

MARCH 2021 ———

# BIOMEDICAL HIV PREVENTION

Adaptable Product Introduction Framework



Biomedical Prevention  
Implementation Collaborative



HIV Prevention  
Market Manager

Accelerating Product Introduction  
Informing Product Development  
Reducing Time to Impact



Supported by the Bill & Melinda Gates Foundation

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## HIV Prevention Market Manager

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## LIST OF ABBREVIATIONS

<b>AGYW</b>	Adolescent girls and young women	<b>LTFU</b>	Lost to follow-up
<b>APWG</b>	ARV Procurement Working Group	<b>M&amp;E</b>	Monitoring and evaluation
<b>ART</b>	Antiretroviral therapy	<b>MoH</b>	Ministry of Health
<b>ARV</b>	Antiretroviral	<b>MSM</b>	Men who have sex with men
<b>BioPIC</b>	Biomedical Prevention Implementation Collaborative	<b>MSW</b>	Men who have sex with women
<b>CAB</b>	Community advisory board	<b>NMRA</b>	National Medicines Regulatory Authority
<b>CBO</b>	Community-based organization	<b>PK</b>	Pharmacokinetic
<b>CHW</b>	Community health worker	<b>PrEP</b>	Pre-exposure prophylaxis
<b>COGs</b>	Cost of goods	<b>PV</b>	Pharmacovigilance
<b>DCE</b>	Discrete choice experiment	<b>PWID</b>	People who inject drugs
<b>DHIS</b>	District Health Information System	<b>SRA</b>	Stringent Regulatory Authorities
<b>DHS</b>	Demographic and Health Surveys	<b>STI</b>	Sexually transmitted infection
<b>DTG</b>	Dolutegravir	<b>TA</b>	Technical assistance
<b>FP</b>	Family planning	<b>TGM</b>	Transgender men
<b>HCD</b>	Human-centered design	<b>TGW</b>	Transgender women
<b>HCW</b>	Healthcare worker	<b>TWG</b>	Technical working group
<b>HIV</b>	Human immunodeficiency virus	<b>VMMC</b>	Voluntary medical male circumcision
<b>HIVST</b>	Human immunodeficiency virus self-testing	<b>WG</b>	Working Group
<b>HPTN</b>	HIV Prevention Trials Network	<b>WHO</b>	World Health Organization
<b>LGBTIQ+</b>	Lesbian, gay, bisexual, transgender/transsexual, intersex, and queer plus	<b>WHO CRP</b>	World Health Organization Collaborative Registration Procedure
<b>LMIC</b>	Low- and middle-income countries	<b>WHO PQ</b>	World Health Organization Prequalification
		<b>UNAIDS</b>	Joint United Nations Program on HIV/AIDS

# ADAPTABLE FRAMEWORK USER GUIDE

## Introduction

The [Biomedical Prevention Implementation Collaborative](#) (BioPIC) was established to address gaps in advanced, coordinated planning for product introduction in the rapidly evolving HIV prevention space. Building on previous product introduction experience with oral pre-exposure prophylaxis (PrEP) and informed by planning for cabotegravir long-acting injectable (CAB-LA), this document presents an overarching product introduction framework that can be adapted to guide the introduction of future biomedical HIV prevention products.<sup>1</sup> A wide range of over 100 global health experts from over 80 organizations and 20 countries created the framework based on their experience developing, funding, planning, implementing, and monitoring HIV prevention programs.<sup>2</sup> While these activities will ultimately need to be adapted to meet the unique needs and attributes of each product, the intention of this framework is to offer a road map to ensure future HIV prevention products are introduced and scaled to achieve maximum public health impact in a timely and efficient manner.

## How to use the framework

**Activity Categories:** Activities in this framework are grouped into five categories. However, these categories do not dictate activity ownership, as ownership will vary according to the product, as well as the stakeholders and organizations involved in the process. The icons and color schemes associated with these categories will help readers quickly identify activities relevant to their topic of interest:



**Navigating inputs and dependencies:** Many of the activities in this framework are closely linked and it will be important for stakeholders to understand these linkages to ensure there is effective coordination and communication between partners carrying out product introduction activities. Certain early stage activities are intended to directly inform later stage activities and contribute to a cohesive body of evidence. To help readers understand and navigate these linkages, all activities reference other framework activities that serve as key inputs or dependencies. These references are clickable links that will bring the reader to the referenced activity within the framework.

For example, the following three activities are linked to one another in the framework:



**User tip:** for more information on any of these three activities, navigate to the full activity description by clicking on the activity box. To view these activities contextualized within the rest of the framework, click [here](#).

<sup>1</sup> Note: While this adaptable product introduction framework focuses on biomedical HIV prevention products, readers are encouraged to consider how this framework can be used as a starting point for other products, including multi-purpose prevention technologies (MPTs).

<sup>2</sup> Note: Please see the [Acknowledgments](#) for a complete list of the individuals who contributed to this framework.

## ADAPTABLE FRAMEWORK USER GUIDE

### Who should use the adaptable product introduction framework?

This framework is intended to inform stakeholders involved in all stages of product introduction from clinical research to rollout in low- and middle-income countries (LMICs). This may include, but is not limited to: donors, product developers, trial investigators, program implementers, researchers, governments, and advocates. While the framework focuses on activities to begin in parallel to efficacy trials, stakeholders in early product development phases may also want to understand what to expect in terms of downstream product introduction needs. These stakeholders may also consider leveraging some of the activities included to anticipate future needs.

### Sample Use Cases

The following sample use cases are intended to provide readers with an understanding of why and how this framework might be used by different stakeholders. These samples are illustrative and do not outline all potential uses.



#### Use Case 1: Donor

**Why?** A donor may want to understand where investments are needed for product introduction and, importantly, the critical linkages involved with each activity so donors understand how to appropriately tie investments to other projects and research.

**How?** Depending on the type of investment a donor is interested in, this framework will outline important preceding steps and dependencies. For example, if a donor is interested in funding an early phase implementation project, this document can help the donor understand how their efforts should be linked to earlier stage activities in order to ensure their investment is complementary and catalytic.



#### Use Case 2: Product Manufacturer

**Why?** For product manufacturers, this document can serve as a road map to understand the key activities necessary to achieve equitable access in LMICs. Specifically, manufacturers may seek to understand when key touch points must occur between the innovator company and generic manufacturers.

**How?** Since this framework draws from the experiences of other products, it will help manufacturers understand barriers to access and how to overcome them. For manufacturers, the activities in the “Manufacturing & Distribution” and “Costing & Modeling” categories are likely to be most relevant. These activities identify how innovators, generic manufacturers, and advisors should work together to improve access.



#### Use Case 3: Modeling Group

**Why?** For an HIV modeler, it will be important to understand what modeling activities are critical for introduction, and when these activities should take place. While different types of modeling studies may be valued differently by decision-makers, modelers will likely want to understand what information is needed for normative bodies and countries to decide to adopt the product.

**How?** Modelers can refer to the “Costing & Modeling” category to understand what activities should be prioritized and when. Since these activities are outlined with their critical inputs and dependencies, modelers will be able to understand how to effectively share their outputs to support product introduction.



#### Use Case 4: Clinical Researcher

**Why?** While clinical trials will ideally be designed to gather all of the evidence needed to achieve an appropriately broad product indication, there are often follow-on studies that are needed among populations not included in the trial (for example, adolescents). A researcher may seek to understand what additional populations should be considered and when.

**How?** This document outlines when planning for additional research should begin, which other stakeholders may need to be consulted, and how this research should inform later stage activities.

# A Collaborative Approach to Product Introduction

The HIV prevention product pipeline offers exciting potential to reduce HIV incidence. But we know from previous products that translating trial efficacy to population impact is challenging.

## Oral PrEP Product Introduction Experience

Without advanced planning and coordination, the introduction and impact of an effective biomedical prevention tool was delayed in LMICs.



**Key components** of product introduction were **not well-timed**, causing delays in introduction and scale-up.



Due to a **complex, fragmented stakeholder landscape**, post-approval studies were not designed to answer critical questions.

## Ideal Product Introduction Experience

To support rapid, successful introduction of HIV prevention products, BioPIC aims to forge a new path forward for future products.



**Plan in parallel to clinical trials** to shorten the time between regulatory approval and large-scale, phased implementation projects in LMICs.



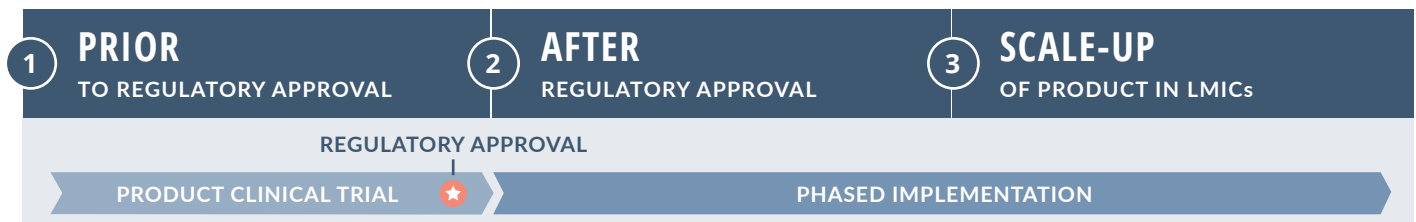
**Coordinate stakeholders in advance** to ensure projects are well-designed to provide evidence to quickly build from small pilots to scale.

The BioPIC has brought together a diverse group of 100+ HIV prevention experts and includes representation across global stakeholder groups such as civil society, donors, researchers, policymakers, normative agencies, program managers, and implementers. The BioPIC was established to facilitate advanced, coordinated HIV prevention product introduction planning to shorten the time from regulatory approval to introduction & scale-up in LMICs. This innovative partnership mechanism initially piloted its approach by developing a coordinated product introduction agenda and access strategy for CAB-LA and creating an overarching product introduction framework that is adaptable to any future biomedical prevention product.

## NAVIGATING THE FRAMEWORK

### Sequence and Timing

To successfully introduce an HIV prevention product, many activities will need to be planned and executed concurrently. Moreover, these same activities often require continuous refinement and iteration as new data and information becomes available. In some cases, it will be critical to initiate activities in parallel to clinical trials to ensure dependent activities can begin rapidly after regulatory approval. Uncoordinated efforts and poorly sequenced and timed activities can lead to major delays in product introduction, scale-up, and impact. To facilitate this type of planning, this framework outlines three distinct periods during which activities should be completed. However, within these three time periods, activities are expected to be executed concurrently and numbering does not represent a specific recommended sequence.



