National Drug Abuse Treatment Clinical Trials Network

Monitoring trial integrity, study progress, and data quality for implementation studies

Ashley Vena, PhD; August F. Holtyn, PhD; Joseph E. Glass, PhD, MSW; Amy K. Lee, MPH; Abigail G. Matthews, PhD; Jennifer McNeely, MD, MS; Jennifer McCormack, MS; Kathryn Hefner, PhD

SCT
SOCIETY FOR CLINICAL TRIALS

MAY 22, 2023

Overview of Today's Session

- **Panel presentations**
  - August F. Holtyn, PhD (NIDA, NIH)
  - Ashley Vena, PhD (Emmes)
  - Joseph E. Glass, PhD, MSW (Kaiser Permanente Washington Health Research Institute)
  - Amy K. Lee, MPH (Kaiser Permanente Washington)
  - Abigail G. Matthews, PhD (Emmes)
- **Open discussion and Q&A**
  - Moderated by Jennifer McNeely, MD, MS (New York University Grossman School of Medicine)

Disclosures

- None

August F. Holtyn, Ph.D.

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Presentation Outline

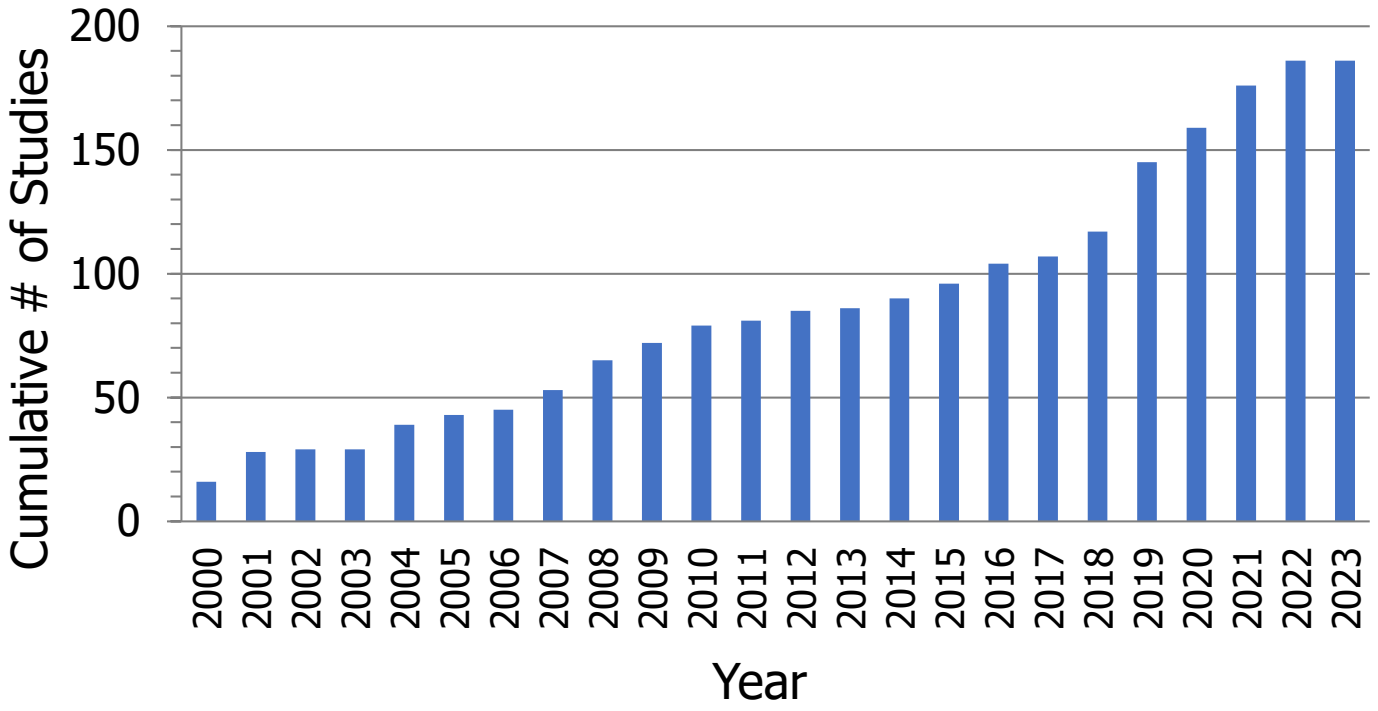
- Introduce the National Drug Abuse Treatment Clinical Trials Network (CTN)
- Describe the types of studies conducted in the CTN
- Discuss the role of sponsors, investigators, and Data and Safety Monitoring Boards (DSMBs) in study monitoring

National Drug Abuse Treatment Clinical Trials Network (CTN)

- A clinical research network established to bridge the gap between research and practice
- Seeks to address critical research questions with direct relevance to clinical practice and the needs of patients
- Conducts studies of substance use treatment interventions, as well as their implementation, in medical settings

CTN Network Organization

Clinical Trials Network (CTN) Studies



- Multi-Site Clinical Studies
- Data Science Studies
- Implementation and Pragmatic Studies

Data and Safety Monitoring Boards (DSMBs)

- Committee of experts that is independent of the trial sponsor and investigators
- Should have no vested interest in the trial or its outcomes
- Oversee and monitor the safety of participants and the validity and integrity of the data

Data and Safety Monitoring Boards (DSMBs)

CTN-0099 ED-INNOVATION

- Clinical trial methodology
- Statistician
- SUD research
- Emergency medicine
- Implementation research

CTN-0138 PHARMTOOL

- Clinical trial methodology
- Statistician
- SUD research
- Pharmacy
- Clinical decision support

Data and Safety Monitoring Boards (DSMBs)

- Periodically review and evaluate study data
  - participant safety
  - study conduct and progress
  - efficacy (when appropriate)
- Make recommendations concerning study continuation, modification, or termination

