ViiV Healthcare Implementation Science Proposal Guidance Document

Dear Sponsor,

Thank you for your interest in ViiV Healthcare's (VH) Investigator Sponsored Research (ISR) program. This guidance document outlines the VH's expectations for Implementation Science research proposals. Following this template can expedite the review process and increase the chance of approval and funding. Please refer to the appendix for additional information that can support you on the Implementation Science components of your proposal. Importantly, the submitting investigators are considered the Sponsors of ISRs. During the ViiV review process, suggestions may be provided by VH on how to strengthen the proposal. Please ensure that the Sponsor's study team is equipped and resourced to independently execute the study as written.

I. Title of Research Project

Provide a descriptive title for the topic your study addresses. Note: This title should align with the title entered on the ISR portal.

II. Background and Scientific Rationale

Provide a brief summary of the overall purpose of this proposed study and any background information that led to this proposal. Example information to include:

a. *Geographic area*
b. *Current HIV epidemiology and outcomes for geographic area*
c. *Setting (health department, healthcare setting (e.g., hospital, clinic, community health center, pharmacy, etc.), school, workplace, places of worship, other community settings)*
d. *Intervention (Defined according to the NIH D&I Working Group codebook as: "Any program, policy, or guideline intended to improve health that has been tested and demonstrated to be effective in a particular context."*
    - *Justification for intervention*
    - *Target population of the intervention*
    - *How the intervention is delivered*
    - *By whom the intervention is delivered*
    - *Evidence base supporting intervention effectiveness*

III. Hypotheses

Provide a description of the hypothesis that you will be testing in this study.

IV. Study Objectives:

Provide a brief summary of the primary and key secondary objective(s) for this proposal and/or what the study is expected to demonstrate. Implementation objectives or aims must be a

primary and/or key secondary. Include your implementation questions and any clinical questions. Example information to include:

a. *Summary of the research question(s), primary purpose of the research, study aims and objectives.*
b. *Implementation Questions*
    i. *e.g: Will in-person provider education (implementation strategy) improve acceptability and feasibility of the EBI (intervention)?*
    ii. *e.g. Do clinics with a specific implementation strategy have greater adherence to the treatment window.*

c. *Clinical Questions (if applicable)*
    i. *e.g. Examine the proportion of participants who are virologically suppressed (plasma HIV-1 RNA <50 c/mL) over time*

V. Study Endpoint

Please include study outcomes, measurement methods, data source, and timepoints. Describe how each outcome will be specifically measured (e.g., quantitative measure, qualitative interview guided by a specific framework) Example information to include:

*(*resources on implementation outcomes*)*

a. *Primary Endpoints: Either clinical or implementation endpoints*
b. *Secondary Endpoints: Either clinical or implementation endpoints*

Implementation Outcome	***Measurement Method(s) (e.g., observations, surveys, routinely collected data)***	***Level of Measurement (i.e., individual patient, individual service provider, health service facility (e.g., hospital))***	***Measurement Time point(s)***
Ex: Acceptability (Proctor et al): degree to which an intervention is perceived to be agreeable	*Acceptability Survey: Weiner et al, Implement Sci 2017;12:108*	*Patients*	*Month 0, 6, 12*

Clinical Outcome (if applicable)	***Measurement Method(s)***	***Level of Measurement***	***Measurement Time point(s)***

	(e.g., observations, surveys, routinely collected data)	*(i.e., individual patient, individual service provider, health service facility (e.g., hospital))*	
Ex: # HIV test performed	*EMR extractions*	*Individual patients*	*Month 0, 3, 6, 12*

VI. Study Design and Methods

Study Design: *Describe the general study design, study groups/arms, main tests or procedures, primary and important secondary outcome variables, design justification, and general approach to analysis. Please identify the methodology proposed to achieve a greater understanding of external validity at the end of the study. Graphical depiction of study designs are helpful. If applicable, describe any randomization you will use. (resources on study design)*