### Thematic Areas

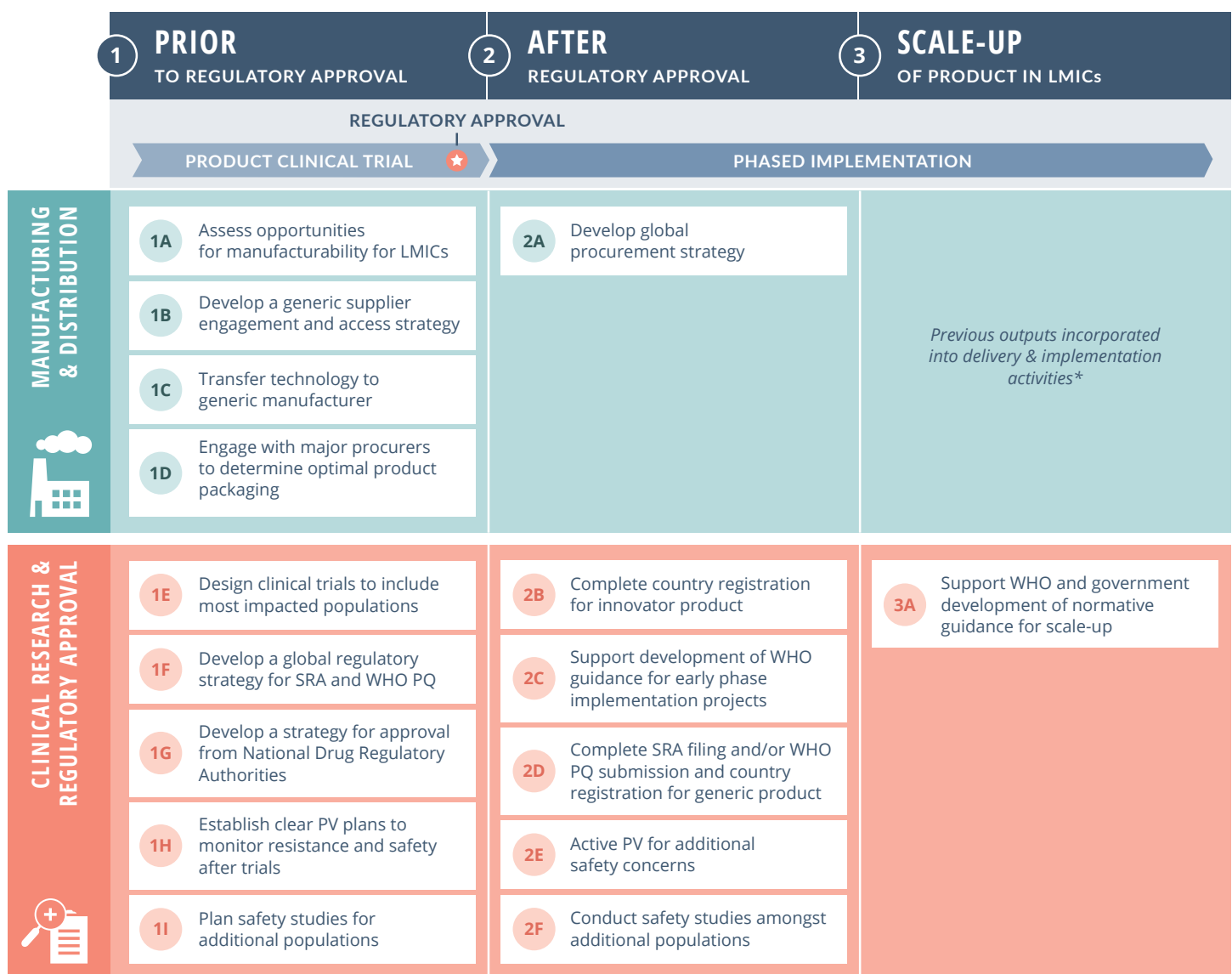
Bringing a product from clinical trials to scale in LMICs requires expertise across a range of thematic areas. This strategy does not dictate activity ownership across these thematic areas, as ownership will vary according to the product, as well as the stakeholders and organizations involved in the process. Additionally, the strategy is not meant to interfere with independent decisions that are required along the product introduction pathway (e.g., regulatory or normative). Rather, where applicable, the strategy will identify the types of organizations and stakeholders that may need to engage to ensure an efficient product introduction process. To provide an understanding of the types of expertise required, this framework categorizes product introduction activities into five thematic areas:




### Critical and Enabling Activities

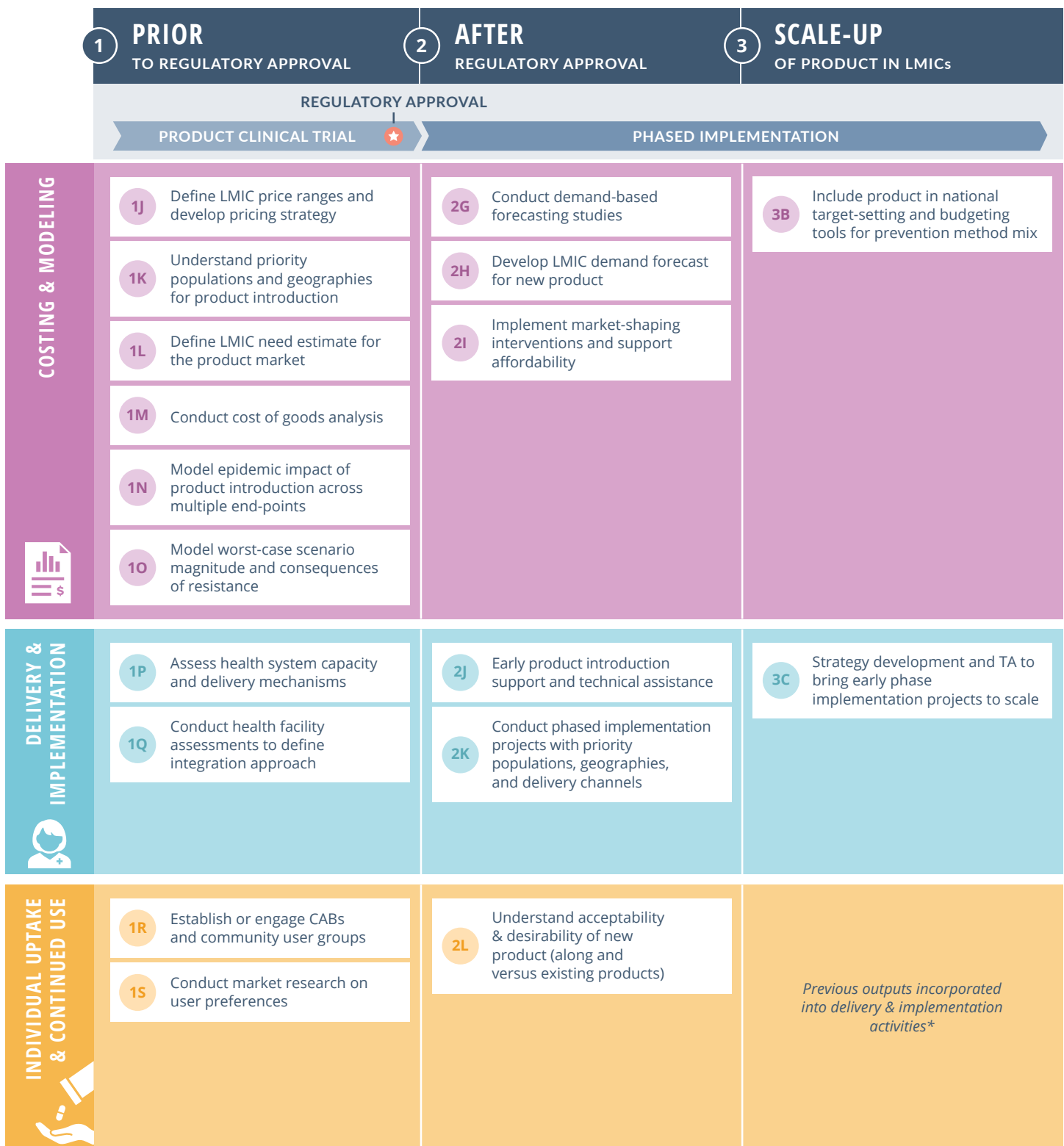
This strategy outlines activities considered to be on the critical pathway of the research to rollout continuum, meaning that they are essential to product introduction. Without a critical pathway activity, decision-makers will not have essential evidence, and the product will not be able to be accessed by those in need in LMICs. [Annex 1](#) details a sequenced list of enabling activities, which will further optimize product introduction; enabling activities should be further considered or added to the critical pathway based on the needs and attributes of a given product.

# Critical Pathway Activities for Biomedical HIV Prevention Products



 **User Tip:** click any activity box to navigate to the relevant activity description

CONTINUED ON THE FOLLOWING PAGE >



\*Note: By the time product scale-up has begun in LMICs, findings from earlier-stage individual uptake & continued use activities should be incorporated into delivery & implementation activities, so there are no critical pathway activities listed in this time section. Similarly, manufacturing and distribution activities will need to be completed before LMIC scale-up to enable broad rollout.

**User Tip:** click any activity box to navigate to the relevant activity description

To return to this framework overview, click the arrow icon at the footer of any activity description page

## 1

## PRIOR TO REGULATORY APPROVAL

## Critical Pathway Activities in Depth

This chapter covers critical activities that will support an efficient, effective stringent regulatory authority approval review process and lay the groundwork for future research and implementation projects. These activities will enable innovator product developers and other stakeholders involved in the product introduction process to achieve the following objectives.



### MANUFACTURING & DISTRIBUTION

Ensure the product is well-positioned to be manufactured at scale with high quality and at an affordable price point for LMIC contexts.

- 1A** [Assess opportunities for manufacturability for LMICs](#)
- 1B** [Develop a generic supplier engagement and access strategy](#)
- 1C** [Transfer technology to generic manufacturer](#)
- 1D** [Engage with major procurers to determine optimal product packaging](#)



### CLINICAL RESEARCH & REGULATORY APPROVAL

Ensure design of clinical trials supports efficient regulatory review and inclusion in global and country normative guidance for all at risk populations.

- 1E** [Design clinical trials to include most impacted populations](#)
- 1F** [Develop a global regulatory strategy for stringent regulatory authority \(SRA\) and World Health Organization prequalification \(WHO PQ\)](#)
- 1G** [Develop a strategy for achieving approval from National Medicines Regulatory Authorities \(NMRAs\)](#)
- 1H** [Establish clear pharmacovigilance \(PV\) plans to monitor resistance and safety in critical populations](#)
- 1I** [Plan for safety studies for additional populations](#)



### COSTING & MODELING

Produce price and cost estimates to inform the delivery approach and develop models to provide an initial understanding of the most critical risks and benefits associated with the product or intervention.

- 1J** [Define LMIC price ranges and develop pricing strategy](#)
- 1K** [Understand priority populations and geographies for product introduction](#)
- 1L** [Define an LMIC need estimate for the product market](#)
- 1M** [Conduct cost of goods \(COGs\) analysis](#)
- 1N** [Model epidemic impact of product introduction across multiple end-points](#)
- 1O** [Model worst-case scenario magnitude and consequences of resistance](#)





## 1

## PRIOR TO REGULATORY APPROVAL

## Critical Pathway Activities in Depth, continued

DELIVERY  
& IMPLEMENTATION

Establish priorities for later-stage implementation projects and delivery approaches through desk research and health facility assessments.

- 1P [Assess health system capacity and delivery mechanisms](#)
- 1Q [Conduct health facility assessments to define integration approach](#)

INDIVIDUAL UPTAKE  
& CONTINUED-USE

Engage end-users to understand product and delivery preferences and establish channels or platforms to facilitate collaboration with the community.

- 1R [Establish or engage community advisory boards \(CABs\) and community user groups](#)
- 1S [Conduct market research on user preferences](#)



Photo: Clinton Health Access Initiative, Inc.



# Manufacturing & Distribution

In order to ensure the product is well-positioned to be manufactured at scale at an affordable price point for LMIC contexts, stakeholders should reference the following critical activities:

## 1A / ASSESS OPPORTUNITIES FOR MANUFACTURABILITY FOR LMICS

### Inputs

The innovator product developer must work with key partners to consider the commercial potential of the product at scale and the target price needed to achieve global access (1J). These decisions should be made in collaboration with relevant stakeholders supporting the generic supplier engagement strategy, including payers and technical advisors (1B). As LMIC markets are assessed, the innovator product developer will need to consider how their approach will impact intellectual property, patents, and related licensing agreements. The innovator company and stakeholders supporting the generic supplier engagement strategy (1B) must decide whether they are willing and able to supply the product at the forecasted volumes at an affordable price to LMICs. In order to make this decision, an innovator product developer should consider close collaboration with outside stakeholders who can help advise on cost, initial market size estimates, and opportunities for licensing (1M, 1L, 1B).

### Outputs

This assessment will ultimately help product developers build a manufacturing and supply strategy for LMICs. It will determine whether engaging a generic manufacturer will be critical to achieving the production volumes and prices needed to provide sufficient access for LMIC markets. As needed, this activity should determine if multiple generic manufacturers are needed to support supply security. Experience with existing HIV treatment and prevention products suggests that a generic product is usually critical for achieving the price ranges necessary to enable broad LMIC access.

### Dependencies

A manufacturability assessment will inform the generic supplier engagement strategy (1B) and will have implications for cost and LMIC pricing (1M, 1J). If the innovator product developer can reliably meet LMIC supply needs at access prices, then a generic manufacturer may not need to be considered.



