs/STD clinics as well as statistical analyses

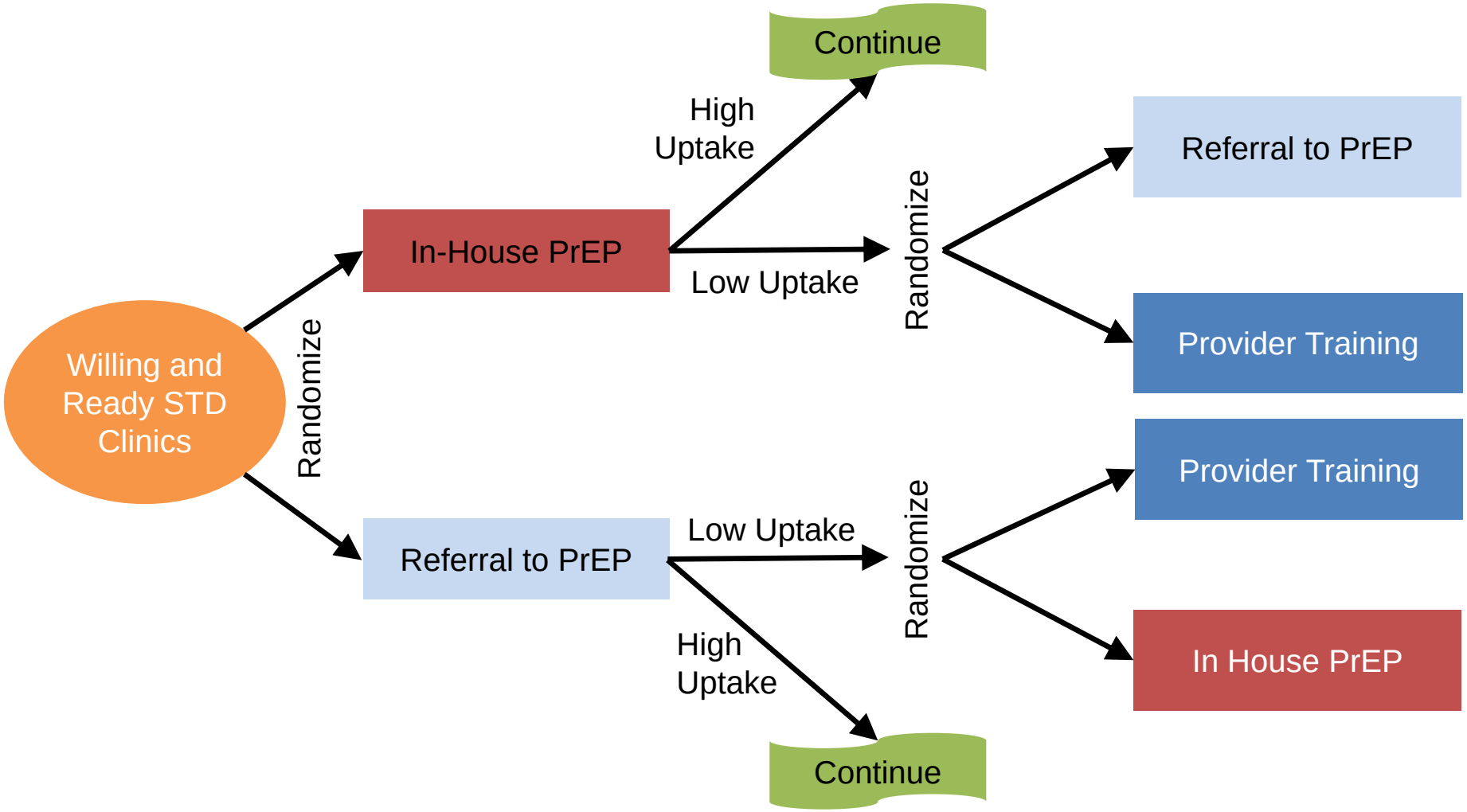
Dagne et al. 2016

Testing and Optimizing Implementation Strategies: SMART Designs

- Sequential, multiple assignment, randomized trial (SMART)
- Optimization of dynamic and adaptive multicomponent implementation strategies
- SMART designs allow implementation strategies to be evaluated while responding to clinic's failure to reach impact

Collins, et al. 2014

SMART Design for PrEP Implementation in STD Clinics



Summary of Between Site Implementation Designs

- Used to compare the impacts of different implementation strategies across sites or groups of sites
- Contribute to generalizable knowledge

- Novel vs routine practice
  - Non-randomized
- Head-to-Head Comparison of Strategies
  - Equipoise
  - Randomization increases internal validity
- Incomplete Block Design
  - Use when few units are available
  - Randomization
- SMART Design
  - Adapt to address differential response to implementation strategies
  - Randomization