Data and Safety Monitoring - Roles

- DSMB monitors for safety and data integrity periodically, typically once a year
- Study sponsor (e.g. NIH) oversees the study progress
- The investigators should monitor the study frequently

Data and Safety Monitoring for Implementation Trials

- Some special considerations may be important to consider for implementation trials
- An appropriate data monitoring plan should be in place before study initiation — one that balances the implementation nature of the trial with the need to maintain trial safety, validity, and integrity

Distinctions in monitoring implementation trials relative to clinical research

Ashley Vena, PhD
Associate Project Leader-Scientist
Emmes

Characteristics of Clinical and Implementation Research Studies

	Clinical Research	Implementation Research
Objective	Establish health impact of a clinical innovation (e.g., efficacy, effectiveness)	Identify and evaluate strategies to increase uptake of evidence-based interventions
Context	Controls/tolerates contextual factors	Engages with the context across multiple levels
Unit of observation	Specific (typically at participant/patient level)	Broad (may be patients, clinicians/providers, teams, facilities, and/or organizations)
Outcome measures	Health outcomes, usually on the patient level	Acceptability, adoption, feasibility, fidelity, cost, reach, and/or sustainability of a clinical innovation

Bauer & Kirchner, Psych Res, 2020; Bauer et al., BMC Psych, 2015

Characteristics of Clinical and Implementation Research Studies

	Clinical Research	Implementation Research
Research infrastructure	Close oversight by researchers (w/ some variability depending on nature of the study, e.g., efficacy vs effectiveness)	Only for implementation tasks
Intervention fidelity	Trained to criterion; ongoing fidelity monitoring	Monitor and intervene to improve fidelity; modifications to the implementation process specified *a priori* ("formative evaluations")
Risk	Evaluated at the level of individual participants	May be evaluated at the level of organization/system, providers, and/or other stakeholder groups, as risk to individual participants is often minimal

Bauer & Kirchner, Psych Res, 2020; Bauer et al., BMC Psych, 2015

Unique challenges in monitoring implementation trials

- Oftentimes, implementation trials are not collecting data on individual safety events related to the clinical innovation/intervention.
- Key outcome and/or adverse event data may not be available in real-time (e.g., EMR data, data from large federal and/or state databases, such as Medicaid, National Death Index)
  - Impacts feasibility of early detection of overwhelming benefit or futility
  - Data quality and integrity may be out of control of the investigators
  - Primary outcome data availability is often "all or nothing."
- Variability in site adherence to the intervention is often expected, and may even be a study outcome

Case Example:

At a DSMB interim meeting, the Board was reviewing two studies presented by the same investigative team:

Study A

Clinical trial evaluating the impact of a study-administered medication on specific patient health outcomes

- Overall study progress
- Participant screening, enrollments, dispositions
- Trial recruitment and retention
- Sample characteristics
- Summary of treatment exposure
- Primary outcome data availability
- Key secondary outcome data availability
- Summary of data validity and integrity
- Operational metrics (e.g. protocol deviations, site performance, etc.)
- Participant-level safety events (e.g. AEs, SAEs, pregnancies, etc.)

Study B

Implementation trial comparing a high vs low intensity implementation strategy (at the hospital level) on uptake of an evidence-based practice

- Overall study progress
- Fidelity to the intervention

Case Example:

At a DSMB interim meeting, the Board was reviewing two studies presented by the same investigative team:

Study A

Clinical trial evaluating the impact of a study-administered medication on specific health outcomes

- Overall study progress
- Participant screening, enrollments, dispositions
- Trial recruitment and retention
- Sample characteristics
- Summary of treatment exposure
- Primary outcome data availability
- Key secondary outcome data availability
- Summary of data validity and integrity
- Operational metrics (e.g. protocol deviations, site performance, etc.)
- Participant-level safety events (e.g. AEs, SAEs, pregnancies, etc.)

Study B

Implementation trial comparing a high vs low intensity implementation strategy on uptake of an evidence-based practice

- Overall study progress
- Fidelity to the intervention
- Number and types of outreach efforts
- Characteristics of providers (survey respondents)
- Primary outcome data availability

Summary

- Fundamental differences exist between clinical (e.g., efficacy, effectiveness, etc.) and implementation trials
- Determination of risk and level of monitoring should be discussed early on and may vary depending on the study to ensure that risk management does not interfere with routine care or the study objectives
- Metrics typically used for monitoring clinical trials may not be feasible or appropriate for implementation trials

HSN

National Drug Abuse Treatment Clinical Trials Network

Monitoring implementation trials: Some Considerations

JOSEPH E. GLASS, PHD, MSW

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Presentation Overview

- Types of implementation studies
- Study team exposure to implementation outcome data (interim results)
- Ways to mitigate risk of bias

Types of implementation studies

- **Implementation Research (IR)**
  - Evaluate the use of implementation strategies intended to integrate evidence-based interventions into real-world settings
  - Evaluate the impact of one or more sets of strategies or versus implementation as usual
  - Compare two or more sets of strategies
- **Implementation Preparation (IP)**
  - Use but not isolate the impact of implementation strategies
  - Characterize contextual barriers and facilitators
  - Measure some implementation outcomes (reach, adoption, feasibility, acceptability, fidelity, appropriateness)

Smith et al., *AIDS Behav,* 2020; Cheng et al., *Drug Alcohol Depend* 2021

Hybrid effectiveness-implementation studies

Effectiveness
Patient health outcomes
Real-world settings with researchers delivering interventions (typically)

Implementation
Process outcomes
Real-world setting with clinicians delivering intervention (typically)

Hybrid Studies

Curran et al., *Med Care,* 2012; Curran et al., *Front Health Serv,* 2022

Hybrid effectiveness-implementation studies

Effectiveness
Patient health outcomes
Real-world settings with researchers delivering interventions (typically)

