

# Similarities and Differences Between Pragmatic Trials and Hybrid Effectiveness-Implementation Trials

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# Definitions

- **Clinical interventions** are treatments (e.g., psychotherapy), treatment modalities (e.g., mhealth) or service models (e.g., patient-centered medical homes) designed to *directly* impact patient outcomes.
- **Implementation strategies** promote the uptake of evidence-based clinical interventions and *indirectly* impact patient outcomes.

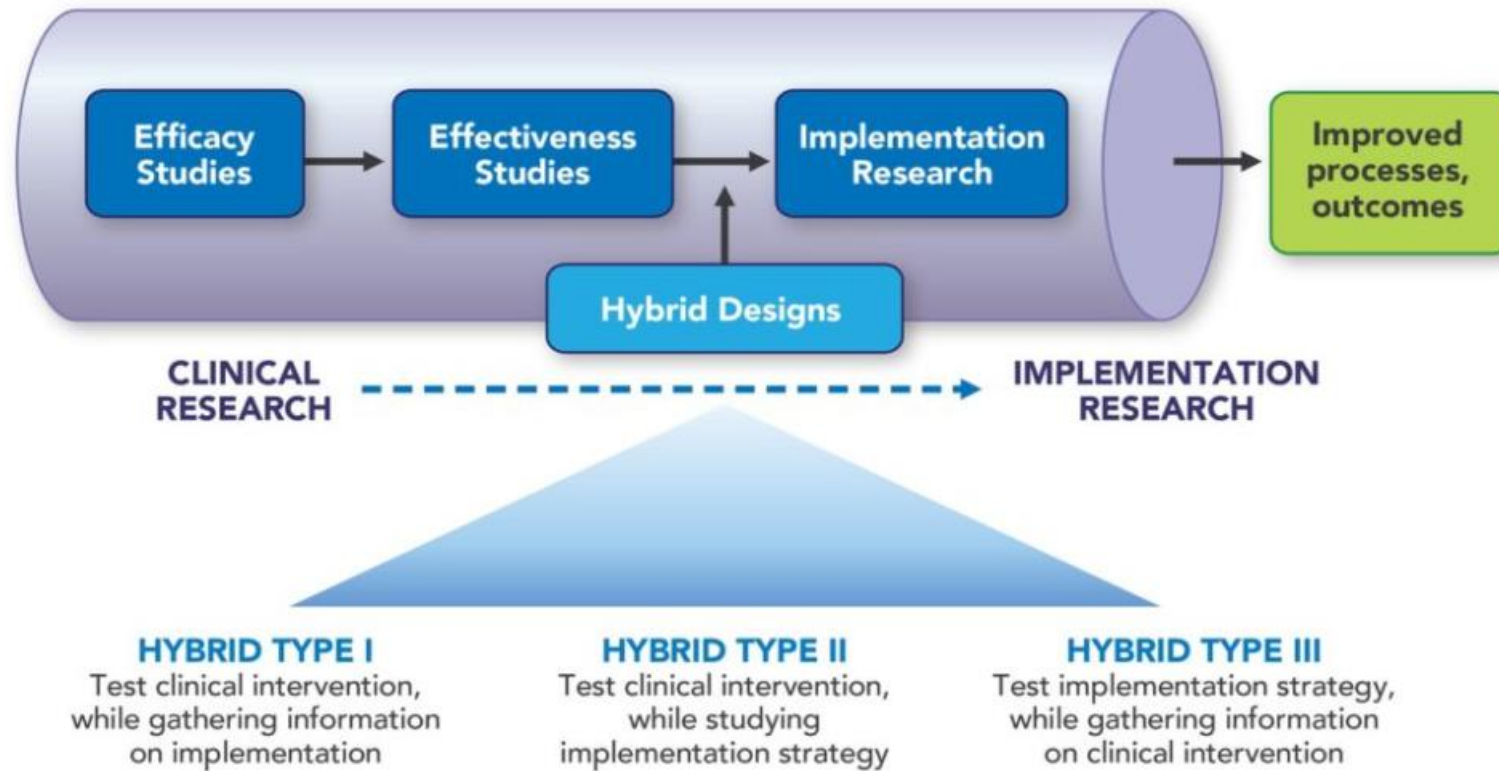
# Definitions

- Thorpe et al. - “**pragmatic trials** are primarily designed to determine the effectiveness of a clinical intervention under the usual conditions in which it will be applied.”
- Curran et al. define a **hybrid effectiveness-implementation trial** as “one that takes a dual focus a priori in assessing clinical effectiveness and implementation.”