Within- and Between-Site Designs

Sites Begin as One Implementation Condition and Move to Another

Roll-Out Designs

Definitions and Types of Roll-Out Designs for Implementation Research

- Stepped Wedge IS EQUIVALENT TO Dynamic Wait-Listed Design
- Other types of roll-out designs: all assign units randomly to when and what implementation strategy is used
- Benefits of roll-out designs
  - Reduce the logistic demands in delivering new implementation strategies across multiple units
  - Equity (benefits for earlier and later start)
  - Beneficial to statistical power by using within and between comparisons of impacts

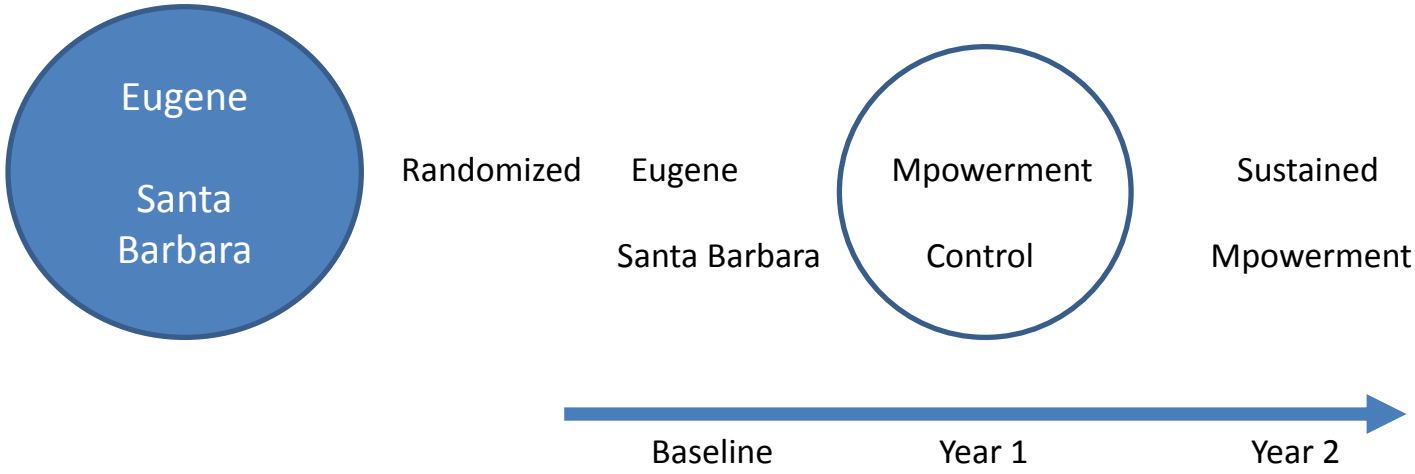
Randomized Stepped Wedge Implementation Trial Comparing Two Strategies (n=20 STD Clinics)

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
COHORT 1 (n = 4)	C	C	I	I	I	I	I	I	I	I	I	I
COHORT 2 (n = 4)	C	C	C	C	I	I	I	I	I	I	I	I
COHORT 3 (n = 4)	C	C	C	C	C	C	I	I	I	I	I	I
COHORT 4 (n = 4)	C	C	C	C	C	C	C	C	I	I	I	I
COHORT 5 (n = 4)	C	C	C	C	C	C	C	C	C	C	I	I