Implementation
Process outcomes
Real-world setting with clinicians delivering intervention (typically)

DIGITS Trial:
Primary focus is implementation

Curran et al., *Med Care,* 2012; Curran et al., *Front Health Serv,* 2022

DIGITS Trial: Optimizing the implementation of digital therapeutics for substance use disorders in primary care

Setting & Population: Primary care patients with substance use disorder

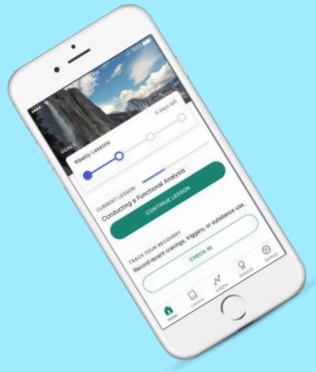
Primary outcomes: Reach, fidelity

Secondary outcomes: Substance use & cost-effectiveness

Implementation strategies

- Practice facilitation
- Health coaching

Comparator strategy: Standard Implementation



Glass et al. Implementation Science (2023) 18:3
https://doi.org/10.1186/s13012-022-01258-9

Implementation Science

STUDY PROTOCOL Open Access

Study protocol for a factorial-randomized controlled trial evaluating the implementation, costs, effectiveness, and sustainment of digital therapeutics for substance use disorder in primary care (DIGITS Trial)

Joseph E. Glass[1*], Caitlin N. Dorsey[1], Tara Beatty[1], Jennifer F. Bobb[1], Edwin S. Wong[2,3], Lorella Palazzo[1], Deborah King[1], Jessica Mogk[1], Kelsey Stefanik-Guizlo[1], Abisola Idu[1], Dustin Key[1], John C. Fortney[3,4], Rosemarie Thomas[5], Angela Garza McWethy[5], Ryan M. Caldeiro[5] and Katharine A. Bradley[1]

Abstract

Background Experts recommend that treatment for substance use disorder (SUD) be integrated into primary care. The Digital Therapeutics for Opioids and Other SUD (DIGITS) Trial tests strategies for implementing reSET® and reSET-O®, which are prescription digital therapeutics for SUD and opioid use disorder, respectively, that include the community reinforcement approach, contingency management, and fluency training to reinforce concept mastery. This purpose of this trial is to test whether two implementation strategies improve implementation success (Aim 1) and achieve better population-level cost effectiveness (Aim 2) over a standard implementation approach.

Methods/Design The DIGITS Trial is a hybrid type III cluster-randomized trial. It examines outcomes of implementation strategies, rather than studying clinical outcomes of a digital therapeutic. It includes 22 primary care clinics from a healthcare system in Washington State and patients with unhealthy substance use who visit clinics during an active implementation period (up to one year). Primary care clinics implemented reSET and reSET-O using a multifaceted implementation strategy previously used by clinical leaders to roll-out smartphone apps ("standard implementation" including discrete strategies such as clinician training, electronic health record tools). Clinics were randomized as 21 sites in a 2x2 factorial design to receive up to two added implementation strategies: (1) practice facilitation, and/or (2) health coaching. Outcome data are derived from electronic health records and logs of digital therapeutic usage. Aim 1's primary outcomes include reach of the digital therapeutics to patients and fidelity of patients' use of the digital therapeutics to clinical recommendations. Substance use and engagement in SUD care are additional outcomes. In Aim 2, population-level cost effectiveness analysis will inform the economic benefit of the implementation strategies compared to standard implementation. Implementation is monitored using formative evaluation, and sustainment will be studied for up to one year using qualitative and quantitative research methods.

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Considerations about what the study team monitors in implementation research

- Implementation research often requires the study team to have knowledge about interim results
  - Very unconventional! Typically, a role for DSMBs
- Traditionally, the PI and study team should not look at outcome data—increases risk of bias
- In implementation studies, the need arises for the study team to look at interim implementation outcome data
  - Keep in mind that implementation outcomes are process outcomes, such as reach of the intervention into the eligible population, or adoption of the intervention by clinicians

The need to monitor implementation outcomes

- Like quality improvement interventions, implementation strategies are designed to respond to real world conditions, where there is variation across settings and within settings over time
  - For example: A minor variation in clinical workflows or policies at a clinic could prevent the EBP from being delivered appropriately.
- To detect and address this lack of fit, many proven implementation strategies include activities to continuously measure and review implementation outcomes, and intervene upon the context when poor performance is identified (e.g., practice facilitation, audit and feedback, plan-do-study-act cycles)
- If the implementation outcome is a primary outcome, this could require monitoring the study's primary outcome
  - e.g., proportion of patients who received the intervention (reach)

Mitigating risk of bias

- The need for the study team to look at implementation outcome data could pose a risk of bias
- To minimize this, the study team practice blinding wherever possible
  - Programmer generates reports about implementation outcomes and gives them directly to implementation practitioners (e.g., practice facilitators, clinicians) without PI review
  - Discuss in depth with study team and create guidelines for who should have access to what information
  - Limit sharing of certain data between teams on a study—e.g., the PI, implementation monitoring team, implementation strategy delivery team

Thank you

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The PROUD Trial: Implementation Monitoring Team and Formative Evaluation

