GAP·f
Global Accelerator for Paediatric formulations
WHO Hosted Network

World Health Organization

# AGNOSTIC TOOLKIT FOR INTRODUCTION OF A NEW PRODUCT FOR CHILDREN

A guide to support the introduction of a new product in country for children

## ACRONYMS

| | |
|---|---|
| AGREE | Appraisal of guidelines, research and evaluation |
| CAB | Community advisory board |
| CALHIV | Children and adolescents living with HIV |
| CHAI | Clinton health access initiative |
| CPP | Certificate of pharmaceutical product |
| CRP | Collaborative registration procedure |
| DALY | Disability adjusted life year |
| DTG | Dolutegravir |
| EMA | European Medicines Agency |
| EPR | European Paediatric Regulation |
| EU | European Union |
| FDA | Food and Drug Administration |
| FPP | Finished pharmaceutical product |
| GF | The Global Fund |
| GAP-f | Global Accelerator for Paediatric Formulations |
| IEC | Information, education and communication |
| ICAP | International Center for AIDS Care and Treatment Program |
| LMICs | Low- and middle-income countries |
| MoH | Ministry of Health |
| NRA | National Regulatory Authority |
| PASS | Post-authorization safety studies |
| PMTCT | Prevention of mother to child transmission |
| PREA | Paediatric Research Equity Act |
| PrEP | Pre-exposure Prophylaxis |
| RCT | Randomised Clinical Trial |
| RMP | Risk Management Plan |
| RWD | Real World Data |
| RWE | Real World Evidence |
| SCEM | Specialist cohort event monitoring |
| SRA | Stringent Regulatory Authority |
| TB | Tuberculosis |
| UNAIDS | The Joint United Nations programme on HIV/AIDS |
| UNICEF | United Nations Children's fund |
| WHA | World Health Assembly |
| WHO | World Health Organisation |

# INTRODUCTION

Children have been left behind when it comes to introduction of new medicines for better clinical management and improved prognoses for children.

Introduction of a new product requires significant investments in advocacy, engagement and planning as well as guideline development and training.

The purpose of this disease agnostic toolkit is to support countries to develop an implementation plan to introduce a new product for children that is financially viable and sustainable. It is meant to serve as a guide and is by no means prescriptive.

Prior to introducing a new pharmaceutical product, there needs to be consensus that the product is required. CHAI has put together a valuable '5' lenses approach to assist in the decision making process:

i) Clinical benefit
ii) Convenience
iii) Cost
iv) Availability
v) Program complexity

Patient Level

Program Level

If the benefits of the new product outweigh current standard of care, a rights-based approach should be used whereby LMICs should be supported to access the product through generic manufacturers as well as pooled procurement so that it is accessible.

The toolkit comes in once the product has been approved by WHO/Stringent regulatory authority (SRAs) for global use and is included in the global recommendations for treatment of the disease in children. It **assumes** that indications, dosing guidance and safety data for use in children will be available.

The resources in this "agnostic" toolkit should be used to develop a product specific rollout plan. Elements of that plan could include:

- Disease specific: burden, prognosis, treatment options etc.
- Product specific: classification, safety and efficacy, paediatric dosing, FDA/EMA/SRA/NRA approval.
- Product specific tools for each step of the rollout developed from the resources provided.
- Any specific country nuances.

This toolkit is proposed as a living document expected to evolve as additional tools and resources become available. The toolkit defines a series of steps which can be initiated concurrently or consecutively as felt appropriate by the country leadership and team.

- Step 1. Community and other Stakeholder Engagement
- Step 2. In Country Registration
- Step 3. Revision of National Guidelines
- Step 4. Planning and Budgeting
- Step 5. Quantification
- Step 6. Procurement and Supply Chain
- Step 7. Health care provider capacitation
- Step 8. Demand Creation
- Step 9. Pharmacovigilance
- Step 10.Tracking and Impact

