Developing an Implementation Protocol: From Study Design to Field-Ready Trial

Translating abstract research designs into operational, field-ready clinical protocols.

PRESENTER

David Otiashvili, MD, PhD (Ilia State University, Tbilisi, Georgia)

Study Design vs. Implementation Protocol

Methodological Attribute	Study Design (Conceptual Architecture)	Implementation Protocol (Operational Execution)
Primary Objective	To establish internal validity, control bias, and ensure statistical power	To define who does what, where, when, how often, and under what rules
Core Questions	Is the trial a cluster randomized design or a stepped-wedge trial?	How are clinicians trained, medications distributed, and fidelity monitored?
Example (ACTS Trial)	Hybrid Type 2, wait-list cluster randomized controlled trial	Standardizing the 5A's pathway across 34 diverse clinic workflows
Key Deliverable	Statistical analysis plans and parallel-group structures	Field-ready provider handbooks, training waves, and decision rules

Start with the Implementation Question

> Among [Population] in [Setting], does [Implementation Strategy] improve [Implementation Outcome] while maintaining or improving [Clinical/Public Health Outcome] compared with [Usual Care]?

Population: Adult daily tobacco users aged ≥18 years willing to quit.
Setting: Primary health care centers and specialist clinics (cardiology, oncology, pulmonology).
Implementation Strategy: Multi-faceted strategy (clinician training, clinical mentoring, audit and feedback) supporting a multi-component cessation package.

Implementation Outcome: Intervention adoption, fidelity, reach, and delivery cost.
Clinical Outcome: Biochemically confirmed 7-day point prevalence abstinence at 12 months.
Usual Care Comparator: Opportunistic brief verbal advice without structured behavioral or pharmacological support.

Population & Setting - Pragmatic or Explanatory?

Operational Parameter	Explanatory Model (Efficacy Focus)	Pragmatic Model (Implementation Focus)
Participant Eligibility / Clinical Setting	Highly selected; extensive exclusion criteria; homogeneous cohorts. Well-resourced, ideal clinical environments; academic centers.	Broad, representative population; minimal exclusion criteria. Routine, real-world clinical settings (incl. oncology, cardiology, pulmonology) where scale-up must occur.
Clinical Staff	Highly specialized, dedicated research clinicians.	Routine healthcare providers (GPs, routine clinic nurses).
Generalizability	Low; prioritized for internal validity and biological mechanisms.	High; prioritized for system fit and external validity.

GENERALIZABILITY TRADE-OFFS

Overly restrictive selection criteria prioritize internal validity but severely limit real-world scale-up. A pragmatic approach ensures testing occurs in actual environments with routine staff.

Intervention vs. Strategy vs. Comparator

Concept	Core Definition	Core Analytical Question	ACTS Trial Example
CLINICAL INTERVENTION	The evidence-based practice, program, or treatment delivered to the patient.	What clinical practice are we trying to deliver?	Multi-component cessation package (5A's, meds, digital tool).
IMPLEMENTATION STRATEGY	The methods and resources used to integrate the intervention into care.	How are we helping the setting deliver it?	Wave-based training, local champions, audit-and-feedback.
COMPARATOR (USUAL CARE)	The baseline care currently provided without the implementation strategy.	What would happen if we did not intervene?	Opportunistic brief verbal advice from a physician.

Proctor's Strategy Specification Framework

Proctor Domain	Formal Definition	Protocol Measurement Method
1. Actor	The specific individual or team responsible for delivering the strategy	Qualitative mapping; credentialing logs
2. Action	The active steps, processes, or behaviors executed by the actor	Process checklists; qualitative observation
3. Action Target	The entity being impacted (e.g., provider, workflow, system)	Theoretical model mapping
4. Temporality	The specific timing, sequencing, or phase of implementation	Longitudinal tracking; milestone logs
5. Dose	The frequency, intensity, and duration of the strategy	Attendance databases; contact hours
6. Outcome Targeted	The specific implementation outcome expected to change	RE-AIM or Proctor outcome frameworks
7. Justification	The empirical or theoretical rationale linking strategy to barrier	CFIR barrier-strategy matching

