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Adaptive Trial Design and Learning Evaluation: Methods for PCOR and Quality Improvement Assessment

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August 18, 2015



Agenda

- Welcome and introduction
- Presentations
- Q&A session with all presenters
- Instructions for obtaining your CME Certificate of Participation

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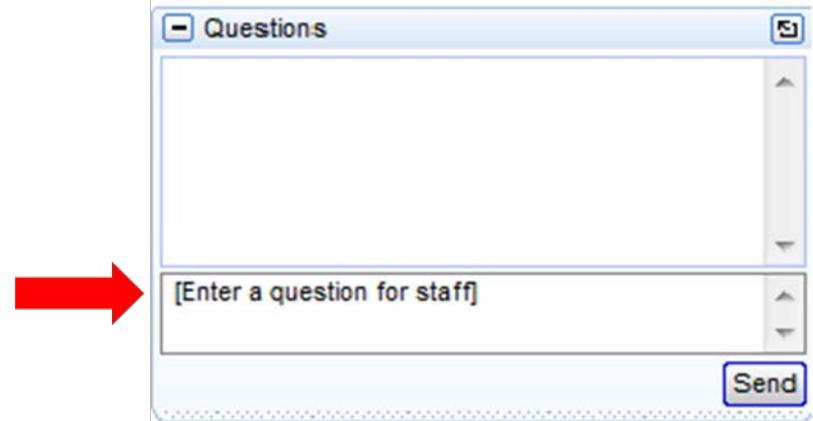
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Today's Presenters

Overview of Adaptive Randomized Clinical Trials



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Today's Presenters

Learning Evaluation: Blending Quality Improvement and Implementation Research Methods to Study Healthcare Innovations



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Overview of Adaptive Randomized Clinical Trials



Michelle Detry
August 18, 2015

Financial Disclosures

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 - Multiple Clients

Overview

- Patient-centered outcomes research goal is to make better treatment decisions by comparing commonly used treatments
- Randomized clinical trials (RCTs) used to compare benefits and risks
- Common for trial structure to remain fixed for entire trial
- But may want to make changes to a trial, “adapt” while trial running to improve trial

Overview

- Original trial design may have been based on assumptions and incomplete information
 - Do not know the treatment effects
 - Do not know the control/standard of care information
 - Do not know the populations where benefit may be seen

Adaptive Clinical Trials

- Allow for key trial characteristics to change during trial according to rules spelled out BEFORE the trial started
- Key trial characteristics
 - Fraction of patients assigned to a treatment
 - Number of patients enrolled
 - Number of treatments compared in a trial
 - Types of patients enrolled in a trial

Adaptive Clinical Trials

- Changes based on experiences of patients already enrolled, i.e. the trial “learns” as it is running
- May learn
 - Treatment/intervention does not work
 - Among multiple drug doses or multiple treatments some are promising, some are not effective
 - Treatment does work very well
 - Certain patient populations do not benefit from treatment

Adaptation Examples

- Early stopping
 - Futility stopping (allows patients to go to other studies)
 - Success stopping
- Arm dropping or adding
- Adaptive Randomization
 - Changes randomization ratio so more subjects are randomized to more effective arms
- Enrichment
 - Enroll more subjects in populations that seem to benefit from the treatment
 - Possibly drops groups of subjects

Adaptive Clinical Trials

- Some Goals of Adaptive RCTs
 - Improved patient outcomes
 - Better ethical balance
 - More effective treatment of patients in trials
 - Complete trial more rapidly
- Later patients may benefit from experiences of earlier patients

Minimum Standards

- Explicit prospective specification of planned adaptations and primary analysis
 - Key standard
- Must be carefully constructed and tested before trial starts
 - Run virtual trials on computers
- Key stakeholders should consider strengths and weaknesses before trial is run

Minimum Standards

- Consider logistics and resources necessary to run trial and implement adaptations
- Think about any possible favoritism or bias that may occur and do best to eliminate these situations
- Form committee/group to supervise trial and make sure run as planned
- Report full details of design