Human participants and data protection*: Please describe the potential risks to participants associated with the proposed study, including risk level, its impact on the study participants, measures to mitigate risks, and where appropriate, alternative treatments and procedures.*

Implementation Strategies: *Implementation strategies are methods or techniques used to improve the adoption, integration, and sustainability of an intervention. Implementation strategies can be discrete (e.g., clinical reminders, training only), multifaceted (e.g., training plus reminders, training + fidelity monitoring +coaching), or blended/comprehensive (e.g., Dynamic Adaption Process, Leadership and Organizational Change for Implementation). Please list and describe the primary implementation strategies to be used in this study. (resources on implementation strategies)*

Your proposal should include the components of table below for each of your key strategies

Implementation strategy	*Describe the strategy*	*Who is involved*	*Outcome impacted*
Clinical Reminders	EMR prompts for clinicians triggered at every patient visit	Provider seeing the patients (can be doctor, nurse, or medical assistant)	Increased fidelity to injection window
Provider Education	Nurse to Nurse face to face training	Nurse trainers – provided by study team and the clinic nurses delivering the intervention	Increased feasibility and acceptability of intervention

1) Framework

Implementation Frameworks are proposed models or factors that are likely to impact the implementation and sustainment of an evidence-based practice (e.g. long acting injectable ART or PrEP). (resources on implementation frameworks)

a) Identify and justify the IS model/framework(s) which best supports your implementation question (Examples: Consolidated Framework for implementation Research, RE-AIM, EPIS, etc.)

b) Describe how the model/framework(s) will guide your data collection and analysis.

2) Describe the research methods you will use to evaluate the questions describe above.

Please note that mixed-methods approaches are highly encouraged to maximize the understanding of the context in which you are proposing your study. Your sampling methods should describe how you will collect data to reflect the perspective of both the setting in which the study takes place, and the population served as part of the study. (500 words or less) (link to resources on research methods)

a) Any methods, sources etc used to conduct the research must be clearly outlined.

b) Methodological approaches to gather data and techniques to analyse should be described.

c) Data collection processes should be clear, including instruments and approaches used.

VII. Analysis plan

1) **Study Sample:** *Please describe the anticipated number of participants for each group of participants. This may include patients, clinic staff, clinic facilities, or other units of analysis. Justify the total sample size on the basis of statistical power to test the primary hypothesis (and important secondary hypotheses, if relevant).*
2) **Data Analysis:** *Provide an overview of the proposed statistical analysis plan, please include:*
    a. *Statistical hypotheses (or if none state why not)*
    b. *Analysis of primary and major secondary endpoints (including qualitative analysis, where applicable)*
    c. *Analytic approaches to control for bias*

VIII. Population

1) **Inclusion/Exclusion Criteria:** Please describe inclusion and exclusion criteria for applicable participants e.g. patients, staff, clinics, or other unit of analysis.
2) **Describe sources and process for recruitment for each type of participant**

IX. Study Intervention/Product Regimens (if applicable)

If applicable, provide a summary of the therapeutic entity(s) and regimen(s), including any proposed controls that will be used in the proposed study.

Safety Lab Reporting: If a ViiV product is being used in the study, please provide a plan for how adverse events will be documented and reported.

X: Schedule of Activities: *Please provide the timepoints for all data collection activities (implementation and clinical), as appropriate.*

Example

Ex data collection activities	*Timepoints*								
Patient Surveys									
Provider Surveys									
Patient Qualitative data									
Provider Qualitative Data									
Vital Signs									
Viral Load									
CD4									
LFTs									
Pregnancy Tests									
AEs									
BMI									

X. References

Include references to any existing published studies and any other background information you believe is relevant to the review of this proposal.