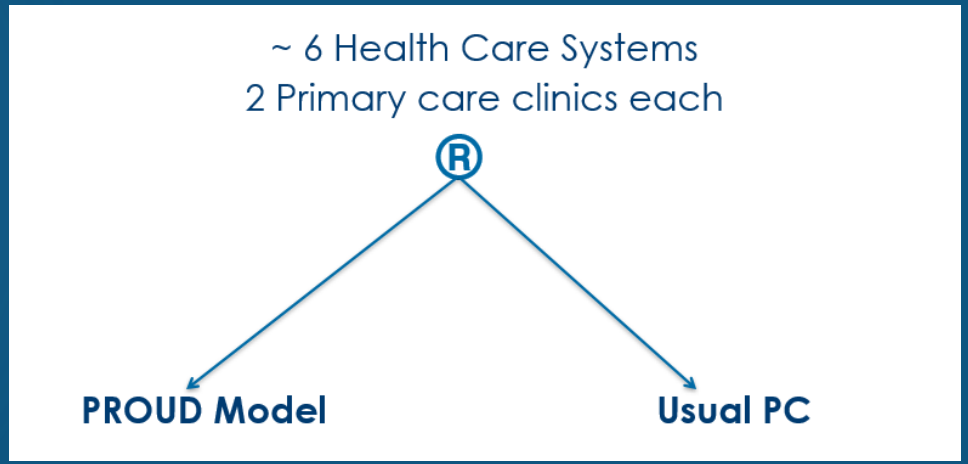
AMY K LEE, MPH

PRimary care Opioid Use Disorders treatment (PROUD) Trial Design

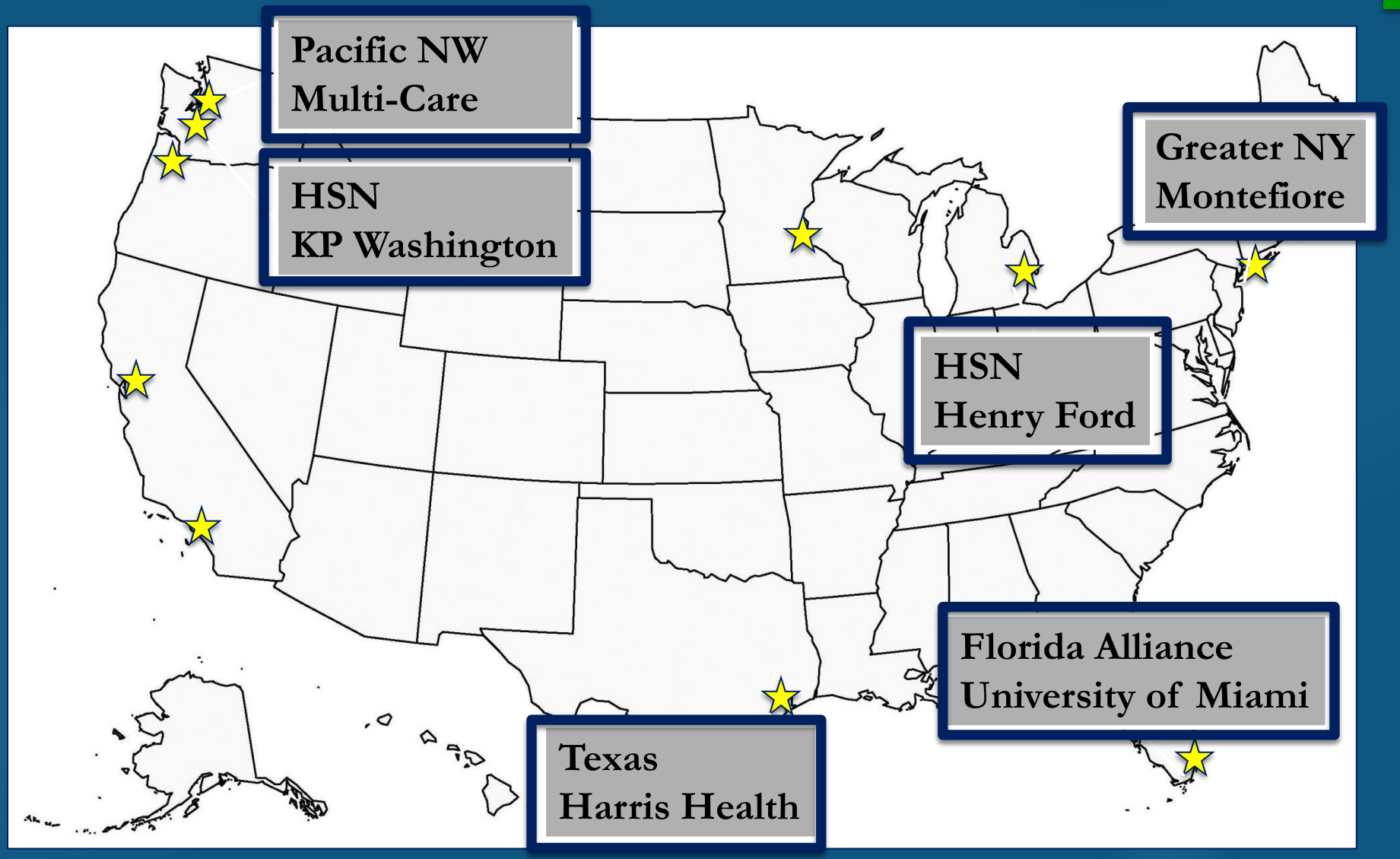
- Mixed-methods cluster-randomized
- Hybrid Type III – implementation-effectiveness trial
- Testing Massachusetts Model of nurse care management for opioid use disorder treatment
- Intervention:
  - Support for a 1.0 FTE nurse care manager
  - Boston Medical Center nurse experts provide training and technical assistance (TA) to nurse care managers
  - 3 primary care providers agree to become waivered

PROUD Trial Design

- In each of 6 health systems:
  - 2 PC clinics or clusters
  - Randomization stratified within health system
  - One clinic per health system implements Massachusetts Model of nurse care management for opioid use disorder