Example

- Established Status Epilepticus Treatment Trial (ESETT)
- Adaptive randomized phase 3 comparative effectiveness trial
- Patients with established status epilepticus who have failed benzodiazepines
- Part of Adaptive Designs Accelerating Promising Trials into Treatments (ADAPT-IT) project
 - Collaborative effort supported by both NIH and FDA

ESETT Example (continued)

- Goal: Identify most effective and/or least effective treatment from 3 common second line therapies for status epilepticus within emergency dept. setting
- 3 Treatments (fosphenytoin, levetiracetam and valproic acid)

ESETT Example (continued)

- Primary outcome: clinical cessation of status epilepticus within 20 min of start of infusion, without recurrent seizures, life-threatening hypotension or cardiac arrhythmia within 1 hr.
- Maximum sample size of 720 unique patients
- Minimum sample size of 400 patients

ESETT Example (continued)

- Adaptive Components:
 - Randomization probabilities updated during trial to increase proportion of patients randomized to better treatments
 - Interim analysis allowing for stopping early for success or futility

ESETT Example (continued)

- Initially randomize 100 subjects on each arm (300 total)
- Adjust randomization probabilities to favor more successful arms
- Update probabilities after every 100 pts randomized
- If randomization probability for an arm less than 5% suspend randomization to that arm

ESETT Example (continued)

- Interim monitoring for early stopping for success or futility will begin after 400 pts have been randomized
- Prespecified stopping criterion at each interim
- If trial continues, repeat after every 100 pts randomized

ESETT Example (continued)

- Paper gives numerous details on design creation process
- Determined key trial characteristics via simulation (Type I error, power, average sample size)
- Compared adaptive design to fixed design (randomize all subjects and do not evaluate data until end of trial)

ESETT Example (continued)

- A Few Conclusions
 - In a situation where 1 treatment superior to other 2, adaptive trial has higher power and lower expected sample size (483 vs. 497) than standard fixed design
 - If all 3 treatments equal, adaptive design slightly larger sample size (8-15 subjects) than fixed trial

ESETT Example (continued)

- Logistical Considerations
 - Trial has waiver of informed consent
 - No voice or internet randomization process
 - Instead, 3 boxes with IV study drug in each site and caregivers instructed to use top box labeled “use next”
 - Boxes reordered after each randomization update
 - Design characteristics chosen with logistics in mind, i.e. how often to update randomization probabilities

ESETT Example (continued)

- Response adaptive randomization feasible here because outcome quickly observed
 - May not work with all outcomes/studies
- Estimated accrual rates, and accrual was not too fast and allowed time for adaptations to occur
- Trial infrastructure in place to ensure ability to implement

Summary

- Adaptive trials allow for prospectively planned changes to trial based on incoming information
- May help shorten trial length or drug development process
- May lead to larger number of patients in trial receiving more effective treatments
- May lead to better treatment of future patients having disease or condition in trial