Appendix

General Implementation Science

To learn more about Implementation Science visit:

https://viivhealthcare.com/ending-hiv/hiv-implementation-science/training-and-education/

Orientation to the Science of Dissemination and Implementation | Division of Cancer Control and Population Sciences (DCCPS)

https://cancercontrol.cancer.gov/is/training-education/training-in-cancer/TIDIRC-open-access

Implementation Science Proposals

Proctor, Powell, Baumann, Hamilton& Santens (2012)

*If relevant to a specific study design, use appropriate StaRI criteria checklist

Implementation Strategies

Review this document for examples of implementation strategies:

https://static-content.springer.com/esm/art%3A10.1186%2Fs13012-015-0209-1/MediaObjects/13012_2015_209_MOESM6_ESM.docx

Guidance on specifying and reporting implementation strategies:

https://implementationscience.biomedcentral.com/articles/10.1186/1748-5908-8-139

Assessing the feasibility and importance of implementation strategies:

Use of concept mapping to characterize relationships among implementation strategies and assess their feasibility and importance: results from the Expert Recommendations for Implementing Change (ERIC) study | Implementation Science | Full Text (biomedcentral.com)

The development of the ERIC strategy compilation:
ERIC Discrete Implementation Strategy Compilation

Implementation Frameworks

There are numerous frameworks to choose between. When deciding between frameworks, it is helpful to choose the one that seems to provide the best fit for your study.

Tool for choosing theories, models and frameworks for your study:

> https://www.nccmt.ca/knowledge-repositories/search/254

Below are examples of theories, models and frameworks used in implementation science (Table adapted from: Nilsen, 2015)

Category	Description	Selected Examples
Process models (describe and/or guide the translation of research into practice)	Specify steps (stages, phases) in the process of translating research into practice, including the implementation and use of research. The aim of process models is to describe and/or guide the process of translating research into practice.	Exploration, Preparation, Implementation, Sustainment (EPIS) Framework Model by Landry et al., model by Davies et al. model by Majdzadeh et al., the CIHR Model of Knowledge Translation, the K2A Framework, the Knowledge-to-Action Model, the Quality Implementation Framework,
Determinant frameworks (understanding and/or explaining what influences implementation outcomes)	Specify types (also known as classes or domains) of determinants and individual determinants, which act as barriers and enablers (independent variables) that influence implementation outcomes (dependent variables).	PARIHS/iPARIHS, Understanding-User-Context Framework, Ecological Framework by Durlak and DuPre, CFIR, TICD, Theoretical Domains Framework
Evaluation frameworks (guide evaluation of implementation)	Specify aspects of implementation that could be evaluated to determine implementation success	RE-AIM; PRECEDE-PROCEED; framework by Proctor et al.

Source: https://implementationscience.biomedcentral.com/articles/10.1186/s13012-015-0242-0

Implementation Stages of Research Projects

- Exploration: identifying the need for change, learning about possible evidence-based interventions that may provide solutions, learning about what it takes to implement the intervention effectively, developing stakeholders and champions, assessing and creating readiness for change, and deciding to proceed (or not).
- Installation/Preparation: establishing the resources needed to use an evidence-based intervention and the resources required to implement the intervention as intended.

- Initial Implementation: the first use of an evidence-based intervention by healthcare professionals or patients/service users and learning how to support the new ways of work.
- Full Implementation: the skillful use of an evidence-based intervention that is well-integrated and routinely and effectively supported.
- Sustainment: processes are ongoing, with limited to no research support, where the evidence-based practice continues to be delivered in the form that results in the greatest public health impact of the implemented innovation. Further adaptations may be made in this phase to support the process.

