Similarities and Differences in the Designs of 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.

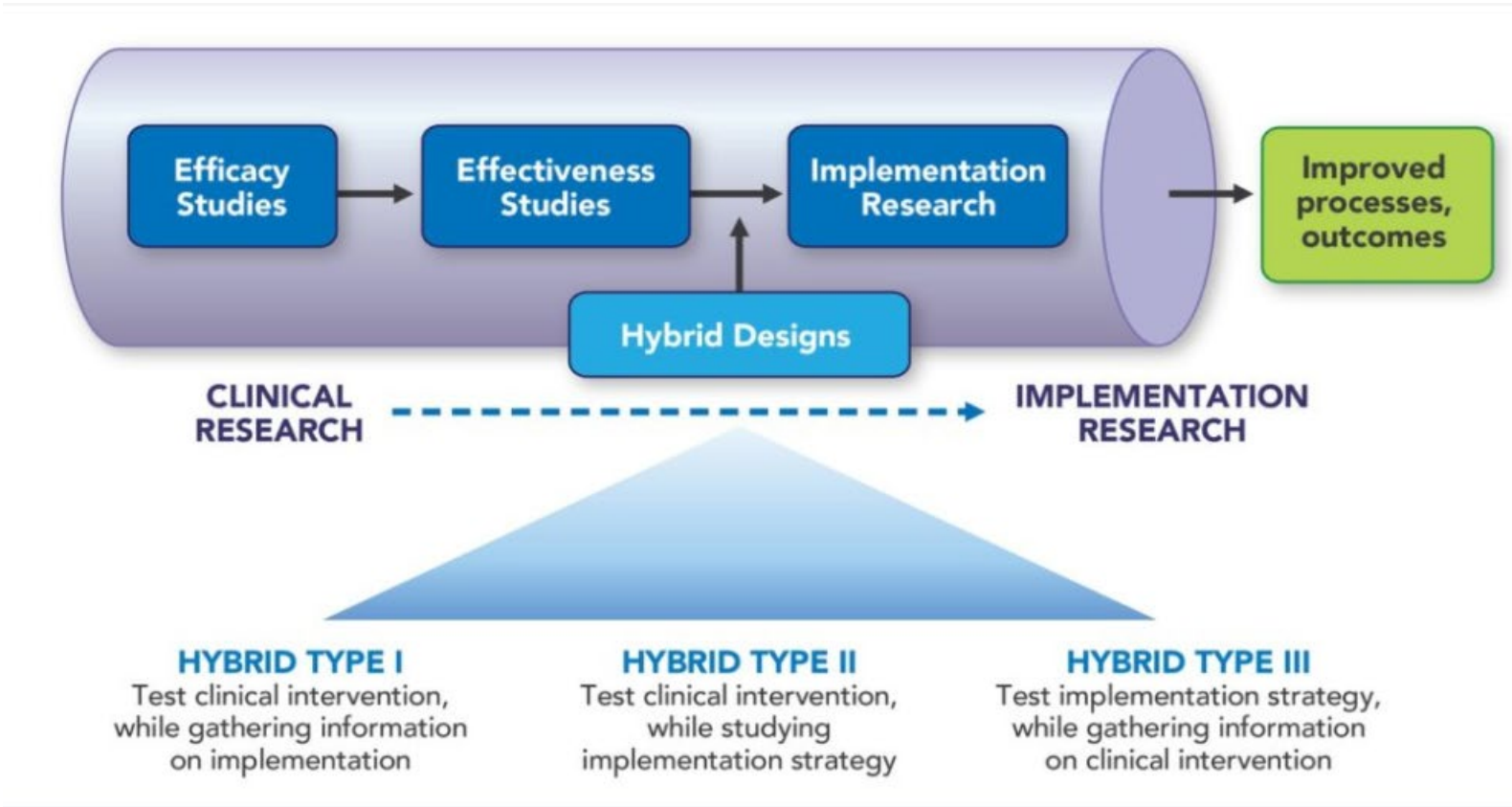
Definitions

- 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
  - Hybrid Type 1
  - Hybrid Type 2
- Test success of implementation strategies
  - Hybrid Type 2
    - 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

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
- 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, *3*2023;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
- **PTs and HT1s -** No
- **HT2 and HT3s –** Yes

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 clinic 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
  - Do not prespecify
  - Report fidelity descriptively
- **PTs**
  - Intervene on fidelity using *practical evidence-based* strategies
  - Prespecify
  - Report fidelity descriptively
- **HT2s and HT3s**
  - Intervention on fidelity using *novel practical* strategies
  - Prespecify
  - 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 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