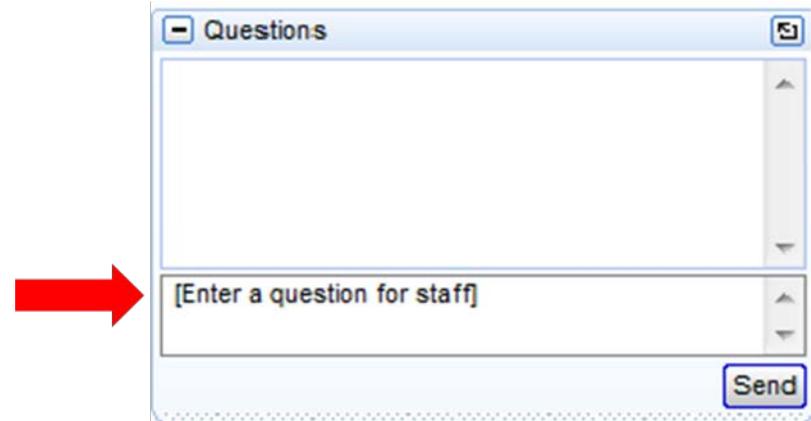
References

- Detry, MA, Lewis, RJ, Broglio, KB, Connor, JT, Berry , SM, Berry, DA; Standards for the Design, Conduct, and Evaluation of Adaptive Randomized Clinical Trials 2012
 - <http://www.pcori.org/assets/Standards-for-the-Design-Conduct-and-Evaluation-of-Adaptive-Randomized-Clinical-Trials.pdf>
- Connor JT, Elm JJ, Broglio KR; ESETT and ADAPT-IT Investigators. Bayesian adaptive trials offer advantages in comparative effectiveness trials: an example in status epilepticus. J Clin Epidemiol. 2013 Aug;66(8 Suppl):S130-7.



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Learning Evaluation

Blending Quality Improvement and Implementation
Research Methods to Study Healthcare Innovations

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Learning Evaluation

- Focuses on evaluating interventions implemented across multiple health care organizations
- Blends quality improvement and implementation research methods

Background

- Primary health care in the U.S. is undergoing rapid and continual change
 - Widespread implementation of demonstration projects (e.g., PCMH, integrated care) in the context of delivering usual care
- There is a unique opportunity to learn from such initiatives

Methodological challenges

- Context in which QI effort is implemented continually changes, making it hard to make sense of outcomes
- Traditional experimental methods guided by principles of randomization, strict inclusion/exclusion criteria, and tight internal validity are hard to attain in real-world settings