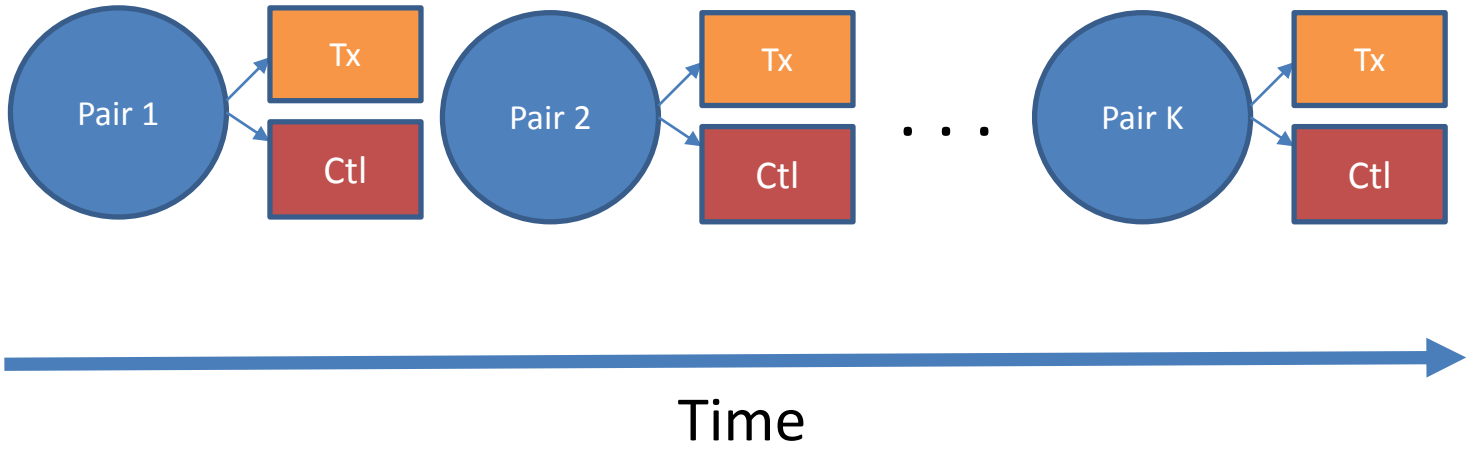
- Cohorts of 4 STD Clinics each (2 Refer to PrEP Provider, 2 provide in-house PrEP)
- Implementation staggered by 6 months for successive cohorts

Roll-Out Even with a Few Units to Randomize

- N = 2
- Mpowerment Young MSM (Kegeles,1987)



Rollout of Repeated Pairs of Randomized Communities



Wyman et al. 2015; Brown et al. 2009

Head-to-Head Roll-Out Designs for Comparing Implementation Strategies X and Y

Adoption of X and Y (*)