**A GENERIC PRODUCT IS USUALLY CRITICAL FOR ACHIEVING THE PRICE RANGES NECESSARY TO ENABLE BROAD LMIC ACCESS**



## 1B / DEVELOP A GENERIC SUPPLIER ENGAGEMENT AND ACCESS STRATEGY

### Inputs

Depending on the assessment on manufacturability (1A), innovator product developers and/or other relevant stakeholders will need to decide whether a generic partner or partners are required to manufacture the product at prices and volumes needed for LMIC access. Ideally, this decision will involve collaboration and consultation with a range of stakeholders, including payers and advisors supporting opportunities for manufacturability (1A). Developing a generic supplier engagement strategy will involve identifying limiting factors for production (e.g. specialized manufacturing equipment, aseptic processing, or sterilization capabilities).

### Outputs

Innovator product developers and/or other relevant stakeholders should create a framework for objectively assessing potential generic manufacturers based on their capacity to execute key production steps. As potential generic manufacturers are identified, innovator product developers and/or relevant stakeholders will develop a business case to support generic buy-in. This business case will be informed by estimates of LMIC need, LMIC price ranges, and the cost of goods sold (COGS) analysis (1L, 1J, 1M). The generic supplier engagement strategy should also determine if this process (generic manufacturer assessment, selection, and potential for a technology transfer) will need to be supported by technical assistance from a partner and/or financial support from a donor. It will also need to consider licensing requirements for the generic product.

### Dependencies

This strategy will inform the generic manufacturer technology transfer (1C) and may also have implications for LMIC price ranges (1J), engagement with major procurers (1D), and global procurement strategy development (2A). It will also have implications for market-shaping activities after regulatory approval (2I).

## 1C / TRANSFER TECHNOLOGY TO GENERIC MANUFACTURER

### Inputs

Earlier planning activities including the development of a generic strategy (1B) and stakeholder engagement should facilitate an efficient technology transfer.

### Outputs

A technology transfer consists of an exchange of any relevant documentation and professional expertise between the innovator product developer and generic manufacturer, and can help to speed development of generic products. This may include patentable aspects of production and specific business guidance, such as recommendations to improve production efficiency or maintain product quality. While a technology transfer to generic manufacturers may be straightforward in the case of a pill, certain delivery forms may require a more intensive, time-consuming transfer process and should be planned for accordingly.

### Dependencies

The technology transfer process will need to be clearly communicated to relevant regulatory stakeholders to support submission for WHO PQ or to an SRA and country registration for the generic product (1E, 1G, 2D).



Certain delivery forms may require a more intensive, time-consuming transfer process

## 1D / ENGAGE WITH REGULATORS AND MAJOR PROCURERS TO DETERMINE OPTIMAL PRODUCT PACKAGING

### Inputs

Experience from across the family planning (FP) field shows that there is significant variation in procurement preferences across procurement agents. Packaging should be informed by relevant regulatory requirements based on the regulatory strategy (1F, 1G), as well as end-user needs and preferences. This activity should involve an initial scoping of packaging options for comparable products from FP and/or HIV prevention.



Photo: Clinton Health Access Initiative, Inc.

### Outputs

As the HIV prevention product gets closer to LMIC scale-up, it will be important to engage major procurers directly on whether they will prefer to procure the product alone or packaged with other required consumables. This activity will primarily assess regulatory and procurement requirements. An analysis of user preferences (1S) may provide additional insights on client preferences for packaging.

### Dependencies

This activity will feed into global procurement strategy and alignment (2A).

## 1 PRIOR TO REGULATORY APPROVAL

# Clinical Research & Regulatory Approval

To effectively design clinical trials to facilitate efficient regulatory review and develop strategic plans for achieving appropriate regulatory approval for all at-risk populations, stakeholders should reference the following critical activities:

## 1E / DESIGN CLINICAL TRIALS TO INCLUDE MOST IMPACTED POPULATIONS

### Input

This activity requires significant early engagement with and input from researchers and regulatory authorities.

### Output

Clinical trials should be designed to produce the evidence needed to satisfy the indications sought for the product label from SRAs and optimal guidance from global and country normative bodies. Ultimately, the owner of the application will be in direct communication with regulatory authorities and will need to make several independent decisions about filing approach. However, outside advisors may play a supportive role in trial design decision-making. Clinical trial design should inform a research agenda to establish equitable access and prove safety and efficacy amongst a wide range of populations including cisgender women, cisgender men who have sex with men (MSM), transgender women (TGW), cisgender men who have sex with women (MSW), and transgender men (TGM).

### Dependencies

Clinical trial design will be critical to ensure global and national regulatory approval ([1F](#), [1G](#), [2B](#), [2D](#)) and inclusion in global and national normative guidance ([2C](#), [3A](#)). Clinical trial design should inform planning for further safety studies for additional populations, as needed ([1I](#), [2D](#)).

### PRIORITY POPULATIONS FOR HIV PREVENTION RESEARCH:\*

- ✓ Cisgender women
- ✓ Cisgender men who have sex with men (MSM)
- ✓ Adolescents
- ✓ Transgender women (TGW)
- ✓ Cisgender men who have sex with women (MSW)
- ✓ Transgender men (TGM)
- ✓ People who inject drugs (PWID)

\*Illustrative



**CLINICAL TRIAL DESIGN SHOULD INFORM A RESEARCH AGENDA TO ESTABLISH EQUITABLE ACCESS AND PROVE SAFETY AND EFFICACY AMONGST A WIDE RANGE OF POPULATIONS**





## 1F / DEVELOP A GLOBAL REGULATORY STRATEGY FOR STRINGENT REGULATORY AUTHORITY (SRA) AND WORLD HEALTH ORGANIZATION PREQUALIFICATION (WHO PQ)

### Inputs

It is critical for innovator product developers and/or generic manufacturers to determine which SRA approvals they will pursue and whether they will submit for WHO PQ. The developers and/or generic manufacturers should lead early coordination to align with the requirements of SRA(s) and the WHO disease teams and ensure that clinical trials are positioned to answer key questions regulators will need to approve the product. Depending on trial design and product attributes (e.g. oral lead-in for long-acting products or continued monitoring of the pharmacokinetic (PK) tail), additional research outside of the original trial design may be required to achieve regulatory approval and inclusion in normative guidelines.



Photo: Clinton Health Access Initiative, Inc.

### Output

This activity should involve developing a strategy to establish consistent, continuous feedback and communication between the innovator product developer and/or generic manufacturers and decision-making bodies to ensure strategic alignment. Innovators should clearly communicate their plan with relevant stakeholders and planning partners. It will be important for partners to understand the regulatory approval process timing in order to plan how research can be sequenced to optimize this process. Where possible, timelines should be clearly communicated in advance. This strategy should also identify which stakeholders will be critical to engage to address unanswered research questions.

### Dependencies

The regulatory strategy will inform subsequent research priorities, including planning any safety studies that will be required for additional populations not sufficiently studied in clinical trials (1).



**ENSURE THAT CLINICAL TRIALS ARE POSITIONED TO ANSWER THE KEY QUESTIONS REGULATORS WILL NEED TO APPROVE THE PRODUCT**

## 1G / DEVELOP A STRATEGY FOR ACHIEVING APPROVAL FROM NATIONAL MEDICINES REGULATORY AUTHORITIES (NMRAS)



**A REGULATORY STRATEGY WILL  
HELP IDENTIFY GAPS IN EVIDENCE  
AND DETERMINE FUTURE RESEARCH  
PRIORITIES**

### Inputs

In order to develop a strategy for approval from NMRAs, stakeholders should consider the target populations, product attributes, and clinical role of the product alongside comparable products. For example, for an injectable HIV prevention product, stakeholders should look at other injectable products (potentially from family planning) to understand requirements for the delivery form. Other biomedical HIV prevention products (oral PrEP) can be used to understand requirements for the target populations and the clinical role as an HIV prevention product.

### Output

Biomedical prevention products are evaluated through innovative trial designs, which are likely to be new to NMRAs. HIV prevention trials have increasingly complex protocols, which must be responsive to declining HIV incidence and ethical considerations, such as providing participants access to existing prevention and treatment interventions. Because there have been limited HIV prevention products adopted by LMICs, innovators and/or generic manufacturers looking to achieve approval should recognize that NMRAs may have limited experience efficiently evaluating applications from these new trial designs. Thus, developing a strategy early on for prioritizing submissions and achieving approval from these regulatory bodies will be critical. As needed, the regulatory strategy should work with normative and collaborative registration bodies to assess needs and opportunities to build capacity with NMRAs ([1T](#)). Consideration of regional regulatory harmonization pathways and the WHO Collaborative Registration Procedure (CRP) may expedite NMRA approvals and mitigate capacity constraints.

### Dependencies

A regulatory strategy will help identify existing gaps in evidence and determine future research priorities, including planning any safety studies that will be required for additional populations not sufficiently studied in clinical trials ([1I](#)).

## 1H / ESTABLISH CLEAR PHARMACOVIGILANCE (PV) PLANS TO MONITOR RESISTANCE AND SAFETY IN CRITICAL POPULATIONS

### Inputs

Clinical trials answer a significant number of product safety questions. However, uncertainties will inevitably persist without “real-world” data outside of a trial setting. Overcoming these uncertainties will be critical to successful product rollout and uptake. Based on research gaps identified in clinical trial designs (1E, 1I) and the strategies developed to support SRA, WHO PQ, and NMRA approval (1E, 1G), it will be critical to set up PV plans to ensure there is adequate monitoring of all populations. This will be particularly important in populations that may have acute safety concerns, such as pregnant and breastfeeding women. Monitoring for resistance is also likely to be an important issue for any antiretroviral (ARV) based HIV prevention product.

### Outputs

PV plans should consider infrastructure required to gather evidence on resistance outside of trial settings. It is critical to begin planning at such an early stage because LMIC contexts have historically faced significant challenges in PV monitoring. As such, PV plans will likely require early strategic prioritization of geographies and sites to ensure sufficient data can be gathered to answer critical safety questions.

### Dependencies

These plans are critical not only to build the infrastructure, such as data systems or testing networks, required to monitor persistent safety concerns after regulatory approval (2E) but also because PV plans will enable policymakers to more confidently proceed with global and national normative guidelines (2C, 3A). Thus, the PV plan will be one aspect of the global and national regulatory strategy (1E, 1G).

### PROJECT SPOTLIGHT



#### GEMS PHARMACOVIGILANCE PROJECT

The project aims to conduct research to better characterize risk of resistance with topical ARV-based microbicides and PrEP agents and the possible effects on future HIV treatment options; model and analyze potential public health harms, benefits, and costs of different intervals and requirements for HIV testing for users of microbicides in resource-constrained settings; develop and evaluating evidence-based policy recommendations for the frequency of HIV testing and resistance monitoring; and monitor seroconverters in ARV-based prevention programs for resistance. GEMS has been critical in informing policies and defining programmatic considerations related to use of oral PrEP.

Source: PrEP Watch. “USAID Microbicide Product Introduction Initiative (MPii)” Available at: <https://www.prepwatch.org/usaids-supported-initiatives/>



## 11 / PLAN FOR SAFETY AND EFFICACY STUDIES FOR ADDITIONAL POPULATIONS

### Inputs

While initial clinical trials (1E) should be as comprehensive as possible, there may be additional safety concerns for certain populations that require further research, often in the form of open-label extensions or follow-on clinical trials. Identifying these populations will require open communication with trial investigators to determine what information clinical trials will and will not provide, as well as close coordination with regulators, global and country normative bodies, policymakers, and civil society. Close coordination with these groups will ensure there is an advanced understanding of both requirements for SRA, WHO PQ, and NMRA approval, as well as the level of evidence needed for broad global and country guidance (1E, 1G, 2C, 3A).



Photo: Clinton Health Access Initiative, Inc.



### BROAD INDICATION AND DELIVERY OF PRODUCTS CAN REDUCE STIGMA AND INCREASE UPTAKE

### Outputs

HIV prevention experience has shown that broad indication from regulatory authorities and making products broadly available can reduce stigma and increase uptake. In particular, additional research should consider populations that may not be part of the initial study populations but may benefit from using the product. For example, if an initial clinical trial focuses on MSM, stakeholders should consider additional trials to achieve a broader indication from regulatory authorities for cisgender women and heterosexual men.

### Dependencies

Identifying additional populations early on will enable stakeholders to plan for research (2E) and ensure that the product receives both broad indication from regulatory authorities and broad delivery recommendations in country-level normative guidance.