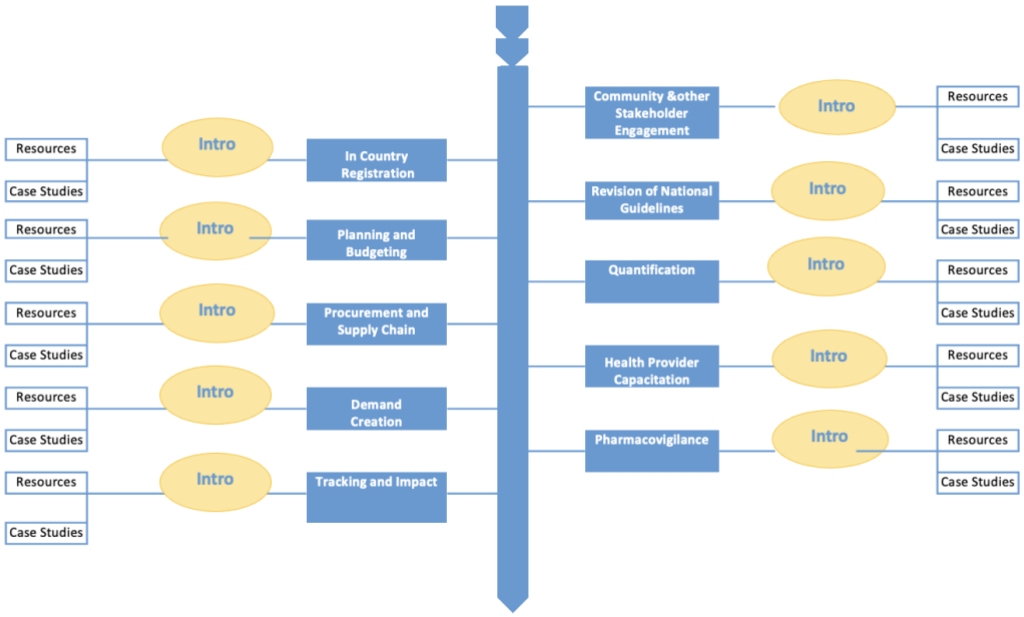


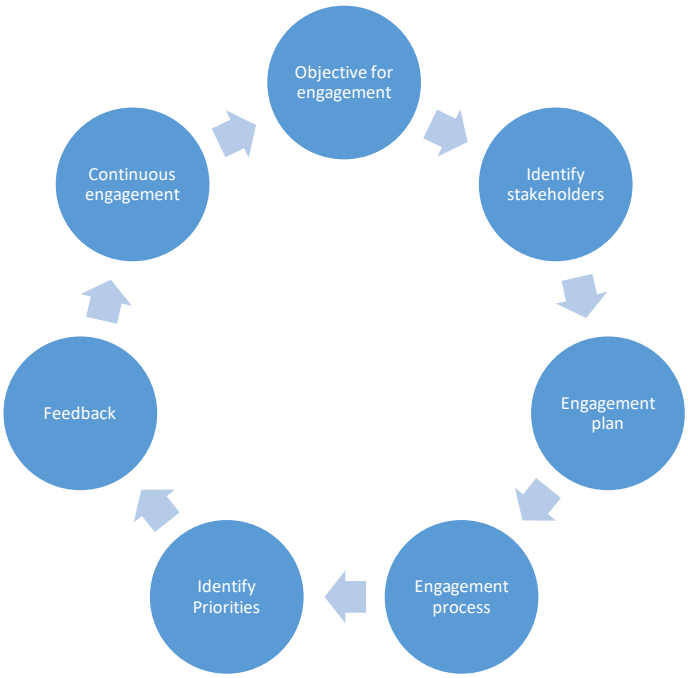

***Fig: Schema of the agnostic toolkit***

# CHAPTER 1: COMMUNITY AND OTHER STAKEHOLDER ENGAGEMENT

## 1.1 INTRODUCTION

Stakeholder engagement is an essential part of the approval and regulatory process in country and could be started prior to the regulatory process for the new product. There needs to be clear stated objectives for the engagement which could include creating awareness and advocacy; inclusion in the national management guidelines; rollout and possible funding opportunities to support procurement; train health care providers; support the transition to the new product, etc.

Parents, caregivers, and patients themselves are strong advocates for better medicines and management for their illness and their involvement can streamline drug development globally and approvals in country, ensure the time taken from regulatory approval to registration is shortened, create demand, and inform on the post marketing surveillance.




***Fia: Enaaaina Stakeholders***

Involving community and traditional leaders who have influence over the community can help increase awareness on the new product as well as validate the use.