Study Designs

Implementation Study Design Examples

(adapted from: https://impsciuw.org/designing-is-research/)

I. **Randomized Control Trials (RCTs):** RCTs are experimental clinical studies where participants are randomly selected to intervention or control groups and followed over a predetermined amount of time. There are several types of RCTs, including:
   a. **Cluster Randomized Control Trial:** An RCT with a parallel or cross-over design that randomly assigns pre-existing groups of participants into an intervention or control group.
      i. Related methodological resources: Hemming et al., 2017; Powell-Jackson et al., 2018
   b. **Stepped-Wedge Design:** A randomized cross-over design where different groups or clusters cross-over to the intervention condition at different time points during the study so that all clusters eventually receive the intervention and the intervention continues in a given cluster once it has begun.
      i. Related methodological resources: Hemming et al., 2014; Ching Ting Fok et al., 2015; Hemming et al., 2015; Copas et al., 2015
   c. **Effectiveness-Implementation Hybrid Design**: A design that allows for a focus on both clinical effectiveness and implementation. The hybrid design is broken into 3 types of designs:
      1. Testing effects of a clinical intervention on relevant outcomes while observing and gathering information on implementation
      2. Dual testing of clinical and implementation interventions/strategies
      3. Testing of an implementation strategy while observing and gathering information on the clinical intervention's impact on relevant outcomes

      i. Related methodological resources: Curran et al., 2012; Bernet et al., 2015
      j. Hybrid designs (see Curran et al., 2012, and brief supplement for more information about Hybrid Designs)
         a. Hybrid design type 1: Primary aim: clinical efficacy. Secondary aim: Implementation Outcomes.
         b. Hybrid design type 2: Co-primary aims: Clinical efficacy and implementation outcomes

c. Hybrid design type 3: Primary aim: Implementation Outcomes and Secondary Aim: Clinical efficacy or effectiveness

II. **Intervention Optimization**
   a. **Multiphase Optimization Strategy (MOST):** A design for building, optimizing, and evaluating interventions via a three-phase method that identifies active intervention components and the levels of each component lead to optimal outcomes.
      i. Related methodological resource: Collins et al., 2007
   b. **Sequential Multiple Assignment Randomized Trial (SMART):** A randomized experimental design developed specifically for building time-varying adaptive interventions.
      i. Related methodological resources: Collins et al., 2007; Chow & Hampton 2018; Wallace et al., 2016

III. **Quasi-Experimental Designs:** estimate if an intervention has a causal impact on a target population without random assignment
   a. Resources for general methodology: Handley et al., 2018; Tugwell et al., 2017;
   b. Interrupted Time Series: routine monitoring data is collected at evenly spaced time points before and after the intervention and the data collected prior to the intervention serves as the control group.
      i. Related methodological resources: Cruz et al., 2017; Linden 2017; Polus et al., 2017
   c. **Regression Discontinuity:** a design that utilized pretest-posttest examination of causal effects of interventions. The threshold determines who receives the intervention, which allows for the estimation of average treatment effect when randomization is not possible
      i. Related methodological resources: Moscoe et al., 2015; Walkey et al., 2018; Venkataramani et al., 2016
   d. **Regression Point Displacement:** pretest-posttest design where data is collected at the group level and often involves one treatment group and more than one control group
      i. Related methodological resources: Linden et al., 2006; Wyman et al., 2015

Implementation Outcomes

Definitions of Implementation Outcomes (adapted from: Proctor et al., 2010):

- Acceptability: Perception among implementation stakeholders that a given treatment, service, practice, or innovation is agreeable, palatable, or satisfactory.
- Adoption: A decision to make full use of an innovation, intervention, or program as the best course of action available. Also defined as the decision of an organization or community to commit to and initiate an evidence-based intervention.
- Appropriateness:
- Cost (incremental or implementation cost): The cost impact of an implementation effort.
- Feasibility: extent to which a new treatment, or an innovation, can be successfully used or carried out within a given agency or setting
- Fidelity: Degree to which an intervention or program is implemented as intended by the developers and as prescribed in the original protocol.

- Penetration: The integration of a practice within a service setting and its subsystems.
- Sustainability: The continued use of program components and activities for the continued achievement of desirable program and population outcome

Learn more about RE-AIM outcomes:

RE-AIM – Home – Reach Effectiveness Adoption Implementation Maintenance