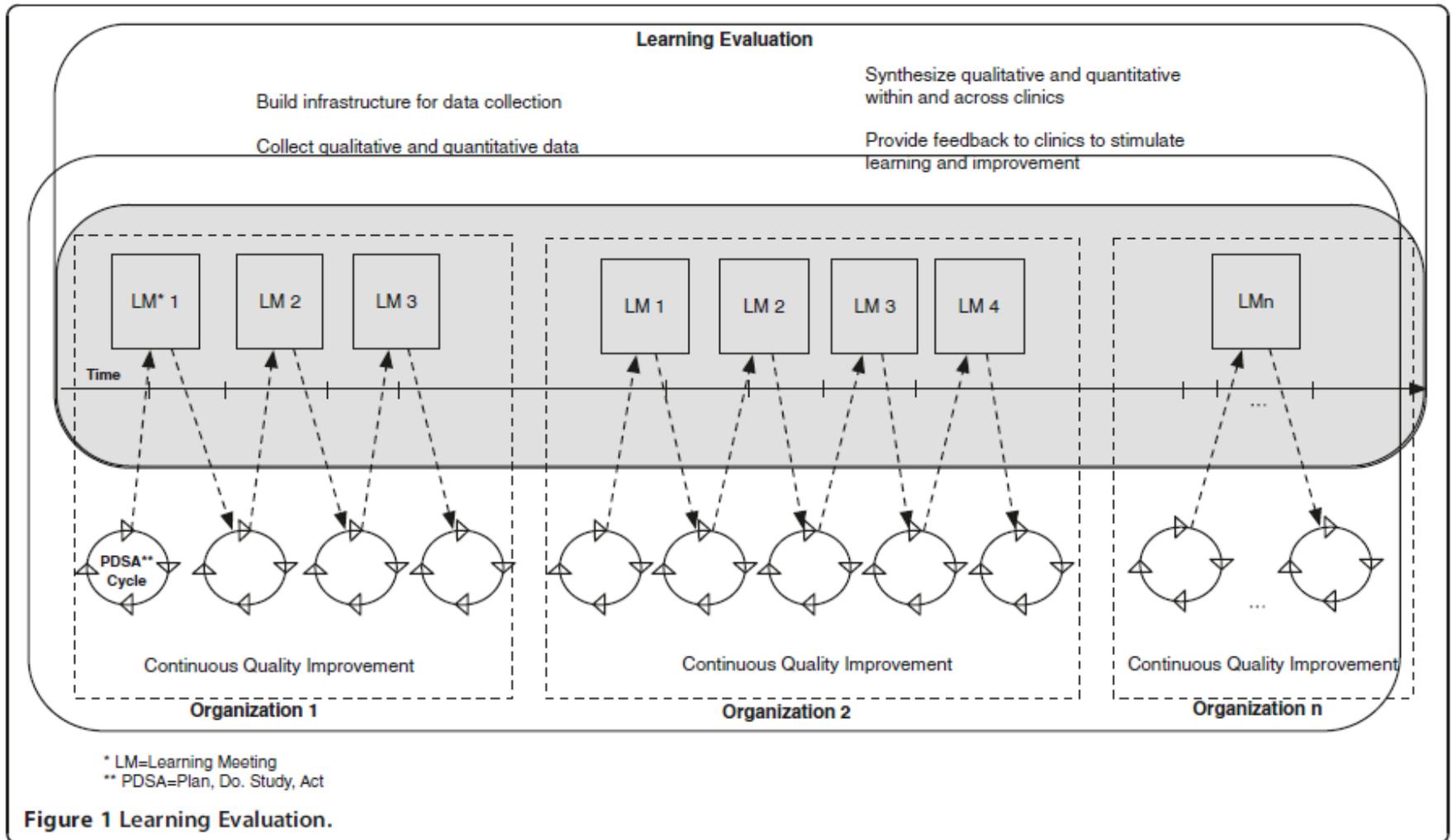
Need

- Innovative study designs that:
 - Are flexible yet rigorous
 - Have good internal validity
 - Help health care systems learn from QI effort through rapid change cycles
 - Continually assess the implementation process
 - Assesses context in which changes are made

Learning Evaluation

- Two key aspects
 - Facilitating learning from rapid cycles of change
 - Capturing contextual and explanatory factors related to implementation and evaluating their effect on outcomes
- Designed to balance:
 - Flexibility needed for within-system innovation and
 - Structure needed to support rigorous evaluation

Learning Evaluation



Principles underlying the Learning Evaluation

- Principle 1: Gather data to describe types of changes made by healthcare organizations, how changes are implemented, and the evolution of the change process.
- Principle 2: Collect process and outcome data that are relevant to healthcare organizations and to the research team.

Principles underlying the Learning Evaluation

- Principle 3: Assess multi-level contextual factors that affect implementation, process, outcome, and transportability.
- Principle 4: Assist healthcare organizations in applying data to monitor the change process and make further improvements.
- Principle 5: Operationalize common measurement and assessment strategies with the aim of generating transportable results.

Advancing Care Together (ACT)