ACTS Trial Strategy: Clinical Mentoring

Proctor Element	Granular ACTS Trial Operational Specification
1. Actor	**Trained Implementation Facilitator / Experienced Clinical Mentor**
2. Action	**Conducts structured clinical case reviews** and collaborative barrier-solving sessions
3. Action Target	**Multidisciplinary site clinical teams** (physicians, routine clinic nurses, managers)
4. Temporality	**Monthly**, commencing immediately following active cluster site activation
5. Dose	Interactive **60-minute sessions** delivered per clinical site per month
6. Outcome Targeted	Maximizing clinical **fidelity to the 5A's model, provider adoption, and feasibility**
7. Justification	Overcomes **limited provider confidence** and **high clinical workloads**

Specify Usual Care with the Same Seriousness

THE SCIENTIFIC HAZARD

A weakly described comparator makes the intervention look artificially better or worse than it really is, compromising the scientific validity of the trial.

ACTS TRIAL USUAL CARE SPECIFICATIONS

1. Active Providers: Routine clinic staff (general practitioners and specialists).

2. Available Services: Opportunistic, brief verbal advice to quit, delivered occasionally during routine encounters.

3. Existing Infrastructure: No structured behavioral support, no provision of free/subsidized pharmacotherapy, and no systematic follow-up.

4. Omissions: Complete lack of mHealth/digital support tools and no standardized clinical guidelines.

5. Secular Trends: Local tobacco control policy changes tracked longitudinally through policy reviews.

6. Cross-Site Heterogeneity: Baseline differences in usual care systematically documented via desk reviews across Georgia, Armenia, Serbia, and Albania.

The Pragmatic-Explanatory Continuum

Explanatory Extreme
Efficacy Trials (Can the clinical intervention work under ideal, highly controlled laboratory conditions?)

Effectiveness Zone
Hybrid Type 2 Trials (Does it work in real-world clinical settings supported by pragmatically viable strategies?)

Pragmatic Extreme
Routine Care Trials (Does it work under routine clinical conditions with no additional research support?)

Key Teaching Point: Trials are not binary. The protocol must specify which elements are pragmatic and which are controlled for scientific reasons.

The Nine Domains of the PRECIS-2 Wheel

Domain	Core Diagnostic Question	Scale Range (1 to 5)	Operational Relevance
1. Eligibility	Who is selected to participate in the trial?	1: Highly selected → 5: All real-world patients	Impact of exclusion criteria on generalizability
2. Recruitment	How are participants recruited into the trial?	1: Research-intensive → 5: Routine clinical pathways	Feasibility of recruitment within standard workflows
3. Setting	Where is the trial being conducted?	1: Specialized centers → 5: Routine clinics	Relevance to national scale-up environments
4. Organisation	What expertise & resources are needed to deliver?	1: Highly specialized → 5: Standard routine care	Complexity of the clinical infrastructure required
5. Flexibility: Delivery	How should the intervention be delivered?	1: Rigidly standardized → 5: Highly flexible	Balance between protocol fidelity and adaptation
6. Flexibility: Adherence	What measures ensure patient adherence?	1: Strictly enforced → 5: No active reinforcement	Feasibility of patient-level compliance in the real world
7. Follow-up	How closely are participants followed up?	1: Intensive research visits → 5: Routine clinical follow-up	Resource burden of long-term data collection
8. Primary Outcome	How relevant is the primary outcome?	1: Surrogate/Biomarker → 5: Patient-centered/Direct	Direct clinical relevance to policymakers
9. Primary Analysis	To what extent are all data included?	1: Per-protocol → 5: Intention-to-treat	Impact of missing data and drop-outs on validity