For each product under consideration, before starting with stakeholder engagement, there is a need to map out the interested parties. The ministry of health could include relevant colleagues from, civil society, community and traditional leaders, community advisory boards, patients, parents, caregivers, patient advocacy organisations, clinical specialists, health care institutions- clinics and hospitals, health care researchers and academic institutions, technical working groups, professional associations, health care industry representatives, health policy makers, funders.

A stakeholder engagement plan will help identify priorities for each stakeholder to support advocacy, adoption, and demand generation for the new product.

The engagement process should include informing the stakeholders, consulting with them on the next steps and ascertaining that the new product is needed, involving them in the decisions and
collaborating with them to ensure the process is sustainable.

The key points to note are that regardless of the group being engaged is to use the same process, be inclusive, maintain good communication, transparency, be respectful of

priorities and expectation of outcomes. This will help the continued engagement and feedback post registration and usage of the new product for post market surveillance.

## 1.2 RESOURCES AND TOOLS

| Tool | Description | Tool Reference and Link |
|---|---|---|
| A stakeholder engagement method navigator webtool for clinical and translational science | The Stakeholder engagement navigator tool is a web based interactive and user centered tool which educates and guides investigators to select the most appropriate engagement method for their study. It uses various criteria including purpose of engagement, budget, time per stakeholder engagement and number of interactions. Purpose of engagement was ranked the highest. It is useful for researchers to identify the best method to engage stakeholders for clinical and translational research. The tool is available at DICEMethods.org. | Kwan BM, Ytell K, Coors M, DeCamp M, Morse B, Ressalam J, Reno JE, Himber M, Maertens J, Wearner R, Gordon K, Wynia MK. A stakeholder engagement method navigator webtool for clinical and translational science. J Clin Transl Sci. 2021 Sep 13;5(1): e180. doi: 10.1017/cts.2021.850. PMID: 34849255; PMCID: PMC8596067. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8596067/ |
| CHAI Stakeholder Mapping for Treatment Optimization_2017 | This is a mapping tool which helps to categorize stakeholders in terms of type of engagement- advocacy, policy, adoption, planning, etc. It also has a Gantt chart which can help to plot the timeline of engagement and the number of interactions. | https://clintonhealth.app.box.com/s/0rtkg3ehakvx92nzi13d1xlg8x6iq0xf |
| ITPC ACT (Advocacy for Community Treatment) Toolkit 2.0. Strengthening Community responses to HIV treatment and Prevention | The purpose of the Advocacy Community treatment toolkit is to train and engage community activists and other key stakeholders for advocating for equitable access to antiretroviral therapy for all populations including key populations. This tool could be used as a template or guide to develop advocacy for neglected and orphan diseases. | https://itpcglobal.org/wp-content/uploads/2015/02/ACT-Toolkit-2.0.pdf |
| UNICEF. Minimum Quality Standards and Indicators for Community Engagement | This is a good document to use for a rights-based approach to community engagement. There is a useful checklist to adopt for community engagement (Page 51-60). | https://www.unicef.org/mena/media/8401/file/19218_MinimumQuality-Report_v07_RC_002.pdf.pdf |
| Community Engagement Toolkit. University of North Dakota, Center for Rural Health. | This toolkit describes the process of engaging a community, laying out first that the user needs to understand that every community is different, and the responses may vary. It has five modules starting with finding a common mission, defining the problem, planning, implementation and evaluation and sustainability of the change. It also includes worksheets and activities, e.g., how to develop a sustainability plan with the community. | https://ruralhealth.und.edu/assets/375-1008/community-engagement-toolkit.pdf |

## 1.3. CASE STUDIES

### 1.3.1 Malawi Treatment CAB Case Study

AfroCab played a key role working with communities and multiple stakeholders in Malawi to increase awareness and successful adoption and rollout of pDTG. They even developed a monitoring framework to identify challenges e.g. stockouts and lack of training among the health care providers at the facility level and worked closely with the MOH to address these issues.
https://clintonhealth.app.box.com/s/f5tw51eded1xeslf0cqnlgkajmn5yk6i

### 1.3.2 Successful community engagement through the Community Advisory Board (CAB) at KEMRI Centre for Global Health, Kenya

The CAB successfully engaged the community to introduce Cabotegravir for PrEP using patient educators.
https://www.hptn.org/news-and-events/featurestories/communityengagement