PROUD Trial Sites



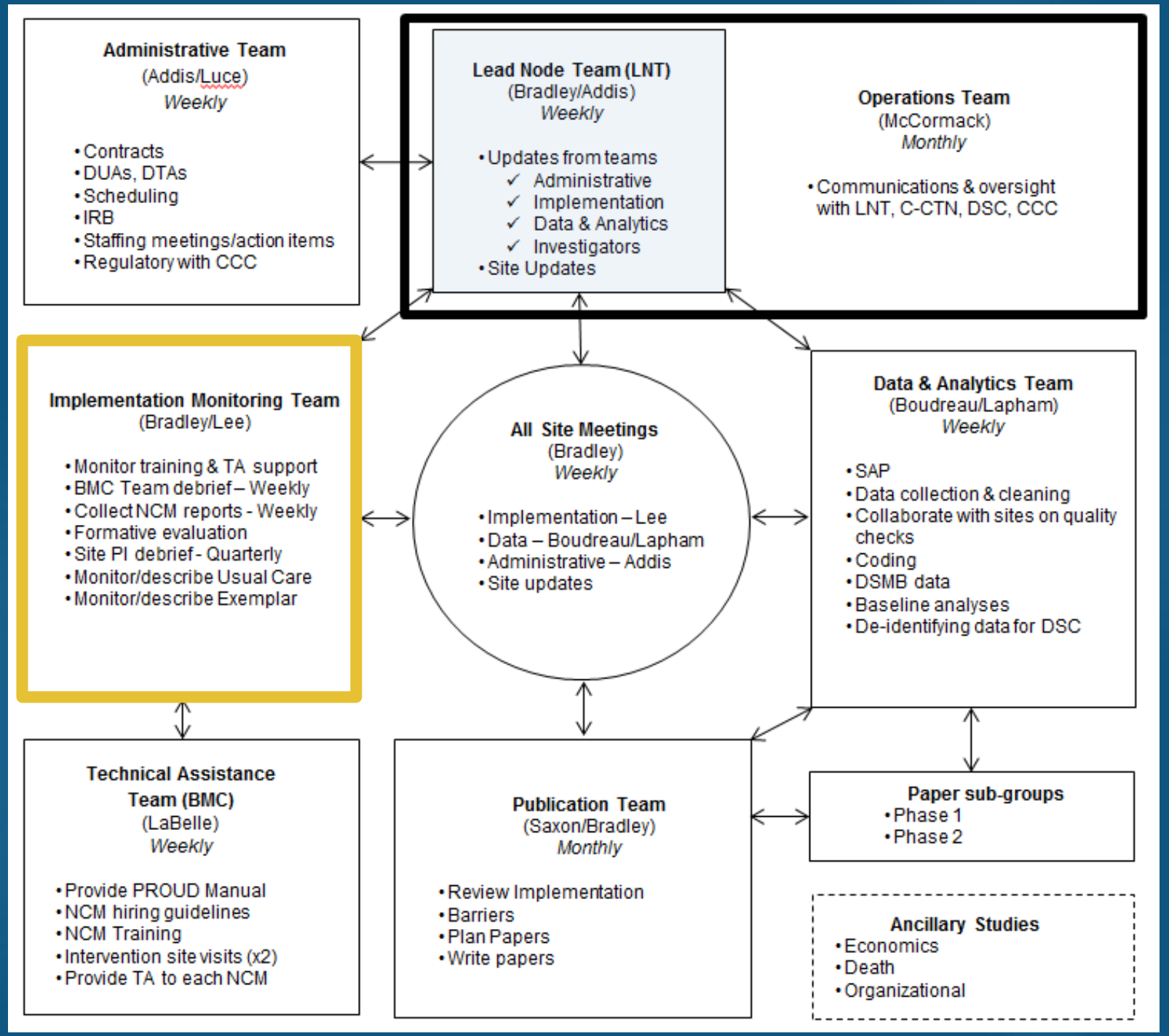
Objective 1: Primary implementation outcome

- Secondary EHR and insurance claims data
- To evaluate whether the PROUD implementation of the Massachusetts Model using nurse care managers increases clinics' treatment of opioid use disorder with buprenorphine or extended-release injectable naltrexone as compared to usual primary care clinics
  - Primary outcome (clinic level): number of patient-days of medication treatment for opioid use disorder per 10,000 primary care patients seen during follow-up

PROUD Trial - Objective 2
Secondary effectiveness outcome

- Secondary EHR and insurance claims data
- To evaluate whether primary care patients with a prior opioid use disorder diagnosis who receive care in PROUD intervention clinics have decreased acute care utilization as compared to patients who receive care at usual primary care clinics
  - Secondary outcome (patient level): number of days of acute care utilization (including urgent care, ED, and hospital care)

Implementation Monitoring


Administrative Team
(Addis/Luce)
Weekly
• Contracts
• DUAs, DTAs
• Scheduling
• IRB
• Staffing meetings/action items
• Regulatory with CCC
Lead Node Team (LNT)
(Bradley/Addis)
Weekly
• Updates from teams
✓ Administrative
✓ Implementation
✓ Data & Analytics
✓ Investigators
• Site Updates
Operations Team
(McCormack)
Monthly
• Communications & oversight with LNT, C-CTN, DSC, CCC
Implementation Monitoring Team
(Bradley/Lee)
• Monitor training & TA support
• BMC Team debrief – Weekly
• Collect NCM reports - Weekly
• Formative evaluation
• Site PI debrief - Quarterly
• Monitor/describe Usual Care
• Monitor/describe Exemplar
All Site Meetings
(Bradley)
Weekly
• Implementation – Lee
• Data – Boudreau/Lapham
• Administrative – Addis
• Site updates
Data & Analytics Team
(Boudreau/Lapham)
Weekly
• SAP
• Data collection & cleaning
• Collaborate with sites on quality checks
• Coding
• DSMB data
• Baseline analyses
• De-identifying data for DSC
Technical Assistance Team (BMC)
(LaBelle)
Weekly
• Provide PROUD Manual
• NCM hiring guidelines
• NCM Training
• Intervention site visits (x2)
• Provide TA to each NCM
Publication Team
(Saxon/Bradley)
Monthly
• Review Implementation
• Barriers
• Plan Papers
• Write papers
Paper sub-groups
• Phase 1
• Phase 2
Ancillary Studies
• Economics
• Death
• Organizational