# Costing & Modeling

In order to produce price and cost estimates to inform manufacturing and delivery approaches and develop models to provide an initial understanding of the most critical risks and benefits associated with the product or intervention, stakeholders should reference the following critical activities:

## 1J / DEFINE LMIC PRICE RANGES AND DEVELOP PRICING STRATEGY

### Input

Based on the LMIC need estimate (1L) and other market size estimates, as well as the COGS analysis (1M), organizations and donors supporting market-shaping interventions will likely lead discussions with generic manufacturers or the product developer for both entry and scale price.

### Output

Stakeholders such as payers or technical advisors should provide potential price ranges for the product for LMIC markets as developers and partners confirm access and generic supplier engagement plan (1B). LMIC price ranges will need to be cross-referenced with the COGS analysis (1M) to understand whether the product cost can meet price ranges and profit margins are not prohibitive.



LMIC price ranges will need to be cross-referenced with COGS analysis

### Dependencies

Considerations on price and the modeled impact of the product across multiple end-points (1N) will ultimately inform several independent decisions, including WHO normative guidance, donor support for product introduction, and national decisions to adopt. Comparing price ranges to the COGS analysis (1M) will help determine where market-shaping interventions (2I) may be required at later stages of product introduction.

## 1K / UNDERSTAND PRIORITY POPULATIONS AND GEOGRAPHIES FOR PRODUCT INTRODUCTION

### Inputs

Priority populations can be understood from a variety of sources, including existing epidemiological and modeling data, trial data, and values and preferences of those who might benefit. This assessment should consider target populations for HIV prevention broadly. However, as with other more complex and costly prevention options, population prioritization needs to consider country and donor thresholds for cost-effectiveness, user preferences, and the likelihood of uptake and adherence. For each new product, this work should build off current HIV prevention product usage and guidelines and should involve early engagement with technical working groups (TWGs) and potential users and community groups.

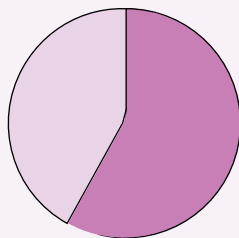
In Sub-Saharan Africa,



**3 IN 4**

new HIV infections among young people aged 15-24 are in girls

Source: UNAIDS 2020.



### KEY POPULATIONS

and their sexual partners  
account for

**62%**

of new HIV infections globally

Source: UNAIDS 2020

### Outputs

This assessment will identify priority populations and geographies to inform initial introduction activities, including early desk research (1P), health facility assessments (1Q), and demand forecasts (2G, 2H). It will also help to ensure phased implementation projects (2K) are strategically focused and efforts progressively build from pre-regulatory scoping to small scale pilots and eventual scale.

### Dependencies

Identifying priority populations and geographies that are likely to need the product will be necessary for forecasting and modeling activities (1N, 1O, 2G, 2H) and should precede human-centered design (HCD) and acceptability activities (1AA, 1AB, 1AC, 2L). This activity should also inform focal populations and geographies for early phase implementation projects (2K).

## 1L / DEFINE AN LMIC NEED ESTIMATE

### Inputs

The geographies in the overall potential LMIC market should consider historically generic-accessible LMICs, HIV incidence and prevalence, and clinical trial sites for the product.

### Output

A “need estimate” should be developed to quantify the size of the at-risk populations in the potential LMIC market. Within the potential LMIC market, at-risk populations can be estimated by quantifying the HIV-negative population anticipated to be included in the initial regulatory indication (e.g. cisgender women, MSM, TGW) and by estimates of HIV risk (e.g. Demographic Health Survey (DHS) data, sexually-transmitted infection (STI) data, and risk screening). The need estimate will not constitute a later stage demand forecast or estimate of the uptake rate over time (2H), but it will provide one critical input to these later analyses. A demand forecast will require additional information on client preferences (1S, 2L), donor support for introduction (1W), and demand-side planning with Ministries of Health (MoHs).



Source: UNAIDS 2020

### Dependencies

This analysis will feed into the later stage demand forecast (2H) and will likely inform the generic supplier engagement strategy (1B).

## 1M / CONDUCT COGS ANALYSIS

### Inputs

To help estimate various associated costs, a cost of goods (COGs) analysis for LMIC contexts should be conducted, considering parts, raw materials, labor, and other overhead costs associated with the product, including profit margins for suppliers.

### Output

As early research more clearly defines product specifications, estimating the total production costs will help to plan for resource needs and overall HIV prevention portfolio allocation.

### Dependencies

Ultimately, this analysis will be used to identify opportunities to maximize affordability and contribute to a generic supplier engagement and access strategy (1B). This analysis is a critical input to any potential market-shaping interventions to accelerate access. In particular, this will be a critical input and consideration for negotiations related to the pricing strategy (1J).

## 1N / MODEL EPIDEMIC IMPACT OF PRODUCT INTRODUCTION ACROSS MULTIPLE END-POINTS

### Inputs

Before assessing the potential impact of product introduction across multiple end-points, modelers should discuss parameters and expected outputs with key decision-makers, including funders, global normative bodies, and MoHs, to help ensure the study is relevant to rollout planning.

### Output

The model will estimate the potential impact and return on investment of new product introduction under different rollout scenarios and product prioritization strategies. Although the ultimate aim of this modeling is to understand the potential impact of the HIV prevention product on HIV incidence, it will be helpful to also understand and measure other benefits. Where possible, modeling for HIV prevention products should include a wide set of indicators (e.g. HIV incidence, person-time with protection, STI incidence, contraceptive coverage, etc.). However, for an analysis of collateral benefits to play a useful role in decision-making, stakeholders will need to understand the risks and challenges associated with attributing collateral benefits to any single HIV prevention product. Experience in voluntary medical male circumcision (VMMC) has shown that gathering data on collateral benefits across various interventions for comparison of impact and cost-effectiveness of different is challenging. Further, oversimplifying the relationship between interventions and their collateral benefits may risk decreased credibility of the analysis.

### Dependencies

This activity is critical for any stakeholders, such as funders, MoHs, and implementers, who will consider how best to include the product in their health programs. Additionally, this activity will inform the design of early phase implementation projects (2K), by providing guidance which endpoints, including collateral benefits, should be measured to build evidence on impact and return on investment.

“

**MODELS OF THE IMPACT AND POTENTIAL RETURN ON INVESTMENT ARE ONE IMPORTANT ELEMENT OF DESIGNING EFFECTIVE PRODUCT INTRODUCTION STRATEGIES**

**PETER GODFREY-FAUSSETT**

UNAIDS

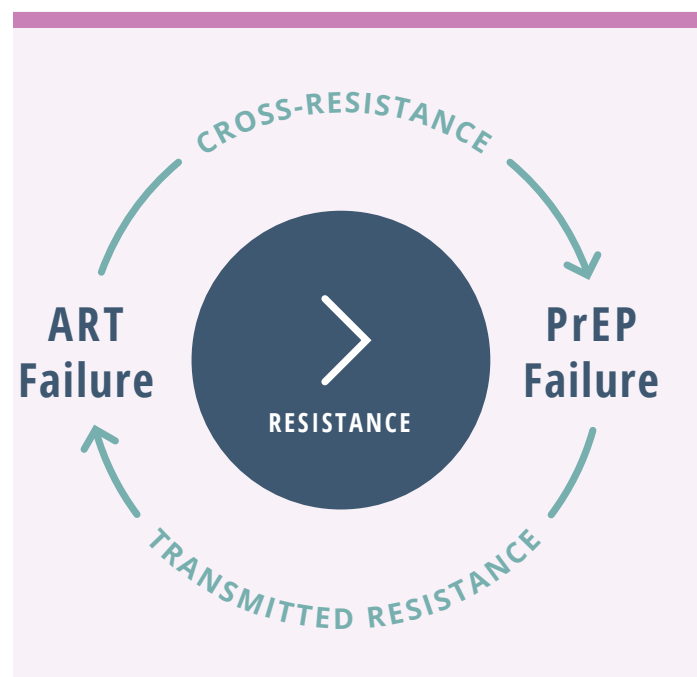
## 10 / MODEL WORST-CASE SCENARIO MAGNITUDE AND CONSEQUENCES OF RESISTANCE

### Inputs

Worst-case scenario modeling will need to take into account preliminary data available from clinical trials, as well as usage rates of products that may increase the risk of cross-resistance.

### Output

Ahead of real-world data on resistance, global stakeholders will want to assess the potential for resistance in various scenarios, including the potential for cross-resistance with products with similar molecular compositions, product failures, and any additional resistance risks driven by the product's PK tail, if it has one. Consideration of different scenarios will enable decision-makers, such as regulators, normative bodies, and MoHs, to plan ahead and independently determine what level of risk is acceptable at both an individual and population level before receiving real-world data on resistance. Experience with oral PrEP has shown that modeling the “worst-case scenario” for resistance played a crucial role in decisions to include the product in normative guidance.



Adapted from: [Parikh and Mellors, 2017](#).

### Dependencies

Where possible, this activity will feed into PV planning for resistance ([1H](#)) and the modeling across multiple end-points ([1N](#)).

## 1 PRIOR TO REGULATORY APPROVAL

# Delivery & Implementation

To establish priorities for later-stage implementation projects and delivery approaches through early-stage desk research and health facility assessments, stakeholders should ensure the following activities take place before regulatory approval:

## 1P / ASSESS HEALTH SYSTEM CAPACITY AND DELIVERY MECHANISMS

### Input

As an initial planning and priority setting activity, early desk research should consolidate information on the current prevention delivery landscape and lessons learned from previous HIV prevention products.

### Output

As relevant to the product, the review should include: current healthcare worker (HCW) training and requirements for providing existing biomedical HIV prevention products and antiretroviral therapy (ART); overall cascade for biomedical prevention products; multi-agency policies or collaborations (e.g. youth-friendly service models, school health programs, family planning services, post-partum programs, sex worker programs, LGBTIQ+ programs, ongoing oral PrEP programs); quality assurance mechanisms; legal constraints that may impact product introduction (e.g. private sector requirements, age of consent, discriminatory laws on homosexuality, religion, or sex work); public vs. private delivery (especially oral PrEP and HIV self-testing (HIVST)); client-facing tools that can support HIV prevention decision-making; and impending policy changes (such as task shifting) that may affect the introduction of the product. It will be important to understand not only the availability of existing delivery mechanisms but also the robustness of these mechanisms based on real-life implementation. Where policy has not translated into implementation (for example, sufficient decentralization of ART services), this desk research should aim to identify potential approaches for strengthening existing implementation. Furthermore, where policy is not currently sufficient, desk research should seek to understand the pathways, necessary stakeholder engagement, critical gatekeepers, and timelines for making critical policy changes.

### Dependencies

This activity will be an initial step in prioritizing delivery channels for phased implementation (2K). It will ensure that early implementation projects anticipate potential systemic policy and programmatic barriers and are well poised to move to scale (3C). Solutions to the barriers identified in this desk research will be further defined in later activities, including health facility assessments ahead of rollout (1Q).



**IT WILL BE IMPORTANT TO UNDERSTAND NOT ONLY THE AVAILABILITY OF EXISTING DELIVERY MECHANISMS BUT ALSO THE ROBUSTNESS OF THESE MECHANISMS BASED ON REAL-LIFE IMPLEMENTATION**



## 1Q / CONDUCT HEALTH FACILITY ASSESSMENTS TO DEFINE INTEGRATION APPROACH

### Inputs

Following and informed by initial desk research that narrows down potential delivery channels (1P), this research will build on existing biomedical HIV prevention product experiences and delivery approaches.

### Output

This health facility assessment activity will aim to determine what additional support is needed to integrate the product into available delivery mechanisms and/or evolve current models. The review in this activity will include: capacity requirements, including systems to remind patients of missed or late visits; improvements needed for patient flow; changes to data collection (including any opportunities to bolster electronic medical record systems); and required HCW training and cadre changes. Task shifting considerations should assess two levels of provider requirements for initiation and follow-up. Another critical part of understanding how new products could be integrated into available delivery mechanisms is mapping out the stakeholders who will need to be engaged for the product to be successfully delivered through prioritized delivery channels. For potential providers involved in each delivery channel, it will be important to understand provider workloads. The approach will include HCW surveys, in-depth interviews, and health facility operations assessments.