### 1.3.3 Stakeholder engagement responsible for the first ever treatment for Primary Hyperoxaluria

Primary Hyperoxaluria (PH1) is a severe rare genetic condition which causes overproduction of oxalate due to a defect in the Alanine Glyoxylate Aminotransferase enzyme. Using the FDA patient focused drug development initiative, stakeholder engagement was done in Oct 2020, leading to the accelerated approval of the first ever treatment for primary hyperoxaluria.
https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-rare-metabolic-disorder

https://ohf.org/wp-content/uploads/2022/02/FINAL-VOP_Primary-HyperoxaluriaReport-compressed.pdf

# CHAPTER 2: IN COUNTRY REGISTRATION

## 2.1 INTRODUCTION

For a pharmaceutical product to be available and accessible to the population, it needs to be registered by the national regulatory authority (NRA). Each NRA has their own requirements in terms of the documentation that needs to be submitted. In some countries, this function is carried out by the stringent regulatory authority (SRA).

The NRAs that participated in the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) until 2015 are considered SRAs by the Global Fund and WHO. These are considered to apply stringent standards for quality, safety and efficacy during their regulatory review of drugs and vaccines for marketing authorization.

In 2013, WHO introduced a collaborative registration procedure (CRP) for accelerating registration of prequalified finished pharmaceutical products (FPPs) through information sharing between WHO prequalification and the NRA. Countries could speed up registration of products by utilizing the assessments and inspection outputs already produced by WHO.

In 2016, this was revised to include products that had been approved by an SRA, as it was found to reduce the time taken for approval, promote collaboration, allow regulatory convergence and build capacity in the country.

For the registration of a new product, the following list (not all inclusive) of items need to have been submitted with the NRA.

- Product dossier filed by the manufacturer.
- Clinical trial data: safety, efficacy, dosing for drugs/formulation (age/weight bands)
- FDA/EMA/SRA approval
- Inclusion in WHO/other global guidelines
- WHO pre-qualification
- CPP- Certificate of Pharmaceutical Product issued by a country's regulatory authority at the request of a product owner or sponsor to support the registration process using another regulatory authority's approval.
- Product sample
- Manufacturer dossier on quality assurance for each raw product and capacity to meet demand.
- Fees

The MOH and other stakeholders need to check in regularly with the NRA to ensure any bottlenecks are addressed in a timely manner otherwise the process can be delayed.

## 2.1. RESOURCES AND TOOLS

| Tool | Description | Tool Link |
|---|---|---|
| CHAI HIV New Product Introduction Toolkit | Guidance for stakeholders on introduction of a new HIV medication/formulation in country, outlines the key steps in detail for registration and has a defined checklist to monitor and support the MoH and | https://www.newhivdrugs.org/registration |

| | | |
|---|---|---|
| | stakeholders when a product introduction is delayed. | |
| Registration of a new pharmaceutical product | Guidance on requirements for new drug registration in South Africa. It takes the reader through the process of registration and evaluation of the new product in South Africa. | https://www.sahpra.org.za/orthodox-medicines/#:~:text=All%20new%20medicine%20applications%20need,included%20in%20the%20relevant%20sections. |
| Global fund quality assurance policy for pharmaceutical products | Useful resource to support quality assurance of the product being registered. It includes guidance for in country monitoring of quality assurance of pharmaceutical products as well as assessing laboratory proficiency to do quality control of pharmaceutical products. | https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/ |
| WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems of medical products, revision VI. Geneva: World Health Organization; 2021. License: CC BY-NC-SA 3.0 IGO. | The GBT helps to categorise the maturity level of the country regulatory system from 1 to 4, 1 having some elements of a regulatory system and 4 being at the highest level of performance and continuous improvement. The tool has several sub indicators with descriptions on what is expected to consider achievement which helps to guide the assessor in their evaluation. The tool and the methods used helps WHO, the assessors and the country to identify areas that need strengthening and improvement and help to develop an institutional development plan (IDP) to address the gaps and build on their strengths and is useful for monitoring progress. | https://iris.who.int/bitstream/handle/10665/341243/9789240020245-eng.pdf?sequence=1 |

## 2.3 CASE STUDIES

### 2.3.1 Successful Registration of Dispersible Amoxicillin in Ghana

The MoH in Ghana in collaboration with UNICEF is implementing the SPRINT (Scaling Pneumonia Response Innovations) initiative to reduce deaths from pneumonia among children through scaling up pneumonia treatment with amoxicillin dispersible tablets (DT) and oxygen through a health systems strengthening approach. The MoH advocated with the Ghana FDA to allow registration of the new product using WHO guidance and the evidence that the dispersible tablets would improve adherence to treatment and completion of the course, leading to the approval for Amoxicillin DT. It has since been included in the essential medicines list and in the standard treatment guidelines.