Thorpe KE, et. al. A pragmatic-explanatory continuum indicator summary (PRECIS): A tool to help trial designers. *Journal of clinical epidemiology*. 2009;62(5):464-475.

Curran GM, et. al. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Medical care*. 2012;50(3):217-226.


# Translational Research Pipeline



# Primary Objective of Trial Types

- Test effectiveness of clinical interventions
  - Pragmatic Trials (PT)
  - Hybrid Type 1 (HT1)
  - Hybrid Type 2 (HT2)
- Test success of implementation strategies
  - Hybrid Type 2 (HT2)
    - Hybrid type 2b trials compare two clinical interventions and two implementation strategies
    - Hybrid type 2a trials compare two clinical interventions with only one implementation strategy
  - Hybrid Type 3 (HT3)

# Example: What type of trial is it?

- **Comparators:**
    - **Arm 1** – Co-location/integration of mental health specialists in primary care
    - **Arm 2** – Co-location/integration of mental health specialists in primary care plus online education, workbooks, remote QI coaching, online community of practice
  - **Primary Outcome**
    - Change in patients' mental health symptoms and functioning
  - **Secondary Outcome**
    - Fidelity to the integrated care model
- 

Crocker AM, Kessler R, van Eeghen C, Bonnell LN, Breshears RE, Callas P, et al. Integrating Behavioral Health and Primary Care (IBH-PC) to improve **patient-centered outcomes** in adults with multiple chronic medical and behavioral health conditions: study protocol for a **pragmatic cluster-randomized control trial**. *Trials*. 2021;22(1):200.

Littenberg B, Clifton J, Crocker AM. A Cluster Randomized Trial of Primary Care Practice Redesign to Integrate Behavioral Health for Those Who Need It Most: Patients With Multiple Chronic Conditions, 32023;21:483-495

# Similarities Between PTs and HEITs

- Clinical intervention(s) are delivered in routine care setting
- Clinical intervention(s) are delivered by routine care providers
- Broad inclusion criteria
- Minimal exclusion criteria
- Fidelity is measured
- Intent to treat statistical analysis

# Differences in PTs and HEITs

- Primary outcomes
- Specification of implementation strategies
- Secondary aims
- Attention to fidelity
- Artificial versus practical implementation strategies
- Evidence-based versus novel implementation strategies

# Primary Outcomes

- **PTs, HT1s and HT2s** - Primary/Co-primary outcomes are usually specified as patient-level outcomes
  - Treatment adherence
  - Procedural complications
  - Side-effects
  - Lab results
  - Symptoms
  - Functioning
  - Hospital readmission
- **HT2 and HT3s** - Primary/Co-primary outcomes are usually specified as implementation success
  - Provider adoption
  - Provider fidelity
  - Patient reach

# Specification of Implementation Strategies

- **Specification of implementation strategies**
  - Grant applications
  - Trial registries (e.g., clinicaltrials.gov)
  - Protocol papers
  - Results papers
- **HT2 and HT3s – Yes**
- **PTs and HT1s - No**

Powell BJ, Waltz TJ, Chinman MJ, Damschroder LJ, Smith JL, Matthieu MM, et al. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. *Implementation science* : IS. 2015;10:21.

# Secondary Aims

- **Moderation Analysis – Interaction effects**
  - Effectiveness of clinical intervention depends on patient characteristics (treatment heterogeneity)
    - Common in PTs and HT1s
  - Success of implementation strategy depends on clinic/provider characteristics
    - Rare in HT2s and HT3s
- **Mediation Analysis – Mechanisms of action**
  - How a clinical intervention is improving patient health
    - Rare in PTs
    - Not unusual in HT1s and HT2s
  - How an implementation strategy is increasing adoption, fidelity and reach
    - Strongly encouraged in HT2s and HT3s

# Fidelity

- **Adaption** (deliberate fidelity-consistent changes to the adaptable periphery of the clinical intervention to improve fit, engagement, and effectiveness) is encouraged.
- **Deviation** from core intervention components is discouraged.