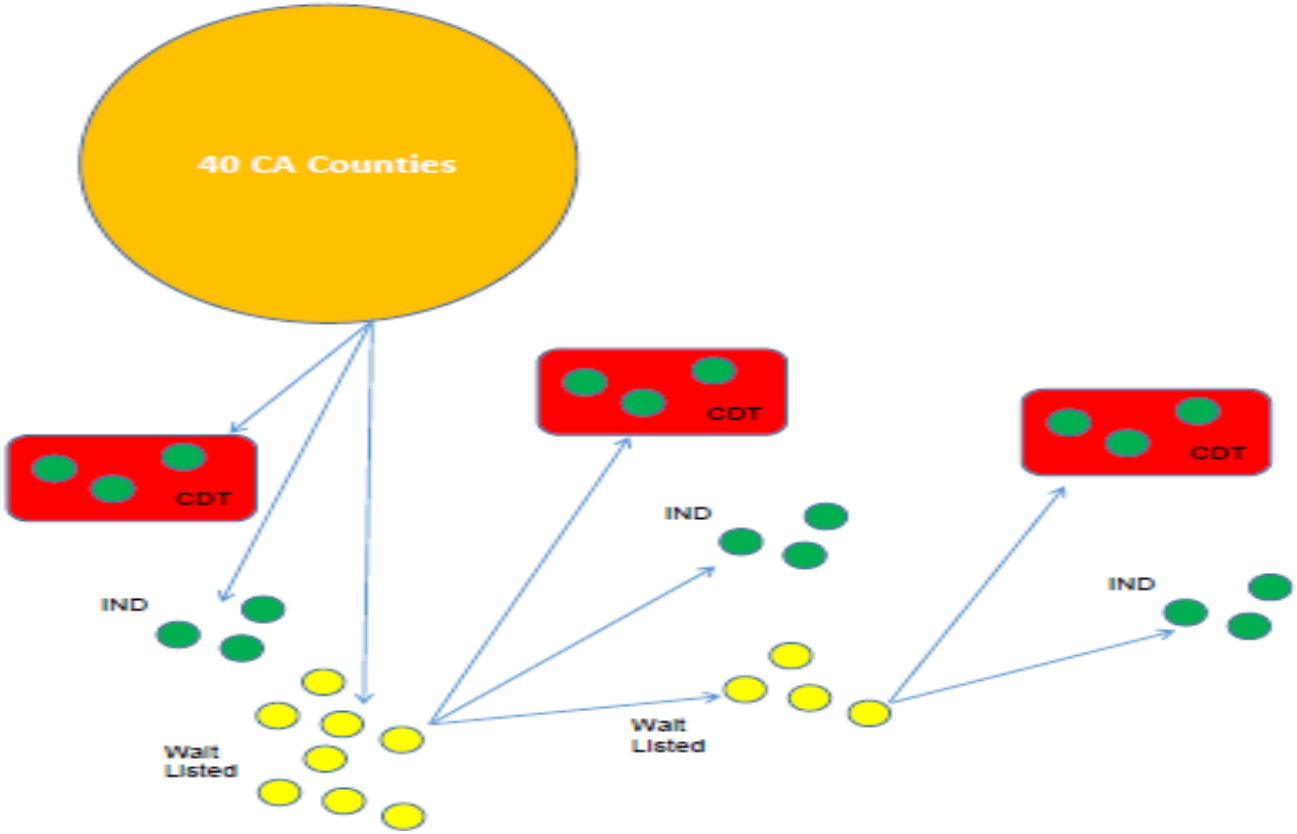
Sustainment of X and Y

Time	1	2	3	4
Cohort A	0	X*	X	X
	0	Y*	Y	Y
Cohort B	0	0	X*	X
	0	0	Y*	Y
Cohort C	0	0	0	X*
	0	0	0	Y*

Brown et al. 2017

Randomizing 40 CA Counties for Head-to-Head Comparison

Learning Collaborative (CDT) and Independent (IND) County Implementation Strategies

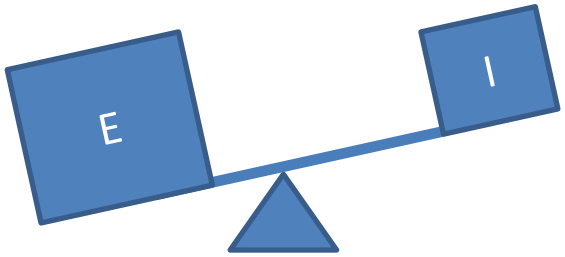


Brown et al. 2014

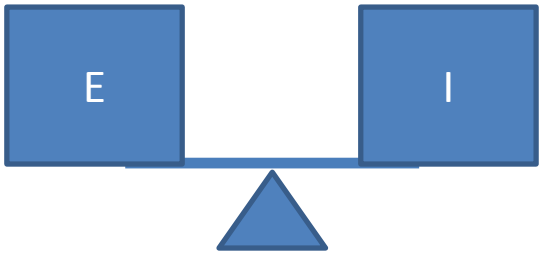
Hybrid Effectiveness-Implementation Trials

Definition and Purpose

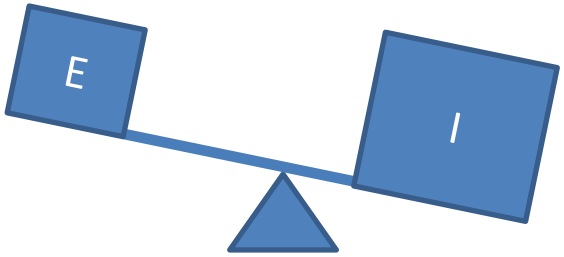
- Simultaneous evaluation of the effectiveness of the clinical intervention and its implementation
- Two levels of data collection (patient & system)
- Measurement intensity on E and I differentiates hybrid types
- Speed translation and efficiently take programs to scale



Type I



Type II



Type III

Curran et al. 2012

Application/Purpose of Each Type

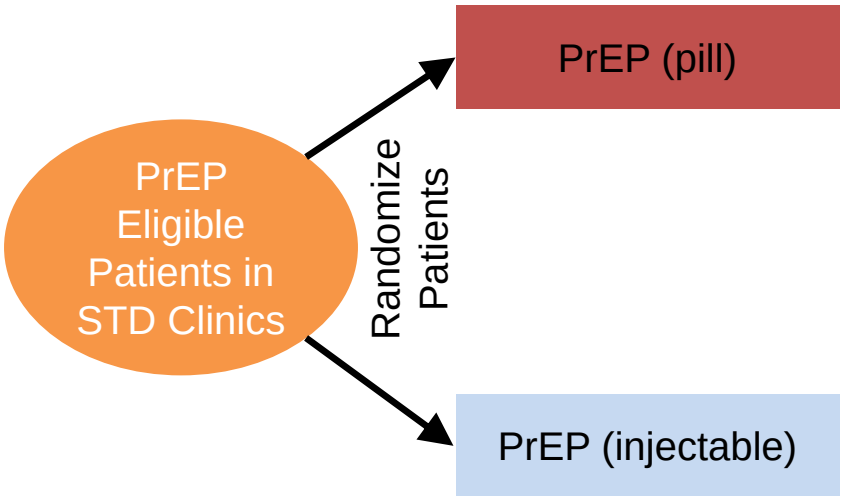
	Primary Aim:	*Secondary Aim:*
Type I	Determine effectiveness of an intervention	Better understand context for implementation
Type II	Determine effectiveness of an intervention	Determine feasibility and/ or (potential) impact of an implementation strategy
Type III	Determine impact of an implementation strategy	Assess clinical outcomes associated with implementation