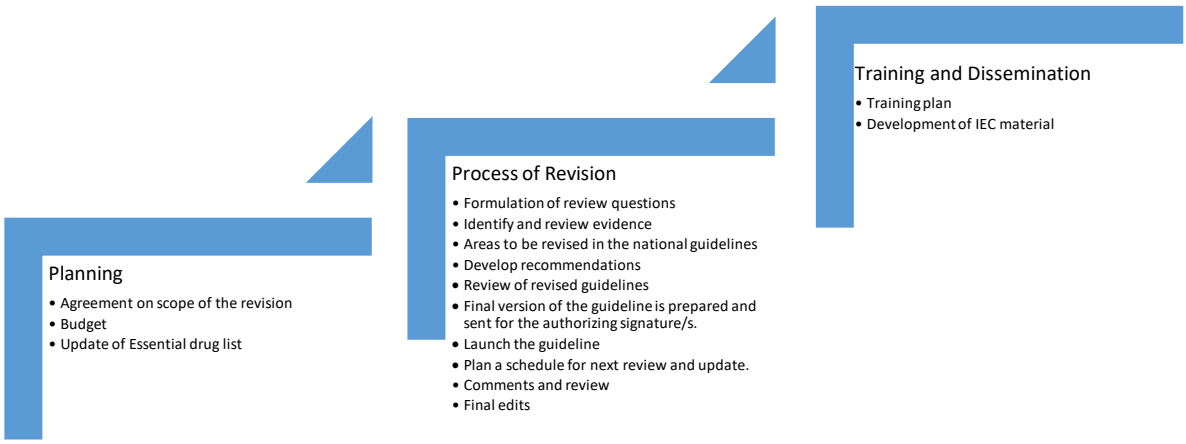
Ministry of Health Ghana. Scaling Pneumonia Response Innovations (SPRINT) Project Report. March 2021. Page 5-7

# CHAPTER 3: REVISION OF NATIONAL CLINICAL MANAGEMENT GUIDELINES

## 3.1. INTRODUCTION

To validate the usage of a new product in country, it needs to be included in the national clinical management guidelines for the disease. This is done in collaboration with the MoH, relevant program and technical specialists, academia, researchers and civil society.

A thorough review of current guidelines needs to be undertaken before a revision is undertaken to determine the scope of the revision. The decision-making process should




be inclusive with the Ministry of Health inviting participation of relevant stakeholders from the community, technical specialists, program managers, implementing partners, non-governmental organisations, academia and researchers.

***Fig: Process of revision of guidelines***

There needs to be agreement on the following:

- Scope of the revision
    - Adoption of new product as per global recommendations
    - Revision of guidelines or a circular with the revised recommendation
    - Style and format of the guidelines
    - Timeline of the revision
- Budget for revision, training, and dissemination
- Timeline of the training and the information, education, and communication (IEC) material that needs to be developed
- Responsibility for the training and development of materials
- Revision of essential drugs list as applicable

A writing committee could be formed through stakeholder representatives (some countries use the technical working group). The process followed can include:

- Formulation of review questions
- Identify and review of evidence
    - Literature including clinical trial data and experience from other countries.
    - FDA/EMA/SRA approval, check for any clauses.

    - WHO and other global recommendations
    - Comparison with current treatment: benefits, side-effects, palatability, adherence, resistance profile etc.
    - Quality of the data
- Review current national guidelines to identify areas that need to be updated.
- Develop recommendations
    - Alignment with National Strategic plan
    - Cost effectiveness of new treatment
    - Research recommendations (expansion of evidence database)
    - Monitoring and evaluation plan
- The revised guidelines are sent for comments to the stakeholders.
- If a circular is being issued, the wording and phrasing should be reviewed to ensure that there is no ambiguity.
- Revisions or clarifications are made as per the review
- Final version of the guideline is prepared and sent for the authorizing signature/s.
- Guidelines launched
- Plan a schedule for next review and update.