Applying PRECIS-2 to the ACTS Trial

PRECIS-2 Domain	Rating (1-5)	Operational Rationale and Trial Specification
1. Eligibility & 3. Setting	**4 (Pragmatic) & 5 (Highly Pragmatic)**	Broad inclusion (daily smokers, age ≥18); exclusion restricted to safety contraindications. Deployed across 34 diverse routine primary/specialist clinics in 4 countries.
5. Flex: Delivery	**4 (Pragmatic)**	Core components are standardized, but delivery format, counselor type, and follow-up are highly flexible.
7. Follow-up	**2 (Explanatory)**	Highly intensive research follow-ups at 6, 12, and 24 months to ensure complete data collection.
8. Primary Outcome	**2 (Explanatory)**	Biochemically confirmed 7-day point prevalence abstinence via salivary cotinine testing.
9. Primary Analysis	**5 (Highly Pragmatic)**	Rigorous Intention-to-Treat (ITT) analysis using mixed-effects logistic regression models.

Outcomes in Protocols: The Three-Layer Model

1. Implementation

Core Definition: The effects of deliberate actions to implement new treatments or practices. Focuses on the delivery system and provider behavior.

Key Examples:
Acceptability, Feasibility, Adoption, Fidelity, Cost, Sustainment

2. Service

Core Definition: The impact of the implementation on the quality of healthcare delivery. Focuses on system performance and care flow.

Key Examples:
Reach, Equity, Timeliness, Efficiency, Care Continuity, Retention

3. Clinical & Public Health

Core Definition: The ultimate impact on patient-level health status and clinical endpoints. Focuses on patient-level outcomes and disease burden.

Key Examples:
Smoking abstinence, QALYs, disease events (e.g., stroke), mortality

Pragmatic or Explanatory Measurement?

EXPLANATORY MEASUREMENT (RESEARCH-INTENSIVE)

- Are outcomes verified through specialized, research-only laboratory tests?
- Does follow-up require intensive, multi-hour participant interviews?
- Are metrics primarily designed to optimize internal validity and scientific mechanism?

PRAGMATIC MEASUREMENT (SYSTEM-ALIGNED)

- Are outcomes captured through routine clinical data sources or electronic health records (EHR)?
- Is the follow-up timeline realistic for national scale-up?
- Are outcomes meaningful to healthcare managers, insurers, and policymakers?

The Operational Rule: A field-ready protocol must justify when intensive, research-only measurement is scientifically mandatory vs. when low-burden, routine metrics should be prioritized.

Mapping ACTS Outcomes to the Three-Layer Model

Category	Specific ACTS Trial Endpoint	Measurement Method & Data Source	RE-AIM Domain
Implementation	Adherence to standard counseling guidelines (Fidelity)	Provider-completed session checklists, clinical site audits, direct observation, & patient surveys (Treatment Receipt)	Implementation
Implementation	Incremental Cost per Quitter (ICQ) & delivery costs	Micro-costing templates and personnel time tracking logs	Implementation
Service	Patient participation and clinical reach rates	Standardized clinical screening logs & enrollment databases	Reach
Service	Clinical setting and provider adoption rates	Training attendance databases and clinic enrollment logs	Adoption
Clinical	Biochemically confirmed 7-day point abstinence at 12 months	Salivary cotinine laboratory testing	Effectiveness
Clinical	Health-Related Quality of Life (HRQoL) changes	Standardized EQ-5D-5L patient questionnaires at follow-up	Effectiveness