# Attention to Fidelity

- **Fidelity** - the degree to which the core intervention components are delivered as intended
  - Whether fidelity is intervened upon
  - How fidelity is intervened upon
  - How much fidelity is intervened upon
  - Is fidelity intervening pre-specified
  - Is fidelity reported as a *descriptive* variable
  - Is fidelity analyzed as a *dependent* variable
- **HT1s**
  - Intervene on fidelity, as much as needed, using *artificial* strategies
  - May or may not prespecify strategies
  - Report fidelity descriptively
- **PTs**
  - Intervene on fidelity using *practical evidence-based* strategies
  - Prespecify strategies
  - Report fidelity descriptively
- **HT2s and HT3s**
  - Intervene on fidelity using *practical novel* strategies
  - Prespecify strategies
  - Analyze fidelity as a dependent variable

# Artificial Versus Practical Strategies

- **Artificial** implementation strategies are not feasibly replicated in routine care settings
  - Adoption is artificially increased by using research funds to pay for intervention delivery
  - Reach is artificially increased by advertising in the community for trial participants
  - Fidelity is artificially increased by monitoring fidelity frequently and re-training and/or removing clinicians with poor fidelity
- **Practical** implementation strategies are expected to be replicable outside the context of a research project
  - Training
  - Audit and feedback
- **HT1s** – Artificial implementation strategies
- **PTs, HT2s and HT3s** – Practical implementation strategies

# Novel Versus Evidence-Based Implementation Strategies

- **Novel** implementation strategies are not known to be effective in the context in which they are used
- **Evidence-based** implementation strategies are known to be effective in the context in which they are used
- **PTs**
  - Use evidence-based implementation strategies
- **HT2s and HT3s**
  - Compare novel implementation strategies to usual care
  - Compare novel implementation strategies evidence-based strategies

# Trial types differentiated

- **HT1s**

- Primary outcome is patient health status
- Fidelity is described
- Fidelity is intervened on using non-specified artificial strategies
- Mediation analysis (clinical mechanism of action)


- **PTs**

- Primary outcome is patient health status
- Fidelity is described
- Fidelity is intervened on using prespecified practical evidence-based strategies
- Moderation analysis (treatment heterogeneity)

- **HT2s and HT3s**

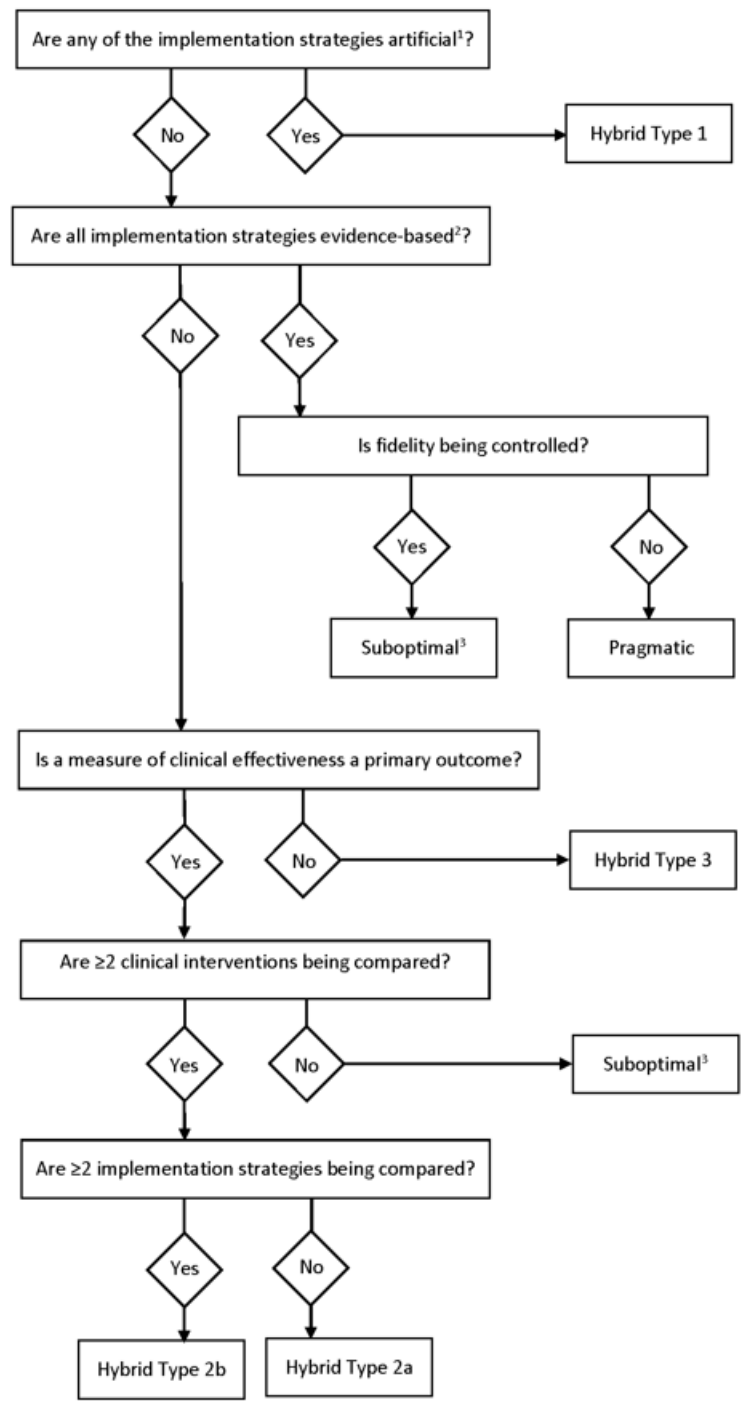
- Primary outcome is implementation success (and patient health for HT2s)
- Fidelity is often a dependent variable
- Fidelity is intervened on using prespecified practical novel strategies
- Mediation analysis (implementation mechanism of action)