- Use Type I or Type II when effectiveness of the P has yet to be established
- Allowed to "backfill" effectiveness data while testing implementation strategies
- Use Type II or III when a relationship between implementation and effectiveness is unknown or hypothesized to occur (head-to-head trial)
- Power and level of randomization are key considerations

Curran et al. 2012; Landsverk, Brown, Smith et al. 2017

Hybrid Type I Example: PrEP as a Long-Acting Injectable

- Assumption: Efficacy trials recently completed – no effectiveness trials
- Test effectiveness of long acting PrEP provided in-house within STD clinics AND gather information about implementation



Specific Aims

Aim 1. Test the comparative effectiveness of long acting PrEP compared to PrEP in pill form.

Aim 2. Gather information about implementation (adoption, acceptability, adherence, fidelity)

Aim 3. Evaluate relations between implementation and effectiveness (e.g., does adherence account for differential effects? Are patients more likely to adopt long acting PrEP?)

Example of a Type II or Type III using a Randomized Stepped Wedge Implementation Trial

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
COHORT 1 (n = 4)	C	C	I	I	I	I	I	I	I	I	I	I
COHORT 2 (n = 4)	C	C	C	C	I	I	I	I	I	I	I	I
COHORT 3 (n = 4)	C	C	C	C	C	C	I	I	I	I	I	I
COHORT 4 (n = 4)	C	C	C	C	C	C	C	C	I	I	I	I
COHORT 5 (n = 4)	C	C	C	C	C	C	C	C	C	C	I	I

- In-house long acting PrEP vs referral to PrEP provider
  - Type II: Evaluate PrEP effectiveness by tracking incidence with quarterly testing.
  - Type III: Evaluate PrEP effectiveness tracking incidence with administrative/EHR data.

Additional Considerations

Choosing a Design

- What design type is required to answer your implementation research question(s)?
  - Consider at what level in the system the primary outcome is measured
- Do you have sufficient units to answer your implementation research question(s)?
- Can you randomize the units?

Implementation Science 301

- Internal and external validity
  - When and how to randomize?
- Power and data analysis considerations

Summary
&
Take Away Points

Summary: When to Use

- Within-site designs:

  generally simpler designs, local knowledge

- Between-site designs:

  comparison of implementation strategies at the same time,
  randomization reduces assignment bias, increases generalized knowledge

- Within- and between-site designs:

  roll-out designs
  randomize timing and implementation

- Hybrid designs:

  address both effectiveness and implementation

Community and Organizations are Much More Involved in Design Decisions and their Ownership

- Legal responsibility
- Moral responsibility
- Ethical responsibility

Key Areas

- developing and maintaining partnerships with diverse stakeholders
- recognizing under-resourced communities or other vulnerable populations have substantial historical trust concerns
- leadership is within a partnered participatory research framework
- methodological and design strategies that may apply when D&I research is conducted from a participatory, stakeholder perspective

A Bestiary of Implementation Designs

- Multi-Level, Multi-Component, Systemic
- Single EBI, evolving EBI, multiple EBIs, menu of EBIs
- Randomized or Not Roll-Out Hybrid designs

SEA-GOD, SCYLLA

Fundamental Challenges: 301

- Developing a strong design that satisfies the needs and obligations of key stakeholders
  - Building and maintaining partnerships
- Sufficient statistical power
  - Smarter ways to:
    - Balance
    - Randomize
    - Analyze
- Conduct of an implementation trial

Implementation Science Resources

Training

- Training Institute in Dissemination and Implementation Research in Health (TIDIRH)
- Implementation Research Institute (IRI)
- Mentored Training in Dissemination and Implementation Research in Cancer (MT-DIRC)
- Certificate Program in Implementation Science (UCSF CTSI)
- Prevention Science and Methodology Group (PSMG)
- NCI D&I Webinar Series
- Brownson RC, Colditz GA, Proctor EK, eds. *Dissemination and Implementation Research in Health: Translating Science to Practice* (2nd Edition). London: Oxford University Press; 2017.

Articles, Measures, News, etc.

- Ce-PIM/Bridges Websites at NU
- *Implementation Science*
- SIRC instrument repository
- NIH Resources on Dissemination and Implementation Research in Health
- Knowledge Translation Resources from Canadian Institutes of Health Research
- WHO's Implementation Research Platform
- UNC Chapel Hill's North Carolina Translational and Clinical Sciences Institute: D&I portal
- UNC Chapel Hill's Active Implementation Hub
- NIH Fogarty International Center's Implementation Science site

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