Purpose of Implementation Monitoring

- 3-person Implementation Monitoring team
- Monitor implementation of the PROUD intervention throughout the trial for the purpose of:
  - Ongoing **formative evaluation** to understand how the PROUD intervention overcomes barriers and facilitates implementation of the MA Model
  - To **inform any adaptations needed to enhance implementation of the intervention**
  - Regular summary of findings of barriers and facilitators and recommendations for any changes in implementation for trial leadership, DSMB reports, and intervention clinics
  - Characterize opioid use disorder and other addictions care in Intervention and Usual Care clinics
  - Provide contextual information to support trial result interpretation

Formative Evaluation

- "A rigorous assessment process designed to identify potential and actual influences on the progress and effectiveness of implementation efforts. …enables researchers to explicitly study the complexity of implementation projects and suggests ways to answer questions about context, adaptations, and response to change." Stetler et al., JGIM, 2006
- PROUD protocol:
  - Specified *a priori* that formative evaluation would be used to guide adaptation of the implementation to the diverse health systems in the trial if necessary
  - Implementation Monitoring Team summarizes barriers and facilitators weekly for the Lead Node Team
  - If significant barriers, Lead Node Team will present results to the CTN Operations Team to discuss

DSMB Reporting

Implementation Monitoring Data, De-identified Sites

Type of information	Examples of data reported
Fidelity to intervention	Nurse Care Manager hiring, training, site visit updates, # of waivered provider
Study progress (reach)	# patients treated by Nurse Care Managers, from weekly nurse reports
High-level implementation barriers and facilitators	Clinic and provider engagement, types of outreach efforts, workflows, cost/insurance coverage

DSMB Reporting

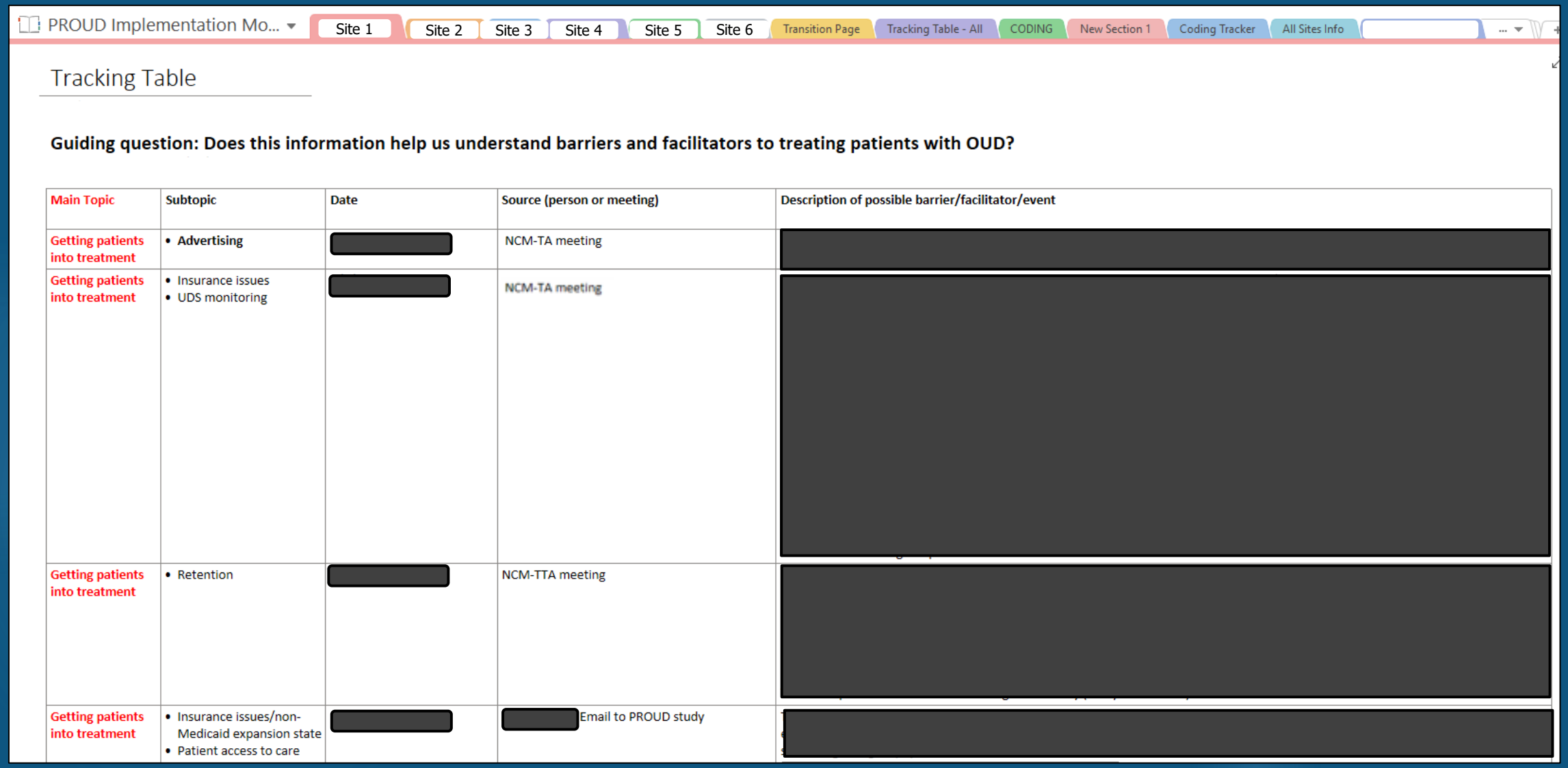
Quantitative Secondary Data, De-identified Sites