### Dependencies

This pre-regulatory research will inform channels to be piloted in early phase implementation projects (2K) will help ensure these projects are well poised to move to scale.

“

**WE NEED TO BE ABLE TO UNDERSTAND THE BARRIERS THAT PROGRAMS MIGHT FACE IN ADVANCE ... SO WE CAN DEPRIORITIZE CERTAIN DELIVERY MECHANISMS AND CONSIDER CHANGES UPFRONT**

**NGONIDZASHE MADIDI**

IAVI/formerly PSI Zimbabwe



# Individual Uptake & Continued Use

In order to engage end-users to understand product and delivery preferences and establish channels or platforms to facilitate collaboration with the community, stakeholders should reference the following critical activities:

## 1R / ESTABLISH OR ENGAGE COMMUNITY ADVISORY BOARDS (CABS) AND COMMUNITY USER GROUPS

### Input

Biomedical prevention product introduction strategies should be co-developed with input from community groups and potential users. [Experience with oral PrEP](#) has shown that community-led implementation is critical for achieving high uptake and continued use. For example, the sex-workers' collective, Ashodaya Samithi, successfully facilitated the introduction of oral PrEP with [high uptake and continuation levels](#).

### Output

As CABS improve HIV prevention literacy amongst potential users, CABS will also provide strategic direction and leadership to strengthen community engagement in project implementation, to foster demand generation, and to ensure biomedical prevention products are rolled out in a way that supports and complements the needs of community members. Additionally, [experience with dolutegravir \(DTG\)](#) has shown that CABS can play a critical role in voicing the needs of community members and influencing the development of WHO guidelines. As seen with global normative guidance on oral PrEP, community members' and potential users' decisions regarding acceptable risks can directly inform normative guidelines. This activity should include establishment or engagement of community mechanisms and structures, including community advisory boards, HIV prevention user groups, family planning user groups, youth groups, and community-based organizations (CBOs) serving LGBTIQ+ individuals and sex workers.

### Dependencies

CABS and community user groups should be involved with policy creation, implementation, and advocacy activities across development, research, rollout, and scale-up of biomedical HIV prevention products, including human-centered design research on enabling environments ([1AA](#), [1AB](#)), demand generation ([1V](#), [1AC](#)), and investigation of delivery channels ([1P](#), [1Q](#), [2K](#)).

“

**EXPERIENCE WITH  
ORAL PREP HAS SHOWN  
THAT COMMUNITY-  
LED IMPLEMENTATION  
CAN TRANSLATE TO  
SIGNIFICANTLY HIGHER  
UPTAKE AND RETENTION**

—  
Frances Cowan  
CeSHHAR  
Zimbabwe



## 1S / CONDUCT MARKET RESEARCH ON USER PREFERENCES

### Inputs

An analysis of existing research, including previous end-user research, HCD, and DCEs, should aggregate and review completed studies to consider how findings can be translated into uptake assumptions and the potential impact on the coverage of other interventions, such as oral PrEP.

### Output

These studies should seek to understand user preferences for product and delivery attributes relevant to the new product. This information will support an understanding of user acceptability for both the current product and next-generation products. To ensure these findings are actionable, this activity should focus on isolating relevant findings for the product at-hand and should include a literature review and analysis of existing DCEs and preferred product attributes.

### Dependencies

This analysis of user preferences is critical because it will help further inform priority delivery points and opportunities to integrate the product with other services (1Q), additional needs for human-centered design projects before regulatory approval (1AA, 1AB, 1AC), and additional context for later stage demand forecasting (2G, 2H). While regulatory and procurement requirements for packaging (1D) may leave limited degrees of freedom, an analysis of user preferences (1S) may provide additional insights on client preferences for packaging.



Photo: Clinton Health Access Initiative, Inc.

## 2

## AFTER REGULATORY APPROVAL

## Critical Pathway Activities in Depth

This chapter will cover critical activities that will support an efficient transition into early phase implementation after stringent regulatory authority approval. These activities will enable stakeholders involved in the product introduction process to achieve the following objectives.



### MANUFACTURING & DISTRIBUTION

Engage appropriate stakeholders to ensure the product is positioned to be procured at the levels required in target LMIC geographies.

**2A** [Develop global procurement strategy and alignment](#)



### CLINICAL RESEARCH & REGULATORY APPROVAL

Position the product to achieve efficient country registration and conduct any necessary additional research to achieve an appropriately broad product indication from regulatory authorities and optimal normative guidance.

**2B** [Complete country registration for innovator product](#)

**2C** [Support development of WHO guidance for early phase implementation projects](#)

**2D** [Complete SRA filing and/or WHO PQ submission and country registration for the generic product](#)

**2E** [Active PV for additional safety concerns](#)

**2F** [Conduct safety studies amongst additional populations](#)



### COSTING & MODELING

Refine early-stage costing activities to develop accurate forecasting analyses.

**2G** [Conduct demand-based forecasting studies](#)

**2H** [Develop LMIC demand forecast for new product](#)

**2I** [Implement market-shaping interventions and support affordability](#)

## 2

## AFTER REGULATORY APPROVAL

## Critical Pathway Activities in Depth, continued

DELIVERY  
& IMPLEMENTATION

Conduct phased implementation projects reflecting priorities established through early desk research and health facility assessments and establish early product introduction support systems or platforms.

- 2J [Early product introduction support and technical assistance \(TA\)](#)
- 2K [Conduct phased implementation projects with priority populations, geographies, and delivery channels](#)

INDIVIDUAL UPTAKE  
& CONTINUED-USE

Refine understanding of acceptability and desirability of a new product based on effectiveness data from trials.

- 2L [Understand the acceptability and desirability of a new product \(alone and versus existing products\)](#)



Photo: Clinton Health Access Initiative, Inc.

## 2 AFTER REGULATORY APPROVAL

# Manufacturing & Distribution

To engage appropriate stakeholders to ensure the product is positioned to be procured at the levels required in target LMIC geographies, stakeholders should complete the following critical activities after regulatory approval:

## 2A / DEVELOP GLOBAL PROCUREMENT STRATEGY AND ALIGNMENT

### Inputs

This activity should build off prior engagement with major procurers to determine optimal product packaging (1D).

### Outputs

Because procurement bodies typically only deal with products that are near-launch or already on the market, the ideal time to engage with them is ~12 months prior to the expected introduction. Procurement groups must be well aligned as the product launches so that they can be prepared when MoHs and donors are ready to adopt the product in national guidelines and bring it to scale. A target procurement process will be cost-efficient, transparent, and facilitate easy engagement and coordination between suppliers, buyers, and procurement agents. A global procurement strategy will inform key factors including how orders will be coordinated; how suppliers and procurers will stay aligned with ongoing market intelligence and updated demand forecasts; and if orders need to be pooled or staggered to support global supply security.

### Dependencies

This activity will inform strategy development to bring early phase implementation projects to scale (3C). The desired packaging may also have regulatory filing implications.

### PROJECT SPOTLIGHT



APWG

### ARV PROCUREMENT WORKING GROUP

The ARV Procurement Working Group (APWG) is currently the main communication and coordination body within the HIV procurement space and has allowed major procurers to share market intelligence and improve visibility and confidence among suppliers by coordinating orders.

Source: ARV Procurement Working Group. Available at: <https://www.arvprocurementworkinggroup.org>



# Clinical Research & Regulatory Approval

To position the product to achieve efficient country registration and conduct any necessary additional research to achieve an appropriately broad product indication from regulatory authorities and optimal normative guidance, stakeholders should reference the following checklist of critical activities:

## 2B / COMPLETE COUNTRY REGISTRATION FOR INNOVATOR PRODUCT

### Input

Facilitated by early alignment with regulatory decision-makers ([1E](#), [1G](#)), country registration for the innovator product should take place as soon as possible. Ideally, registration would follow immediately after SRA approval and/or WHO PQ.

### Output

With sufficient initial stakeholder engagement, early buy-in by country-level decision-makers can ensure this takes place as rapidly as possible. After the dossier is filed with the NMRA, while approval is pending, stakeholders should consider using waivers to accelerate delivery of first orders. Innovators should also consider regional regulatory harmonization pathways and the WHO Collaborative Registration Procedure (CRP) as options to expedite NMRA approvals and minimize capacity constraints.

### Dependencies

This activity is critical to have the product included in national HIV prevention guidelines and bring early phase implementation projects to scale ([3C](#)).

## 2C / SUPPORT DEVELOPMENT OF WHO GUIDANCE FOR EARLY PHASE IMPLEMENTATION PROJECTS

### Input

In supporting the development of effective, clear WHO guidance, it will be important to understand what types of guidance worked well for previous products and what types of guidance led to delays and ineffective implementation. The main input for this activity will be evidence from clinical trials and additional research ([2F](#)). For additional details, see [Annex III: WHO Evidence to Decision Framework](#).

### Output

As soon as possible after SRA approval, the product developer or other global stakeholders involved in product introduction planning will need to share evidence with WHO to support the development of early guidance on implementation projects.

### Dependencies

This activity will be critical to ensure that guidance is actionable and translatable to country-level implementation ([3A](#)) and target-setting ([3B](#)).



## 2D / COMPLETE SRA FILING AND/OR WHO PQ SUBMISSION AND COUNTRY REGISTRATION FOR THE GENERIC PRODUCT

### Input

This activity will be informed by previous activities related to engaging generic manufacturers (1B, 1C), evidence from clinical trials (1E), and additional safety research (2E), as well as the development of a global regulatory strategy (1F).

### Output

The generic manufacturer will need to file for SRA approval and/or WHO PQ and register the product with NMRAs. In some cases, it may be important to consider visibility and partnership with outside stakeholders to ensure registration is quickly obtained and there is not a substantial delay between access to the innovator product and the generic product. As with the innovator product, consideration of regional regulatory harmonization pathways and the WHO Collaborative Registration Procedure (CRP) may greatly expedite NMRA approvals and minimize capacity constraints.



### Dependencies

Generic access is essential for achieving a high public health impact at an affordable price; this activity is critical for bringing early phase implementation projects to scale (3C).

## 2E / ACTIVE PV FOR ADDITIONAL SAFETY CONCERNS

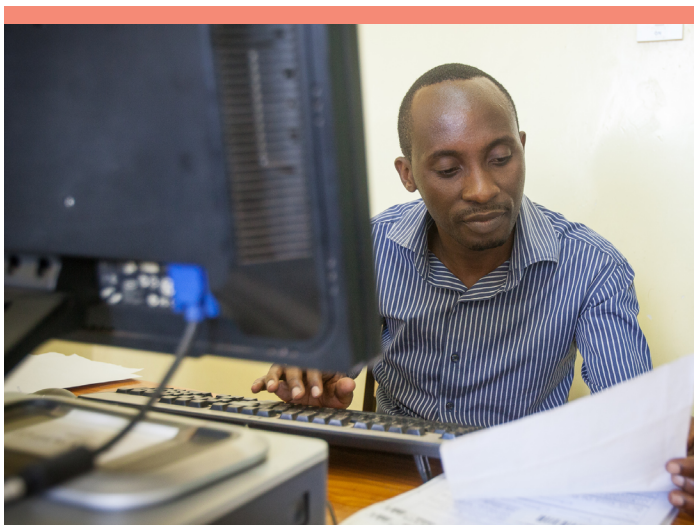


Photo: Clinton Health Access Initiative, Inc.

### Inputs

Active PV should be informed by early-stage PV planning (1H).

### Output

This activity will involve carrying out ongoing PV based on priorities established in early-stage planning efforts. Strengthening country PV systems will also facilitate the introduction of other pipeline products in the future and, if executed comprehensively enough, both catch early critical safety signals and ensure accurate safety information is disseminated.

### Dependencies

Ongoing, active PV will be critical to achieve country buy-in for the product and ensure safety monitoring continues outside of the trial context. Ultimately, this will be critical for bringing early phase implementation projects to scale (3C).

## 2F / CONDUCT SAFETY STUDIES AMONGST ADDITIONAL POPULATIONS

### Inputs

Additional clinical studies should be based on evidence gaps identified in earlier stage activities ([1J](#)).