- **PTs**
  - Primary outcome is patient health status
  - Moderation analysis (treatment heterogeneity)
  - Fidelity is described
  - Fidelity is intervened on using prespecified practical evidence-based strategies
- **HT1s**
  - Primary outcome is patient health status
  - Mediation analysis (clinical mechanism of action)
  - Fidelity is described
  - Fidelity is intervened on using non-specified artificial strategies
- **HT2s and HT3s**
  - Primary outcome implementation success (and patient health for HT2s)
  - Mediation analysis (implementation mechanism of action)
  - Fidelity is a dependent variable
  - Fidelity is intervened on using prespecified practical novel strategies

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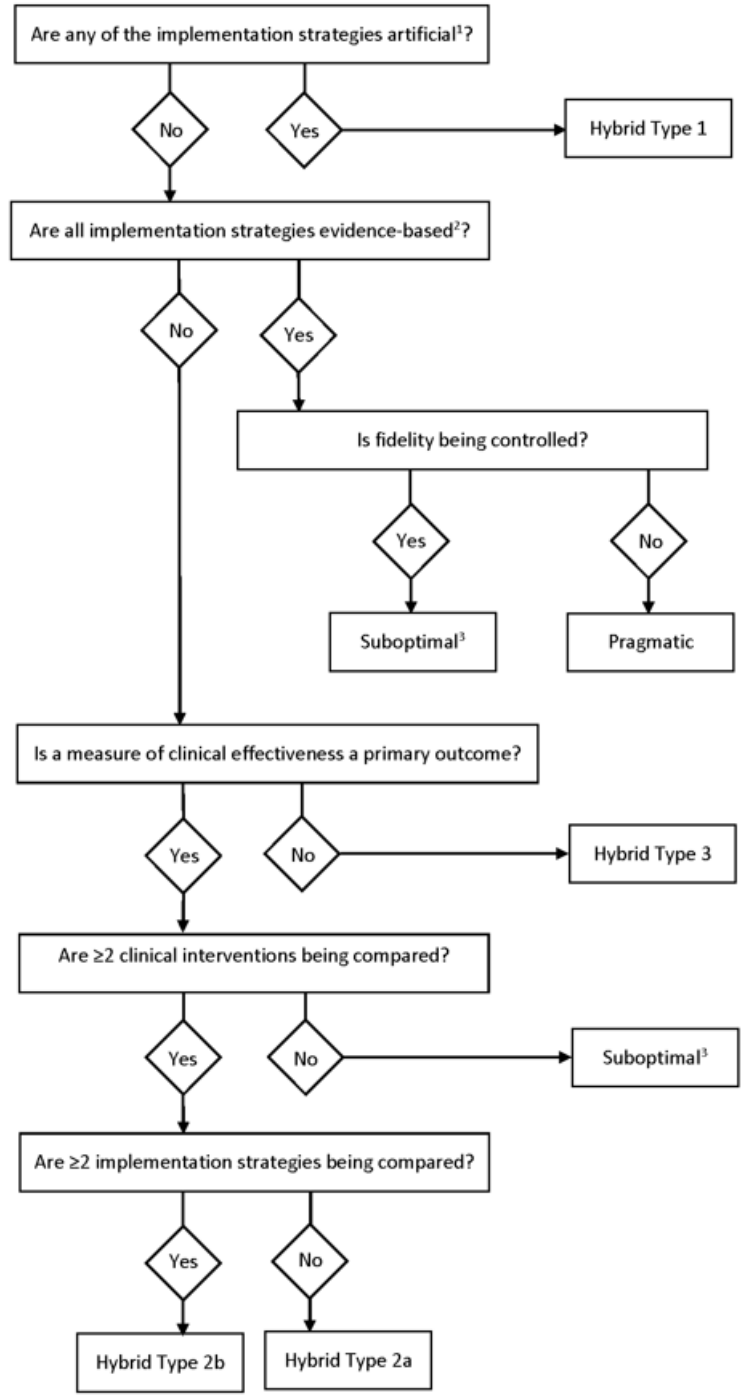
Are any of the implementation strategies artificial[1]?
No
Yes
Hybrid Type 1
Are all implementation strategies evidence-based[2]?
No
Yes
Is fidelity being controlled?
Yes
No
Suboptimal[3]
Pragmatic
Is a measure of clinical effectiveness a primary outcome?
Yes
No
Hybrid Type 3
Are ≥2 clinical interventions being compared?
Yes
No
Suboptimal[3]
Are ≥2 implementation strategies being compared?
Yes
No
Hybrid Type 2b
Hybrid Type 2a

Fidelity Ditches and Guardrails

- Both pragmatic and hybrid type 2 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