Type of information	Examples of data reported
To provide DSMB assessment and assurance of data quality and completeness	• Measure of accumulation of eligible subjects across health systems and diverse patient characteristics, including demographics, health care utilization • Measure of data completeness across variety of patient diagnoses
Safety	At request of DSMB, measures of patient overdose events by site and treatment arm • Noting expected ascertainment bias which could increase measured prevalence in intervention clinics over control clinics

Implementation Monitoring Activities

- At all randomized clinics, describe existing practices at baseline, with quarterly debriefs
  - OUD treatment practices
  - Barriers and facilitators to implementation of OUD treatment
  - Health system infrastructure
  - External environment
- Observation at initial Nurse Care Manager training in Boston
- Site visits with Boston nurse experts at randomized intervention sites
- Weekly virtual calls between Nurse Care Managers & Boston nurse experts
- Debriefs with Boston nurse experts (every 2-4 weeks)
- Interviews with Nurse Care Managers at the end of the trial

Implementation Monitoring Tracker



Tracking Table

Guiding question: Does this information help us understand barriers and facilitators to treating patients with OUD?

Main Topic	Subtopic	Date	Source (person or meeting)	Description of possible barrier/facilitator/event
Getting patients into treatment	• **Advertising**	[redacted]	NCM-TA meeting	[redacted]
Getting patients into treatment	• Insurance issues • UDS monitoring	[redacted]	NCM-TA meeting	[redacted]
Getting patients into treatment	• Retention	[redacted]	NCM-TTA meeting	[redacted]
Getting patients into treatment	• Insurance issues/non-Medicaid expansion state • Patient access to care	[redacted]	[redacted] Email to PROUD study	[redacted]

Lessons Learned

- When making adaptations, outline ahead of time:
  - Who is the decider (ideal for it to be someone who knows intervention well/has expertise to decide)
  - How often they will receive information from implementation monitoring team
  - Have targets/threshold for change (e.g. previous data on rate of change on process measure)
  - E.g. in another trial (SPARC), weekly formative evaluation meetings followed by weekly meetings where all deciders met to review barriers and discuss potential adaptations, with targets set

FRAME-IS: Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies

Miller et al., Implementation Science, 2021

Module 1: BRIEFLY DESCRIBE the EBP, implementation strategy, and modification(s)

The EBP being implemented is: _____

The implementation strategy being modified is: _____

The modification(s) being made is/are: _____

The reason(s) for the modification(s) is/are: _____

Module 2: WHAT is modified?

❑ ***Content***
Modifications made to content of the implementation strategy itself, or that impact how aspects of the implementation strategy are delivered

❑ ***Evaluation***
Modifications made to the way that the implementation strategy is evaluated

❑ ***Training***
Modifications to the ways that implementers are trained

❑ ***Context***
Modifications made to the way the overall implementation strategy is delivered. For Context modifications, specify which of the following was modified:

- ❑ ***Format*** (e.g. group vs. individual format for delivering the implementation strategy)
- ❑ ***Setting*** (e.g. delivering the implementation strategy in a new clinical or training setting than was originally planned)
- ❑ ***Personnel*** (e.g. having the implementation strategy be delivered by a systems engineer rather than a clinician facilitator)
- ❑ ***Population*** (e.g. delivering the implementation strategy to middle managers instead of frontline clinicians)
- ❑ ***Other*** context modification: write in here:
  _____

Module 3: What is the NATURE of the content, evaluation, or training modification?

- ❑ Tailoring/tweaking/refining
- ❑ Changes in packaging or materials
- ❑ Adding elements
- ❑ Removing/skipping elements
- ❑ Shortening/condensing (pacing/timing)
- ❑ Lengthening/ extending (pacing/timing)
- ❑ Substituting
- ❑ Reordering of implementation modules or segments
- ❑ Spreading (breaking up implementation content over multiple sessions)
- ❑ Integrating parts of the implementation strategy into another strategy (e.g., selecting elements)
- ❑ Integrating another strategy into the implementation strategy in primary use (e.g. adding an audit/feedback component to an implementation facilitation strategy that did not originally include audit/feedback)
- ❑ Repeating elements or modules of the implementation strategy
- ❑ Loosening structure
- ❑ Departing from the implementation strategy ("drift") followed by a return to strategy within the implementation encounter
- ❑ Drift from the implementation strategy without returning (e.g., stopped providing consultation, stopped sending feedback reports)
- ❑ Other (write in here):
  _____

Module 3, OPTIONAL Component: Relationship to fidelity/core elements?

- ❑ Fidelity Consistent/Core elements or functions preserved
- ❑ Fidelity Inconsistent/Core elements or functions changed
- ❑ Unknown

Module 4, Part 1: What is the GOAL?

- ❑ Increase reach of the EBP (i.e. the number of patients receiving the EBP)
- ❑ Increase the clinical effectiveness of the EBP (i.e. the clinical outcomes of the patients or others receiving the EBP)
- ❑ Increase adoption of the EBP (i.e. the number of clinicians or teachers using the EBP)
- ❑ Increase the acceptability, appropriateness, or feasibility of the implementation effort (i.e. improve the fit between the implementation effort and the needs of those delivering the EBP)
- ❑ Decrease costs of the implementation effort
- ❑ Improve fidelity to the EBP (i.e. improve the extent to which the EBP is delivered as intended)
- ❑ Improve sustainability of the EBP (i.e. increase the chances that the EBP remains in practice after the implementation effort ends)
- ❑ Increase health equity or decrease disparities in EBP delivery
- ❑ Other (write in here):
  _____

Module 4, Part 2: What is the LEVEL of the rationale for modification?