# Example: What type of trial is it?

- **Comparators:**
    - **Arm 1** – Co-location/integration of mental health specialists in primary care
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# Fidelity Ditches and Guardrails

- Both PTs and HT2s trials must ensure that fidelity to the clinical intervention(s) is sufficient to produce pre-post clinical improvement among patients.
- **Ditch** - whenever fidelity is so low that patients are not benefiting clinically, the trial should be “rescued”
- **Guardrails** – increase the intensity of *pre-specified* practical implementation strategies and/or adding *post hoc* practical implementation strategies.

# Recommendations

- HT1 trial types should be used to determine whether a *clinical intervention* can be effective when delivered in routine care.
- Pragmatic and HT2 trial types should be used to determine whether an evidence-based clinical intervention(s) is effective when delivered with practical implementation strategies in routine care.
- HT2 and HT3 trial types should be used to determine whether practical and novel *implementation strategies* successfully promote the uptake of evidence-based clinical interventions.

# Recommendations, continued

- In all PTs and HEITs, the implementation strategies used to intervene on fidelity should be pre-specified, and classified as *artificial/practical* and *novel/evidence-based* in the target healthcare system.
  - If not clear cut, the degree of artificiality and the quality of the evidence should be described/discussed.
  - The implementation strategies used should be reported in research proposals, study protocols and publications.

# Recommendations, continued

- HT1 may (and usually do) use *artificial* fidelity monitoring methodologies and *artificial* implementation strategies to ensure high fidelity, but should conduct process evaluations to explore the potential for using more practical strategies.

# Recommendations, continued

- Pragmatic trialists should consider conducting process evaluations to facilitate the large-scale rollout of clinical interventions proven to be effective in routine care.
- Such process evaluations could be used to:
  1. Optimize the “implementability” of the clinical intervention if found to be overly complex
  2. Improve the “practicality” of implementation strategies if any are determined to be artificial for the setting
  3. Identify settings that are conducive to future implementation based on observed provider-level, organization-level, and/or environmental-level barriers

# Recommendations, continued

- HT2 and HT3 trials are expected to test *novel* implementation strategies or implementation strategies *without an evidence-base* in the targeted setting.
- In contrast, PTs should use *practical* implementation strategies that have an *evidence-base* in the target setting.
  - Otherwise investigators run the risk of having to apply artificial implementation strategies post hoc to maintain adequate fidelity.
  - Ideally, implementation strategies used to intervene on fidelity should also be *pre-specified* in grant applications and protocol papers, although *post hoc* additions to the implementation strategies may be needed if there are unforeseen barriers to fidelity.

# Recommendations, continued

- During PTs and HT2s, fidelity should be monitored using *practical* methodologies
- If fidelity drops below a minimum threshold (*ditch*) that is expected to result in a lack of pre-post clinical improvement among patients, the research team should increase the number/intensity of practical implementation strategies to promote fidelity (*guardrails*).
  - Such guardrails are not necessary in HT3s because clinical effectiveness is not a primary outcome, although similar adaptive implementation strategies may be used.

# Questions and Suggestions