- An Illustrative Example

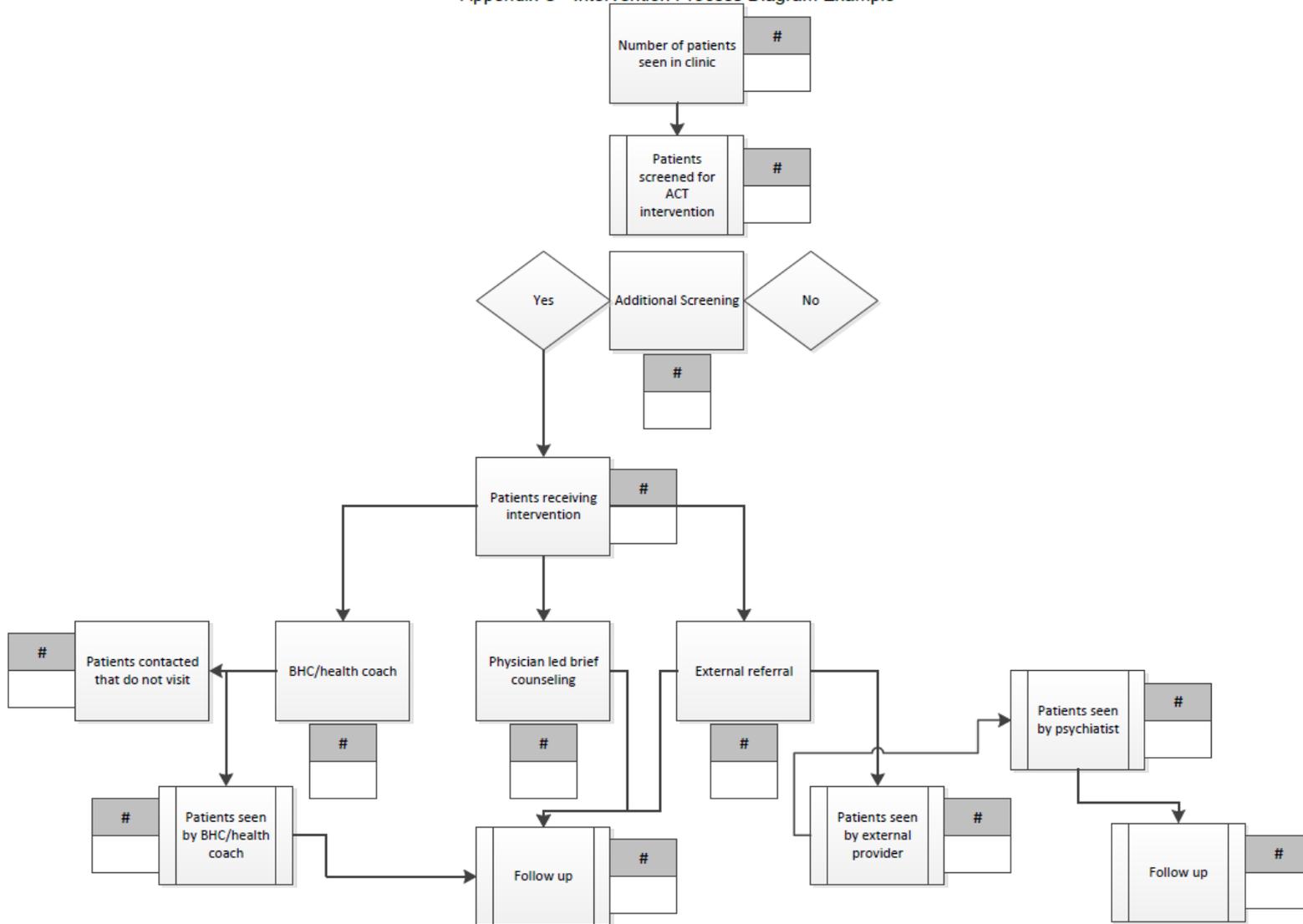
- ACT was designed to transform delivery of healthcare by learning from 11 demonstration projects about what it takes to implement models of integrated care in real-world settings.
 - 9 primary care practices and 2 mental health centers
- Practices varied on the evidence-based strategies they implemented:
 - Systematic screening for primary care and/or behavioral health needs using evidence-based screening tools (e.g., PHQ9, GAD7, BMI)
 - A shared medical record for recording and sharing patient information,
 - Co-locating primary care and behavioral care professionals in the same site.

Principle 1: Collect qualitative data to establish initial conditions and describe change process

- Guided by four research questions
 - What were the initial conditions to implement change among ACT practices?
 - What types of changes were they making to integrate care?
 - How were they making these changes; what facilitated or hindered this process; and
 - What were key stakeholders' (clinicians, clinical team members, patients) experiences with these changes?
- Types of data collected
 - Key documents
 - Direct observation at site visits
 - Interviews
 - Online diary

Intervention Process Diagram

Appendix C - Intervention Process Diagram Example



Principle 2: Collect quantitative data to assess process and outcome changes

- Quantitative data were collected to:
 - Obtain descriptive data on practice structural and functional characteristics, including patient panel characteristics – Practice Information Form
 - Estimate reach of the implementation strategies – Reach Reporter and Patient Tracking Sheet
 - Assess process and outcome measures to evaluate implementation success – EHR data