### Output

Additional research may be needed for populations (e.g. cisgender men who have sex with women or transgender men). The innovator product developer and research partners should advance any additional required studies after regulatory approval.

### Dependencies

This activity will be critical to support access to the product for at-risk populations that are not often highly prioritized in clinical trial design. These safety studies will feed into early phase implementation projects involving these populations ([2K](#)) and later stage scale-up ([3C](#)).



**THIS ACTIVITY WILL BE CRITICAL FOR SUPPORTING ACCESS TO THE PRODUCT FOR AT-RISK POPULATIONS THAT ARE NOT OFTEN HIGHLY PRIORITIZED IN CLINICAL TRIAL DESIGN**



# Costing & Modeling

To refine early stage costing activities to develop accurate forecasting, stakeholders should ensure the following activities take place after regulatory approval:

## 2G / CONDUCT DEMAND-BASED FORECASTING STUDIES

### Input

Demand-based forecasting studies will primarily build upon programmatic data from existing biomedical HIV prevention products and research on user preferences [\(1S\)](#).

### Output

This activity involves conducting demand-based forecasting studies to understand the incremental increase in the number of individuals seeking HIV prevention tools and/or replacement of currently available tools. This would need to be studied with priority populations (e.g. adolescent girls and young women, women 25+, MSM, TGW). This type of study has been used in the past to understand the potential incremental [uptake of VMMC](#) and replacement with the introduction of devices.

### Dependencies

This activity will inform later stage demand forecasting [\(2H\)](#) and target-setting and budgeting activities [\(3B\)](#), as well as technical assistance for product scale-up [\(3C\)](#).

## 2H / DEVELOP LMIC DEMAND FORECAST FOR NEW PRODUCT

### Input

A demand forecast will build upon earlier stage LMIC need estimates (1L), existing programmatic data, user preferences (1S), and demand studies (2G). It will be informed by demand-side planning with donors and MoHs (1W) and will rely on independent decisions, including WHO normative guidance and the national decisions to adopt.

### Output

It is critical to develop a demand forecast to inform the anticipated demand of the new product and an incremental increase in the number of individuals seeking HIV prevention tools and/or replacement of currently available tools. This forecast will also help programs anticipate system capacity requirements, including associated consumables and testing, required for implementation. A demand forecast is also critical for procurers to anticipate demand, as well as for suppliers, to ensure sufficient manufacturing capacity and ability to scale.



### Dependencies

A demand forecast would further inform entry and scale prices, including ranges previously provided by the manufacturer and generics (1J), as well as national target setting and budgeting tools (3B).

## 2I / IMPLEMENT MARKET-SHAPING INTERVENTIONS AND SUPPORT AFFORDABILITY

### Input

While early stage activities to develop a generic supplier engagement and access strategy (1B) and LMIC need estimate (1L), fed into the LMIC price ranges and initial price strategy (1J), it will be critical to build upon this strategy after regulatory approval to develop a launch pricing strategy and determine if any market-shaping interventions are required to support affordability and access. This activity will also be informed early-stage procurement alignment activities (2A).

### Output

Donors, technical assistance partners, and governments should consider implementing a number of potential market-shaping interventions, including catalytic procurement, volume guarantees, and/or subsidies, to avoid a high-cost/low-demand barrier. This activity should take into account considerations specific to a product launch that may not have been defined during earlier stage pricing strategy planning (1J), such interest in the product from governments and donors based on trial outcomes and regulatory approval. To support affordable pricing and sustainable supply security, stakeholders may consider market-shaping interventions like placing early orders immediately after regulatory approval to kick-start the market and enable early phase implementation projects (2K) in LMICs to quickly begin.

### Dependencies

The launch pricing strategy and market-shaping interventions should be closely linked to the global procurement strategy and alignment (2A). This activity will also impact early product introduction support (2J) and product availability for phased implementation projects (2K), as well as national target-setting and budgeting tools during scale-up (3B).

## 2 AFTER REGULATORY APPROVAL

# Delivery & Implementation

Based on priorities identified prior to regulatory approval, stakeholders should reference the following critical activities to conduct phased implementation projects and to establish delivery platforms for the product:

## 2J / EARLY PRODUCT INTRODUCTION AND TECHNICAL ASSISTANCE

### Input

Where applicable, TA will be designed leveraging activities carried out before regulatory approval ([1K](#), [1L](#), [1P](#), [1Q](#), [1R](#), [1S](#)) to make policy recommendations on priority populations, geographies, and delivery channels. TA focus will also be informed by HCD research ([1AA](#), [1AB](#), [1AC](#)) and end-user preferences ([2L](#)).

### Output

National programs in early-adopter countries will likely need TA to adapt global guidelines, launch and support TWGs, develop relevant training materials, and plan for national rollout. TA will be crucial to ensuring that policy-making bodies are well linked to early phase implementation projects ([2K](#)) and to ensuring these projects continue to be designed to gather the evidence needed by country-level decision-makers. Support in early-adopter countries and rapid dissemination of findings will catalyze adoption more broadly.

### Dependencies

This assistance will further ensure that findings from early phase implementation projects are rapidly incorporated into national planning to bring the product to scale ([3B](#), [3C](#)). As early phase implementation projects are underway, TA will ensure that data gathered based on global implementation guidance ([2C](#)) can be used to inform how strategies are impacting product adoption, continuation/discontinuation, and method switching.



Photo: Clinton Health Access Initiative, Inc.

## 2K / CONDUCT PHASED IMPLEMENTATION PROJECTS WITH PRIORITY POPULATIONS, GEOGRAPHIES, AND DELIVERY CHANNELS

### Inputs

Priority populations, geographies, and delivery channels for phased implementation projects will be informed by planning ahead of regulatory approval (1K, 1L, 1P, 1Q, 1R, 1S). These previous activities aim to ensure that early phase implementation is well poised to address the needs of the epidemic and to overcome barriers to implementation. Early phase implementation projects should obtain ethics approval as needed before initiating.

### Outputs

To ensure a shorter time between SRA approval and national scale-up, early phase implementation projects should not be one-off, small-scale pilots, but rather larger early phase implementation projects that align with existing country needs and are well poised to scale (3C). While oral PrEP rollout involved a large number of small pilots and demonstration projects, this activity should prioritize critical considerations and research questions based on the evidence gathered through preceding desk research, community advisory boards and user groups, and health facility assessments. Early phase implementation projects should include a diversity of countries and health systems to ensure the fewer number of projects are as broadly applicable as possible across countries. These projects should prioritize building evidence on issues that will be critical for later-stage scale-up, including understanding how much product integration would cost, integrating delivery with other health services, implementing with specific populations such as transgender men and women and adolescents, evaluating scalable options to link testing with prevention services, evaluating patient monitoring guidelines for healthcare providers, and conducting willingness-to-pay studies.

### Dependencies

Phased implementation projects will inform WHO guidance for scale-up (3A), development of national target-setting and budgeting tools (3B), as well as strategy development and TA, to bring early phase implementation projects to scale (3C).

#### PROJECT SPOTLIGHT



#### BRIDGE-TO-SCALE ORAL PrEP PROJECT

The Bridge-to-Scale project, also known as Jilinde, is a four-year project launched in July 2016. Jilinde is one of the projects at the fore front of the rollout of PrEP in Kenya, working in close partnership with the government of Kenya. The Jhpiego-led project, funded by Bill and Melinda Gates Foundation, seeks to move oral PrEP from research and demonstration settings into a large-scale public health response in Kenya. Because of its large scale, the project is positioned to generate evidence that population-level PrEP interventions are feasible and effective in LMICs.

Source: Jilinde. Available at: <https://www.jilinde.org>

# Individual Uptake & Continued Use

To refine previous end-user research and improve understandings of acceptability and desirability of the new product, stakeholders should ensure the following activities is complete after regulatory approval:

## 2L / UNDERSTAND ACCEPTABILITY AND DESIRABILITY OF A NEW PRODUCT (ALONE AND VERSUS EXISTING PRODUCTS)

### Input

This activity will be informed by clinical trial evidence ([1E](#)) as well as product attributes and clinical considerations established by the drug indication approved by regulatory authorities and guidelines from normative bodies ([2B](#), [2C](#), [2D](#)).

### Output

Product attributes and clinical considerations (e.g. testing, packaging, or kitting plans) need to be consolidated to define the unique selling points, including what attributes are potentially problematic or enabling for uptake and use. With the product available outside of clinical trials, targeted surveys on knowledge, attitudes, and practices can be used to assess perceived risk, current choices in product/service use, and acceptability/desirability of the new product. As part of this exercise, studies should evaluate the new product against alternative products and behaviors.

### Dependencies

This activity will inform demand-based forecasting studies ([2G](#)) and inform a demand forecast ([2H](#)).



## 3

## SCALE-UP OF PRODUCT IN LMICS

## Critical Pathway Activities in Depth

This chapter will cover critical activities that will support efficient LMIC scale-up after early phase implementation. These activities will enable stakeholders involved in the product introduction process to achieve the following objectives.



### MANUFACTURING & DISTRIBUTION

Manufacturing and distribution activities will need to be completed before LMIC scale-up to enable broad rollout so there is no distinct objective for this focus area for this time period.



### CLINICAL RESEARCH & REGULATORY APPROVAL

Support global guidance development for scale-up.

**3A** [Support WHO and government development of normative guidance for scale-up](#)



### COSTING & MODELING

Support the development of national target-setting and budgeting tools for the new product in the context of the broader HIV prevention method mix.

**3B** [Include product in national target-setting and budgeting tools for prevention method mix](#)

## 3

## SCALE-UP OF PRODUCT IN LMICS

## Critical Pathway Activities in Depth, continued

DELIVERY  
& IMPLEMENTATION

Support transition from early phase implementation projects to optimal scale.

**3C** [Strategy development and TA to bring early phase implementation projects to scale](#)

INDIVIDUAL UPTAKE  
& CONTINUED-USE

By the time product scale-up has begun in LMICs, findings from earlier-stage individual uptake & continued use activities should be incorporated into delivery & implementation activities, so there is no distinct objective for this focus area for this time period.



Photo: Clinton Health Access Initiative, Inc.



# Clinical Research & Regulatory Approval

In order to support the development of global guidance for scale-up, stakeholders should consider the following critical activities:

## 3A / SUPPORT WHO AND GOVERNMENT DEVELOPMENT OF NORMATIVE GUIDANCE FOR SCALE-UP

### Input

Evidence from early phase implementation projects ([2K](#)), ongoing PV ([2E](#)), and additional research ([2F](#)) should inform global normative guidance for scale-up.



### Output

The above evidence should be monitored and communicated to normative bodies and governments so they can rapidly translate evidence into global and national guidance for wide-scale implementation. If there is initially limited global guidance based on clinical trials (e.g., initial oral PrEP WHO guidance for specific populations in 2012), partners should consider how additional evidence may support more expansive guidance (e.g., more broad oral PrEP WHO guidance for anyone at substantial risk). Experience with previous biomedical HIV prevention products, such as VMMC and oral PrEP, has shown that clear, detailed WHO normative guidance is critical in catalyzing national scale-up in LMICs.

### Dependencies

Effective global normative guidance will inform strategy development and TA to bring early phase implementation projects to scale ([3C](#)).



## Costing & Modeling

To facilitate country-level costing and modeling for target-setting and budgeting, stakeholders should ensure the following critical activities is completed during LMIC scale-up:

### 3B / INCLUDE PRODUCT IN NATIONAL TARGET-SETTING AND BUDGETING TOOLS FOR PREVENTION METHOD MIX

#### Input

This activity will be informed by early phase implementation projects (2K) as well as demand-based forecasting studies (2G) and market-shaping interventions (2I).

#### Output

After product introduction, countries will need to set targets for product scale-up and develop estimated budgetary needs throughout different phases of scale-up. Target-setting, budgeting, and program monitoring and evaluation tools have been developed to support the introduction of individual HIV prevention tools, including VMMC, condoms, and existing biomedical HIV prevention products. As the number of HIV prevention delivery modalities expands, country decision-makers have highlighted the need for tools that will allow them to set targets, estimate program costs, and identify capacity gaps – as well as estimate return-on-investment based on program performance – across the PrEP method mix.