Monitoring During Implementation: The Living Protocol

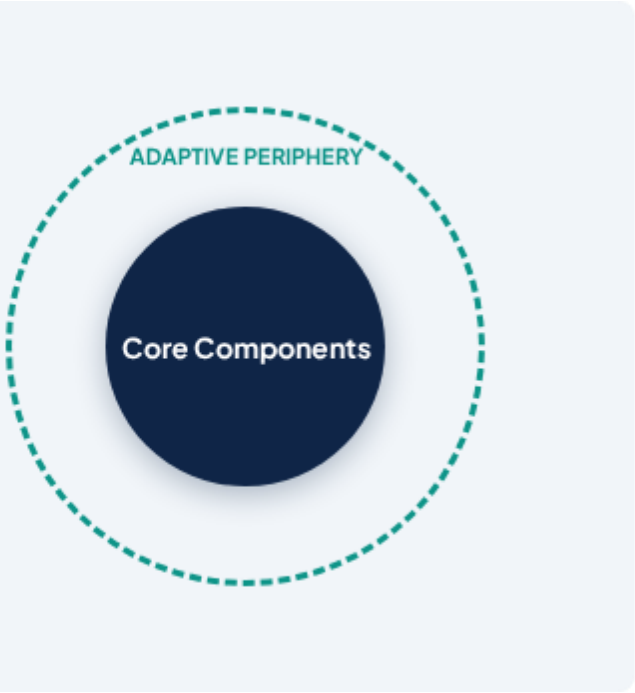
THE OPERATIONAL SHIFT

A successful implementation protocol cannot remain a static document; it must function as a living operational guide that actively monitors site performance in real-time.

KEY OPERATIONAL ELEMENTS MONITORED IN ACTS

1. **Training Completion:** Tracking Wave-1 (Arm A) and Wave-2 (Arm B) clinician training logs.
2. **Site Activation:** Verifying the completion of Clinical Trial Agreements and regulatory sign-offs.
3. **Reach and Recruitment:** Monitoring the number of patients screened vs. enrolled in real-time.
4. **Intervention Fidelity:** Conducting regular provider audits and checklist checks.
5. **Unintended Consequences:** Systematic logging of Adverse Events (AEs) and Serious Adverse Events (SAEs).
6. **Data Completeness:** Automated validation checks within the secure, GDPR-compliant Electronic Data Capture (EDC) system.

Fidelity vs. Adaptation: Core and Periphery



Intervention Pillar	Core Components (Non-Negotiable "What")	Adaptive Periphery (Contextual "How")
Behavioral Support	Systematic screening (Ask & Advise) and offering structured 5A's-based counseling	Counseling dose (e.g., 3 vs. 5 sessions), Session duration (e.g., 15 vs. 30 minutes), Delivery format (individual vs. group), Provider cadre (GP, nurse, counselor)
Pharmacotherapy	Offering at least one form of evidence-based cessation medication	Specific medication selection (NRT, cytisine, varenicline, or bupropion), Combination therapy regimens, Dosing schedule based on registration
Digital & Follow-up	Offering a structured follow-up plan and referral to a digital support tool	Specific digital application used (mHealth app vs. SMS text program), Frequency of mobile messaging, Modality of follow-up (phone vs. in-person)

Actionable Course Correction: Protocol Decision Rules

Trigger Event	Protocol-Specified Action / Response	Responsible Actor	Scientific Justification
1. Site Under-Recruitment	Deploy patient-facing materials; provide refresher clinician training; activate pre-identified backup sites.	National Trial Coordinator & Local SPAG	Preserves statistical power and maintains the trial timeline.
2. Fidelity Score Drop	Conduct targeted academic detailing and interactive, facilitator-led workflow optimization sessions.	Clinical Mentor / Facilitator	Prevents Type III error and ensures the delivery of active ingredients.
3. Routine Usual Care Shift	Document changes systematically using standard checklists; adjust statistical models to control for trends.	National Public Health Institutes	Preserves the validity of the parallel comparator condition.
4. Unapproved Adaptations	Convene immediate meeting with site staff to review core vs. periphery; document adaptation in the process log.	Clinical Mentor & WP5 Lead	Maintains protocol integrity and allows for systematic process mapping.

The Checklist & Closing Takeaways

THE FIELD-READY PROTOCOL CHECKLIST

- ☑ Is the multi-level implementation question explicitly defined?
- ☑ Have the population and setting been evaluated using the PRECIS-2 continuum?
- ☑ Are the clinical intervention, strategy, and usual care conceptually separated?
- ☑ Is the implementation strategy specified using Proctor's framework?
- ☑ Are the outcomes structured across the three-layer model?
- ☑ Is there an active monitoring plan for fidelity and adaptations?
- ☑ Have pre-planned decision rules been established for course correction?

THE FINAL TAKEAWAY

A study design tells us how the trial answers the research question. An implementation protocol tells us how the intervention and implementation strategies will actually be delivered, monitored, compared, adapted, and interpreted in real-world settings.