- ❑ Sociopolitical level (i.e. existing national mandates)
- ❑ Organizational level (i.e. available staffing or materials)
- ❑ Implementer level (i.e. those charged with leading the implementation effort)
- ❑ Clinician or Teacher level (i.e. those implementing the EBP)
- ❑ Patient or Other Recipient level (i.e. those who will ideally benefit from the EBP)
- ❑ Other (write in here):
  _____

The FRAME-IS (core modules)

FRAME-IS: Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies

Miller et al., Implementation Science, 2021

Module 5, Part 1: WHEN is the modification initiated?

- ❑ Pre-implementation/planning/pilot phase
- ❑ Implementation phase
- ❑ Scale up (i.e. when the EBP is being spread to additional clinics/settings within your system)
- ❑ Maintenance/Sustainment
- ❑ Other (write in here):

_____

Module 5, Part 2: Is modification PLANNED?

- ❑ Planned/Proactive (proactive adaptation)
- ❑ Planned/Reactive (reactive adaptation)
- ❑ Unplanned/Reactive (modification)
- ❑ Other (write in here):

_____

Module 6: WHO participates in the decision to modify?

- ❑ Political leader(s)
- ❑ Program Leader, Manager, or Administrator
- ❑ Funder
- ❑ Implementer or implementation strategy expert
- ❑ Researcher
- ❑ Clinician(s) or teacher(s) who are being asked to use the EBP being implemented
- ❑ Community members
- ❑ Patients or other recipients who will be the ultimate target of the EBP being implemented
- ❑ Other: write in here:

_____

- ❑ **Optional: Indicate who makes the ultimate decision:**

_____

Module 7: How WIDESPREAD is the modification? (i.e. for whom/what is the modification made?)

- ❑ Individual patient or other recipient for whom the EBP is being implemented
- ❑ Group of patients or other recipients for whom the EBP is being implemented
- ❑ Patients or other recipients that share a particular characteristic (e.g. all patients from a specific language background)
- ❑ Individual clinician or teacher charged with implementing the EBP
- ❑ Clinic/unit
- ❑ Organization
- ❑ Network system/community
- ❑ Specific implementer/facilitator
- ❑ Implementation/facilitation team

The FRAME-IS (optional modules)

Statistical Perspective and Report Preparation

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Emmes

Topics

- Compare traditional RCT DSMB reporting and that for an implementation study
- Information sharing
- Other challenges
- Recommendations

Comparison of DSMB Objectives

Emmes

Objective	Traditional RCT	Implementation Study
Monitor safety of participants	Top priority	What does safety mean in this context?
Monitor data quality and integrity	Priority	What is data quality/integrity for qualitative data? Surveys?
Review need for protocol/design modifications	Priority	What does this mean in this context? If there is fidelity to intervention – stop study?
Use data to make decisions about study conduct that reveals nothing about study outcomes or treatment effect	Mask treatment assignment; review outcome availability (not actual outcome data)	Mask sites? How to mask outcome measures?
Preserve integrity of deliberations by having open and closed sessions	Open session = blinded Closed session = unblinded/safety & frank discussion amongst members	Is this relevant?
Intervention/medication adherence	Treatment exposure/compliance	Fidelity?

What Information is Presented?

Data Points	Traditional RCT	Implementation Study
Recruitment	• Number of participants randomized • Compare actual and expected recruitment rates	• Survey completion • Focus group attendance • Participant enrollment/ randomization (if relevant)
Safety	• AEs and SAEs	• SAEs (deaths, ED visits, hospitalizations) • Other?
Data quality	• Missing forms • Missing fields	• Survey completion rates • Other?
Protocol deviations	• Protocol deviations	• Protocol deviations • Implementation challenges
Outcomes	• Outcome availability	• Fidelity • Intervention rollout progression • Outcome availability (if relevant)

Information Sharing

- DSMB needs to know:
  - Is participant safety/health being compromised?
  - Are there any study conduct concerns (PDs, data quality, outcome availability, treatment exposure)?

- DSMB may not want to know:
  - Breakdown of information by site and/or intervention group
  - Outcome data, such as
    - Are providers adhering to the intervention?
    - Is there any evidence of effectiveness of intervention?
    - Is implementation being successfully rolled out?

→ Utilize a different team to monitor progress of intervention ("TA Team") – if necessary, TA Team present to DSMB in closed session
→ Talk with your DSMB about what they want to see

Other Challenges – Interim Analyses

- Types
  - Sample size re-estimation
  - Early effectiveness
  - Futility

- Estimating outcome rates:
  - In only one arm – what if the rate changes over time? (e.g., providers improve at delivering intervention in that arm)
  - Intervention difference
    - There will likely be a hit to the overall type I error unless handled appropriately
    - Difference may take time to emerge → potential for early futility

Other Challenges – DSMB Membership

- Two or more members with experience monitoring or running implementation studies
- At least one member with familiar with challenges and limitations of secondary data if the study is pragmatic
- All members, including statistician, need to be flexible and understand that implementation studies are inherently different from traditional RCTs

Recommendations

- Prior to study start
  - Determine who is responsible for monitoring intervention implementation
  - Empanel DSMB with the appropriate expertise, including implementation studies
  - Discuss what information DSMB would like to see and what information they want excluded, or included by masked
  - Identify who will be in open session and who will be in closed session
  - Consider utility of interim analyses and if appropriate, identify the best approach given potential for substantial time and site effects
- Reporting
  - Be mindful of site and/or treatment group masking
  - Consider not presenting usual quantities if they are not relevant or could reveal information about effectiveness or implementation outcomes
  - Do not be afraid of narrative text!

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