Data collection instruments

- Reach Reporter: practice-level data
 - Target population
 - Screening
 - Receipt of integrated care services
- Patient Tracking Sheet: patient-level data
 - Number and types of services received
 - Referrals, warm handoffs, traditional counseling
 - Location of services

Principle 3: Assess multi-level contextual and explanatory factors

- Data collection and analysis is done iteratively in real time
 - Tracking and analyzing implementation events using diary data
 - Creating run charts using reach and tracking data
 - Mapping implementation events on run charts

Principle 4: Audit and feedback to help practices reflect and stimulate further change

- Learning meetings
 - Share performance on screening and referral/ counseling rates with practice leaders
 - Facilitate reflection on practice members' experiences integrating care in the context of their reported screening and referral rates.
 - Discuss strategies that worked and did not work and as needed, identified changes to test in PDSA cycles in the next 3-month period.
 - This process was repeated quarterly until the end of the funding period

Principle 5: Use mixed methods to generate valid and transportable findings

- Incorporate multiple design features to mitigate lack of randomization
 - Multiple data collection time points
 - Qualitative data on implementation
 - Member checking
 - Harmonize process and outcome measures across organizations
- Conduct mixed-methods analyses focused on:
 - Triangulating findings
 - Identifying contextual factors that explain successful implementation and process outcomes
 - Examining change in intermediate outcomes (such as PHQ9) and integrating qualitative findings to make sense of observed changes

Principle 5: Use mixed methods to generate valid and transportable findings

- Upcoming JABFM supplement on Integrated Care
 1. Understanding Care Integration from the Ground Up: Five Organizing Constructs that Shape Integrated Practices
 2. Integrating Behavioral Health and Primary Care: Consulting, Coordinating, and Collaborating among Professionals
 3. REACH of Interventions Integrating Primary Care and Behavioral Health
 4. Clinician Staffing, Scheduling, and Engagement Strategies among Primary Care Practices Delivering Integrated Care
 5. Designing Clinical Space for the Delivery of Integrated Behavioral Health and Primary Care
 6. Strategies to Support the Integration of Behavioral Health and Primary Care: What Have We Learned Thus Far? (Commentary)

Some Considerations

- Principles are foundational; can be readily adapted
- Emphasis on engagement and openness to learning is crucial for success.
- Data must be shared with implementation teams regularly and often.
- Some healthcare organizations may not be able to collect the data initially agreed upon.
- Including control practices, when feasible, adds rigor

Innovative Features

- Blends quality improvement and implementation research
- Blends evaluation theories – Realist and empowerment
- Builds practice capacity
- Accelerates research translation pipeline

Conclusion

- Learning Evaluation
 - Facilitates continuous learning
 - Generates rigorous and transportable findings
 - Adds contextualized, ongoing knowledge essential to rapidly advance implementation science



Our Team

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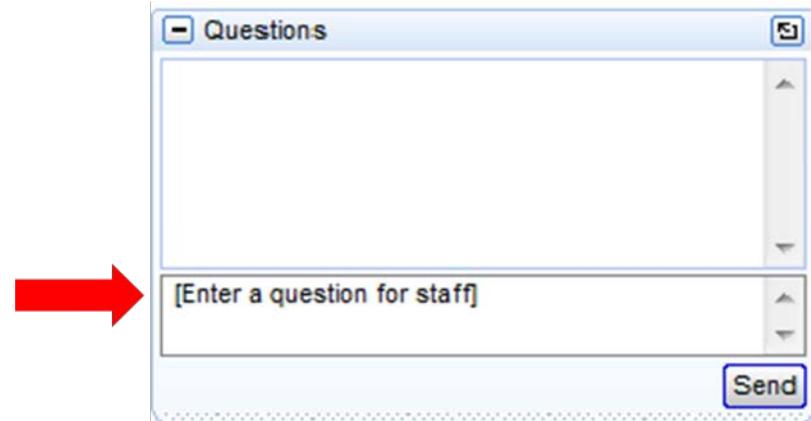
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