#### Dependencies

This activity will ensure that the new product is included in the current national target-setting tools and will feed into strategy development and TA to bring early phase implementation projects to scale (3C).

“

**THE CONVERSATION ABOUT HOW GUIDANCE IS TRANSLATED TO ACTUAL COUNTRY-LEVEL TARGETS NEEDS TO HAPPEN WELL IN ADVANCE. WITH ORAL PREP, LINKING GUIDANCE WITH ELIGIBILITY CRITERIA WAS A MAJOR CHALLENGE.**

IRENE MUKUI

DNDi/formerly Kenya NASCOP

# Delivery & Implementation

To support transition from early phase implementation projects to optimal scale, stakeholders should ensure the following activities take place before regulatory approval:

## 3C / STRATEGY DEVELOPMENT AND TA TO BRING EARLY PHASE IMPLEMENTATION PROJECTS TO SCALE

### Input

In order for rollout to be evidence-based and informed by user groups and the community, there will need to be continuous communication and learning from early phase implementation projects (2K). On an ongoing basis, results from these projects will need to be assessed and incorporated into later-stage rollout planning. As such, it is essential that this strategic planning activity is closely linked to previous activities, including the creation of an information clearinghouse (1Z), end-user preferences (1S, 2L), and community advisory boards and user-groups (1R). As implementation scales, TA will ensure that data gathered based on global implementation guidance (2C) can be used to inform how strategies impact product continuation/discontinuation and method switching.

### Output

After regulatory approval, early phase implementation projects will focus on testing the strategies that have been identified as feasible, acceptable, and cost-effective by preceding research and input from community advisory boards and user groups. As early projects identify successful strategies, it will be critical to link these early phase implementation projects to national scale-up in early-adopter countries. As early-adopter countries plan to bring the product to scale, TA will support continued coordination between TWGs and stakeholders crucial for new policy development. TA will work with national policymakers to map and overcome barriers to implementation at scale and to develop comprehensive costing, budgeting, target setting, and demand generation for broad implementation.

### Dependencies

This activity will ensure early phase implementation projects (2K) do not remain small pilot programs but are instead expanded to support broad access to the new intervention through evidence-based approaches.

“

**MAKE SURE THERE IS A CLEAR LINK BETWEEN FIRST MOVERS DOING DEMO PROJECTS AT LEARNING SITES AND SCALE-UP**

**NGONIDZASHE MADIDI**  
IAVI/formerly PSI Zimbabwe

# ANNEXES

# ANNEX I: ENABLING ACTIVITIES

The following annex outlines activities that will improve the product introduction process but are not critical to product introduction. In order to focus on activities that are essential to product introduction, these “enabling” activities are presented separately. Pending resource availability, it is highly recommended that stakeholders consider carrying out these activities. However, priority should be given to the critical pathway activities outlined in the main body of this framework.

While this document aims to provide a clear recommendation on which activities are critical, authors recognize that individual products have unique attributes and needs. Enabling activities should be carefully evaluated to consider if these should be elevated to become a critical activity for the given product.

## 1 PRIOR TO REGULATORY APPROVAL

The following outlines activities that will support an efficient product introduction process and should be carried out prior to regulatory approval:

### Clinical Research & Regulatory Approval



#### 1T / PLAN AND BUILD CAPACITY FOR NORMATIVE & REGULATORY EVALUATION

##### Inputs

Capacity building for normative and regulatory evaluation (i.e. WHO CRP) should be informed by the NMRA strategy developed ([1G](#)).

##### Outputs

Biomedical prevention products are evaluated through innovative, complex trial designs, which will require NMRAs to develop additional capacity to efficiently evaluate applications. As each new HIV prevention product hits the market, NMRAs will likely be increasingly prepared to evaluate new applications. However, stakeholders should consider whether additional resources are needed to ensure that the WHO normative and collaborative/regional regulatory bodies can effectively coordinate decision-making with NMRAs and prepare for the review.

##### Dependencies

Capacity building will support more efficient evaluation processes for future pipeline products but has no critical dependencies.



**CAPACITY BUILDING WILL SUPPORT MORE EFFICIENT EVALUATION PROCESSES FOR FUTURE PIPELINE PRODUCTS**

## Costing & Modeling



### 1U / PRIOR TO INTRODUCTION, UNDERSTAND THE ADDED COSTS OF INTRODUCING THE PRODUCT INTO THE CURRENT LANDSCAPE

#### Inputs

This analysis will be based on early-stage research to understand how the new product could be integrated into delivery mechanisms ([1P](#), [1Q](#)).

#### Outputs

After understanding how the new product could be integrated into delivery mechanisms ([1Q](#)), a cost analysis will inform an initial understanding of which added costs should be expected for product integration. This may differ between channels, including private versus public channels.

#### Dependencies

This pre-regulatory cost analysis will help prioritize which channels need to be piloted in early phase implementation projects ([2K](#)), but this is not a prerequisite to these projects beginning.

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### 1V / DEVELOP INVESTMENT CASE AND ADVOCATE FOR DEMAND GENERATION

#### Inputs

This activity should be based on stakeholder consultations and the demand generation approach defined through HCD ([1AC](#)).

#### Outputs

Metrics to track the effectiveness of marketing approaches and communication strategies will have to be developed to take into account the different needs of donors, governments, and programs. These will need to fit into routine data collection wherever possible. To do this and provide a comprehensive marketing approach, research budgets and resources must be allocated to test these strategies. In general, this should be incorporated into the overall service delivery cost. However, experience with oral PrEP and other products has shown demand generation and marketing have been major gaps in terms of focus and funding. To overcome these obstacles, this activity will primarily consist of defining what information is needed to establish an investment case.

#### Dependencies

This activity will increase the likelihood of generating sufficient resources for evidence-based demand-generation.

## 1W / ANALYSIS AND ADVOCACY ON DONOR SUPPORT FOR PRODUCT INTRODUCTION

### Inputs

This analysis and advocacy should be informed by pricing and costing activities (1J, 1M), need estimates (1L), and modeling of epidemic impact (1N).

### Outputs

As the product moves closer to the introduction, the field will need to understand major donors' appetites to fund introduction. Different donors may also have specific requirements around cost, cost-effectiveness, target populations, etc.

### Dependencies

An analysis of donor support would inform demand forecasting efforts (2G, 2H), planning for service delivery, and civil society engagement. It could also be used by advocates to highlight the need for additional resources if funding is limited.

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## 1X / CONSOLIDATE COST-EFFICIENCY INFORMATION FOR EXISTING BIOMEDICAL HIV PREVENTION PRODUCTS

### Inputs

This analysis should be based on costing studies for existing biomedical HIV prevention products.

### Outputs

To ensure the new product can be evaluated against existing biomedical HIV prevention interventions, information on cost-efficiency should be analyzed and consolidated. Where possible, this information should include time-motion studies that estimate the time involved in dispensing a product to inform facility costs. Differential adherence and acceptability should be considered in this analysis. While the cost of products will change over time, this analysis will provide preliminary information on the price the market will bear.

### Dependencies

The directional estimates can inform subsequent pricing and cost-related activities.

## Delivery & Implementation



### 1Y / GLOBAL IMPLEMENTATION TOOLKIT PLANNING

#### Inputs

It will be important for a global authority, such as WHO, to begin developing consolidated delivery guidance quickly after clinical trials. As such, planning for this toolkit should begin pre-approval.

#### Outputs

The toolkit should include a basic framework/example templates for countries to develop clinical guidelines and clear guidance on steps of care for the product. Additionally, the toolkit should include information on client flow and filing systems at facilities, addressing common facility-level challenges experienced with existing HIV prevention products. Additionally, the toolkit should include guidance on monitoring indicators ([1Y.i](#)) and clinical management ([1Y.ii](#)).

#### Dependencies

A global implementation toolkit will be important in translating lessons from previous products, consolidating clinical recommendations, and aligning early phase implementation projects ([2K](#)) around consistent monitoring and evaluation measures.

### 1Y.i / GLOBAL CONSENSUS ON MONITORING INDICATORS

#### Inputs

It will be critical to build this activity on the progress already made with the monitoring of other biomedical HIV prevention products.

#### Outputs

Ahead of early phase implementation projects, global authorities, including WHO and UNAIDS, should convene a consultation group comprised of biomedical HIV prevention implementers, FP implementers, MoH representatives, and clinical trial representatives to draft guidance to define initial best practices for monitoring and evaluation (M&E) for the new product and M&E issues that need further exploration in early phase implementation projects ([2K](#)). The consultation should focus on defining essential indicators for target setting, measuring impact, and monitoring additional clinical or safety considerations.

#### Dependencies

This activity will feed into target setting and impact measurement activities ([3B](#)) and IT system guidance ([2M](#)). Additionally, this activity will help align early phase implementation projects ([2K](#)) around consistent measures for success.

## 1Y.ii / DEVELOP CLEAR PATIENT MONITORING GUIDELINES FOR HEALTHCARE PROVIDERS REGARDING MANAGEMENT OF PATIENTS WHO ARE LOST TO FOLLOW-UP

### Inputs

Relevant technical assistance stakeholders should consult country policymakers on any specific apprehensions, so these can be considered in guidance before early phase implementation. Additionally, guidelines should be informed by approaches developed through HCD on providers ([1AA](#)).

### Outputs

Following Phase III trials ([1E](#)) and any additional clinical research ([2E](#)), guidance should be provided to define categories of use (e.g. what constitutes “delayed use” versus LTFU) and provider actions that should be initiated based on client data. Experience from oral PrEP has shown that countries are eager to understand baseline testing and additional monitoring requirements (i.e. creatinine testing).

### Dependencies

This activity will feed into consensus on monitoring indicators ([1Y.i](#)).

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## 1Z / CLEARINGHOUSE AND MONITORING OF EARLY CLINICAL FINDINGS AND IMPLEMENTATION GUIDELINES

### Inputs

This activity will receive input from implementation projects and early TA efforts ([2J](#), [2K](#)).

### Outputs

Based on experience with oral PrEP and other new innovations in global health, global stakeholders can anticipate that a new product will spur a wide number of early publications. To enable implementers and national programs to quickly incorporate early learnings into practice, a global clearinghouse would be useful to quickly compile and distribute findings. As funding is available, the clearinghouse could disseminate major clinical findings before regulatory and normative approval, so countries can more rapidly evaluate these findings (concurrently to a formal SRA and WHO). Beyond collecting and disseminating findings, the partner leading this activity should also aim to provide top-line guidance about how findings or publications will impact implementation and provider messaging. Importantly, the clearinghouse should play a role in coordinating partners, decreasing duplication of efforts between partners, and supporting implementers to publish and disseminate their findings. This activity needs to be ongoing to best serve implementing partners and ensure the information on biomedical prevention products is continually updated as more evidence is compiled.

### Dependencies

The clearinghouse should inform scale-up TA efforts ([3C](#)) and share lessons from different country contexts.



## Individual Uptake & Continued Use



### 1AA / CONDUCT HCD RESEARCH ON ENABLING ENVIRONMENTS: PROVIDER ATTITUDES & PREFERENCES

#### Inputs

This activity should take into account the growing body of evidence about the need for empathy from providers to support client uptake and continued use.

#### Outputs

Looking at community healthcare workers (CHW) and medical providers (nurses and doctors) as one of the 'end-users' of prevention, this research should seek to understand the CHW and providers' behavioral and emotional drivers and barriers to providing prevention products. Where possible, this research should disaggregate cadres of providers, be product agnostic, and build off experience with existing products. Researchers should anticipate that there will also be product-specific behaviors.

#### Dependencies

This information will feed into developing and piloting training approaches to improve how providers and CHW talk about prevention, overcome personal biases in delivery, and provide empathetic services ([2K](#)). It will also feed into costing and health facility assessments ([1U](#), [1Q](#)).

### 1AB / CONDUCT HCD RESEARCH ON ENABLING ENVIRONMENTS: COMMUNITY ENGAGEMENT

#### Inputs

This activity should build off existing research in the space. This activity should be further informed by the CABs and community user groups ([1R](#)).

#### Outputs

Looking at the broader community and guardians, particularly those who may not be likely candidates for the product, this research should seek to understand how enabling environments for both the prescription and use of prevention products will facilitate uptake and mitigate barriers at a client level. The research should identify opportunities to improve product literacy and to ensure active community participation throughout the process of bringing a product to market.

#### Dependencies

This research will inform the demand-generation approach ([1AC](#)).

## 1AC / CONDUCT HCD RESEARCH WITH PRIORITY POPULATIONS AND DEFINE A DEMAND GENERATION APPROACH FOR THEM

### Inputs

This activity will build off existing research on identified priority populations and effective demand generation approaches.

### Outputs

This research should seek to understand target populations, including how they behave and what they want. It should include identifying distinguishable segments that can be implemented against, knowing how the product fulfills population needs, journey mapping for populations, the size of the segments, and how and what information they want to receive and from whom. Understanding unique selling points per segment will help drive uptake. As relevant, the demand generation approach should consider what additional access platforms are needed to support uptake and use (e.g. providing more broad education, support, client-facing tools that can support HIV prevention decision-making, land information services for adolescent girls and young women (AGYW)).

### Dependencies

It is critical for this research to feed directly into early phase implementation projects ([2K](#)) so projects are prioritizing delivery channels and mechanisms that are acceptable to clients and driven by their preferences.

## 2 AFTER REGULATORY APPROVAL

The following list outlines activities that will support an efficient product introduction process and should be carried out after regulatory approval:

### Costing & Modeling



#### 2M / COUNTRY-SPECIFIC MODELING TO DETERMINE THE OPTIMAL ALLOCATION OF HIV PREVENTION RESOURCES

##### Inputs

This activity will be informed by existing models and will need to consider the country context in terms of resource use, health system capacity, and product preferences.

##### Outputs

As the package of HIV prevention tools grows, countries will have to make decisions about the relative benefit of introducing a new tool to the existing package of services. To support introduction decisions around the new product, donors and countries will need to have access to new or updated mathematical modeling approaches that illustrate how available resources could be allocated across available interventions, risk groups, age groups, and geographies to achieve maximum impact.

##### Dependencies

This will provide a data point to payers about how to prioritize funding for different interventions.

### Delivery & Implementation



#### 2N / IT GUIDANCE ON SYSTEM REQUIREMENTS FOR M&E

##### Inputs

This activity would be a follow-on to the global consensus on monitoring indicators ahead of phased implementation ([1Y.i](#)).

##### Outputs

M&E for oral PrEP has faced challenges in information systems using aggregate data for District Health Information System (DHIS)/MoH tracking. After alignment on indicators for the new product, IT systems requirements will need to be defined in consultation with IT experts and national governments and should be based on program experience with products like oral PrEP and contraceptives. Guidance should also include considerations for anonymity and data security, particularly for key populations, and evaluate country-specific opportunities to bolster electronic medical record systems (EMR).

##### Dependencies

This activity should feed into early-stage technical assistance efforts and scale-up technical assistance ([2J](#), [3C](#)).

## Individual Uptake & Continued Use



### 20 / STUDY END-USER PREFERENCES, ONCE THE PRODUCT IS AVAILABLE

#### Inputs

This activity should come as a follow-on to initial HCD research conducted before product availability ([1AA](#), [1AB](#), [1AC](#)).

#### Outputs

Additional research should aim to better understand acceptability, product preferences, and preferred delivery channel/entry points. Studies should include a discrete choice experiment on how an injectable meets the desires and preferences of the target population.

#### Dependencies

This will inform an understanding of potential uptake and provide additional insights for a demand forecast ([2H](#)).

# ANNEX II: ACTIVITY CHECKLIST

This document presents an overarching product introduction framework that can be adapted to support the introduction of future HIV prevention products.<sup>1</sup> The following annex is intended to serve as a checklist to allow the user to review how various introduction activities are being taken forward for each product and to record notes about how activities need to be adapted to meet the unique needs and attributes of each product.

- › [Activities to begin prior to Stringent Regulatory Authority approval](#)
- › [Activities to begin after Stringent Regulatory Authority approval](#)
- › [Activities to begin during LMIC scale-up](#)

## 1 PRIOR TO REGULATORY APPROVAL

Critical Pathway Activities		
ACTIVITY	POTENTIAL FUNDERS/LEADS	STATUS/OTHER CONSIDERATIONS
1A. Assess opportunities for manufacturability for LMICs		
1B. Develop a generic supplier engagement and access strategy		
1C. Transfer technology to generic manufacturer		
1D. Engage with major procurers to determine optimal product packaging		
1E. Design clinical trials to include most impacted populations		
1F. Develop a global regulatory strategy for stringent regulatory authority (SRA) and World Health Organization prequalification (WHO PQ)		
1G. Develop a strategy for achieving approval from National Medicines Regulatory Authorities (NMRAs)		

<sup>1</sup> **Note:** While this adaptable product introduction framework primarily focuses on biomedical HIV prevention products, readers are encouraged to consider how this framework can be used as a starting point for other products, including multi-purpose prevention technologies (MPTs).

## Critical Pathway Activities, continued

ACTIVITY	POTENTIAL FUNDERS/LEADS	STATUS/OTHER CONSIDERATIONS
1H. Establish clear pharmacovigilance (PV) plans to monitor resistance and safety in critical populations		
1I. Plan for safety studies for additional populations		
1J. Define LMIC Price Ranges		
1K. Understand priority populations and geographies for product introduction		
1L. Define an LMIC need estimate		
1M. Conduct COGs analysis		
1N. Model epidemic impact of product introduction across multiple end-points		
1O. Model worst-case scenario magnitude and consequences of resistance		
1P. Assess health system capacity and delivery mechanisms		
1Q. Conduct health facility assessments to define integration approach		
1R. Establish or engage community advisory boards (CABs) and community user groups		
1S. Conduct market research on user preferences		

Enabling Activities		
ACTIVITY	POTENTIAL FUNDERS/LEADS	STATUS/OTHER CONSIDERATIONS
1T. Plan and Build Capacity for Normative and Regulatory Evaluation		
1U. Prior to introduction, understand the added costs of introducing the product into the current landscape		
1V. Develop investment case and advocate for demand generation		
1W. Analysis and advocacy on donor support for product introduction		
1X. Consolidate cost-efficiency information for existing biomedical HIV prevention products		
1Y. Global implementation toolkit planning		
1Y.i. Global consensus on monitoring indicators		
1Y.ii Develop clear patient monitoring guidelines for healthcare providers regarding management of patients who are lost to follow-up (LTFU)		
1Z. Clearinghouse and monitoring of early clinical findings and implementation guidelines		
1AA. Conduct HCD research on enabling environments: provider attitudes and preferences		
1AB. Conduct HCD research on enabling environments: community engagement		
1AC. Conduct HCD research with priority populations and define a demand generation approach for them		

## 2 AFTER REGULATORY APPROVAL

Critical Pathway Activities		
ACTIVITY	POTENTIAL FUNDERS/LEADS	STATUS/OTHER CONSIDERATIONS
2A. Develop global procurement strategy and alignment		
2B. Complete country registration for innovator product		
2C. Support development of WHO guidance for early phase implementation projects		
2E. Active PV for additional safety concerns		
2F. Conduct safety studies amongst additional populations		
2G. Conduct demand-based forecasting studies		
2H. Develop LMIC demand forecast for new product		
2I. Implement market-shaping interventions and support affordability		
2J. Early product introduction support & technical assistance (TA)		
2K. Conduct phased implementation projects with priority populations, geographies, and delivery channels		
2L. Understand acceptability and desirability of a new product (alone and versus existing products)		
Enabling Activities		
ACTIVITY	POTENTIAL FUNDERS/LEADS	STATUS/OTHER CONSIDERATIONS
2M. Country-specific modeling to determine the optimal allocation of HIV prevention resources		
2N. IT guidance on system requirements for impact M&E		
2N. Study end-user preferences, once the product is available		



### 3 SCALE-UP OF PRODUCT IN LMICS

Critical Pathway Activities		
ACTIVITY	POTENTIAL FUNDERS/LEADS	STATUS/OTHER CONSIDERATIONS
2A. Support WHO development of global normative guidance for scale-up		
2B. Include product in national target-setting and budgeting tools for PrEP method mix		
2C. Strategy development and TA to bring early phase implementation projects to scale		

# ANNEX III: WHO EVIDENCE TO DECISION FRAMEWORK

To inform evidence required for WHO guidelines, the following annex is an excerpt from:

The WHO-INTEGRATE evidence to decision framework version 1.0: Integrating WHO norms and values and a complexity perspective<sup>1</sup>

## ABSTRACT:

**Introduction:** Evidence-to-decision (EtD) frameworks intend to ensure that all criteria of relevance to a health decision are systematically considered. This paper, part of a series commissioned by the WHO, reports on the development of an EtD framework that is rooted in WHO norms and values, reflective of the changing global health landscape, and suitable for a range of interventions and complexity features. We also sought to assess the value of this framework to decision-makers at global and national levels, and to facilitate uptake through suggestions on how to prioritise criteria and methods to collect evidence.

**Methods:** In an iterative, principles-based approach, we developed the framework structure from WHO norms and values. Preliminary criteria were derived from key documents and supplemented with comprehensive subcriteria obtained through an overview of systematic reviews of criteria employed in health decision-making. We assessed to what extent the framework can accommodate features of complexity, and conducted key informant interviews among WHO guideline developers. Suggestions on methods were drawn from the literature and expert consultation.

**Results:** The new WHO-INTEGRATE (INTEGRATE Evidence) framework comprises six substantive criteria—balance of health benefits and harms, human rights and sociocultural acceptability, health equity, equality and non-discrimination, societal implications, financial and economic considerations, and feasibility and health system considerations—and the meta-criterion quality of evidence. It is intended to facilitate a structured process of reflection and discussion in a problem-specific and context-specific manner from the start of a guideline development or other health decision-making process. For each criterion, the framework offers a definition, subcriteria and example questions; it also suggests relevant primary research and evidence synthesis methods and approaches to assessing quality of evidence.

**Conclusion:** The framework is deliberately labelled version 1.0. We expect further modifications based on focus group discussions in four countries, example applications and input across concerned disciplines.

<sup>1</sup> Rehfuess EA, Stratil JM, Scheel IB, et al. The WHO INTEGRATE evidence to decision framework version 1.0: integrating WHO norms and values and a complexity perspective. *BMJ Glob Health* 2019;4:e000844. doi:10.1136/bmjgh-2018-000844. [\[Link\]](#)

TABLE S2. WHO-INTEGRATE FRAMEWORK VERSION 1.0: CRITERIA WITH DETAILED DEFINITIONS AND IMPLICATIONS FOR A RECOMMENDATION, SUB-CRITERIA AND EXAMPLE QUESTIONS

CRITERIA	SUB-CRITERIA
Balance of health benefits and harms	Efficacy or effectiveness on health of individuals
	Effectiveness or impact on health of population
	Patients'/beneficiaries' values in relation to health outcomes
	Safety-risk-profile of intervention
	Broader positive or negative health-related impacts
Human rights and socio-cultural acceptability	Accordance with universal human rights standards
	Socio-cultural acceptability of intervention to patients/ beneficiaries and those implementing the intervention
	Socio-cultural acceptability of intervention to the public and other relevant stakeholder groups
	Impact on autonomy of concerned stakeholders
	Intrusiveness of intervention
Health equity, equality, and non-discrimination	Impact on health equality and/or health equity
	Distribution of benefits and harms of intervention
	Affordability of intervention
	Accessibility of intervention
	Severity and/or rarity of the condition
	Lack of a suitable alternative
Societal implications	Social impact
	Environmental impact
Financial and economic considerations	Financial impact
	Impact on economy
	Ratio of costs and benefits

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TABLE S2. WHO-INTEGRATE FRAMEWORK VERSION 1.0: CRITERIA WITH DETAILED DEFINITIONS AND IMPLICATIONS FOR A RECOMMENDATION, SUB-CRITERIA AND EXAMPLE QUESTIONS

CRITERIA	SUB-CRITERIA
<b>Feasibility and health system considerations</b>	<b>Legislation</b>
	<b>Leadership and governance</b>
	<b>Interaction with and impact on health system</b>
	<b>Need for, usage of and impact on health workforce and human resources</b>
	<b>Need for, usage of and impact on infrastructure</b>
<b>Meta-criterion: Quality of evidence</b>	