### 3.2. RESOURCES AND TOOLS

| Tool | Description | Tool Link |
|---|---|---|
| Clinical Practice Guideline Appraisal Tools (Annex C) | The book itself 'Clinical Practice Guidelines We Can Trust' discusses the quality of the Clinical practice guideline development process and the need to establish standards. It suggests eight standards for adoption to develop trustworthy guidelines "highlighting transparency; management of conflict of interest; systematic review--guideline development intersection; establishing evidence foundations for and rating strength of guideline recommendations; articulation of recommendations; external review; and updating."<br>The book has a list of tools in Annex C which include a provisional instrument for assessing clinical practice guidelines; Appraisal of guidelines for research and evaluation (AGREE); AGREE II (Updated version of AGREE); Cluzeau's "Appraisal Instrument"; Hayward et al.'s "Structured Abstracts of CPGs"; and Shaneyfelt's "Methodological Standards". | https://www.ncbi.nlm.nih.gov/books/NBK209533/<br><br>IOM (Institute of Medicine). 2011. *Clinical Practice Guidelines We Can Trust.* Washington, DC: The National Academies Press. |
| Treatment guidelines and formulary manuals | A great resource for development and revision of guidelines, takes the reader step by step through the process of formulation of the guidelines as well as the essential drug list.<br>Discusses the importance of regular review and update of guidelines and standardizing them. The authors also discuss cost benefit ratios. | https://msh.org/wp-content/uploads/2013/04/mds3-ch17-stgs-mar2012.pdf<br>Management Sciences for Health. 2012. MDS-3: Managing Access to Medicines and Health Technologies. Arlington, |

| | | |
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| | | VA: Management Sciences for Health. Chapter 17 |
| The AGREE II Instrument | AGREE II (Appraisal of Guidelines, Research and Evaluation) instrument was developed to help to standardize guidelines. It evaluates the "methodological rigor and transparency" of the guideline development process. It assesses the quality of the guidelines, provides the strategy for the development of the guidelines and informs what needs to be included and how it should be reported in the guidelines. | https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf Brouwers MC et al., for the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. CMAJ 2010;182: E839-842. |
| UNAIDS. Developing HIV/AIDS treatment guidelines. | This is a UNAIDS tool which guides the reader on the appraisal and development of treatment guidelines targeted specifically to HIV/AIDS. It also identifies gaps in the guidelines that were in circulation which is quite useful for the reader to use to improve the guidelines for their country. | https://data.unaids.org/publications/irc-pub03/developingkm_en.pdf UNAIDS Best Practice Collection, 99.13E, 1999. |
| WHO Handbook for Guideline Development | This handbook was developed by WHO and helps to guide the reader on the planning, development, and publication of WHO guidelines. It includes the method, process, and procedure for development of a WHO guideline meeting WHO standards. | https://iris.who.int/bitstream/handle/10665/145714/9789241548960_eng.pdf?sequence=1 WHO. WHO Handbook for Guideline Development. 2nd Edition 2014. **ISBN:** 978 92 4 154896 0 |

### 3.3. Case Studies

**3.3.1** South Africa 2023 ART Clinical Guidelines for the management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.
The SA 2023 ART clinical guidelines have been updated to include optimization of treatment for all clients including children and infants, there have been changes in timing of viral load and visit schedules to move to a client centred model of care.

https://knowledgehub.health.gov.za/system/files/2023-07/ART%20Clinical%20Guidelines%20Webinar%20-%20%20Session%202%20%281%29.pdf

# CHAPTER 4: PLANNING AND BUDGETING

### 4.1 INTRODUCTION

In preparation for the rollout of the new product, a transition/implementation plan needs to be developed.
The Implementation Plan needs to specify the following:

- Priority population groups for the rollout
- If the transition would be phased with an estimated time frame
- Estimated volume of product with associated budget by year
- Source of financing
    - MoH meeting with treasury on the required budget.
    - Cost-benefit ratio
    - Alternative source of financing (donors, patient interest groups, philanthropic organisations etc.)

There may be current products in use for the clinical management of the disease. To limit wastage of resources, LMICs prefer to use the currently available product unless the old product is ineffective.
Depending on the status and stock of the old product, and budget available, program managers will work with the technical specialists, technical working group and MoH officials to develop a prioritisation matrix highlighting patients/population groups who would have access to the new product first followed by the rest of the population with an associated time frame by which all patients will have access to the new product.
The plan would include planned coverage of the patients by the new product by quarter and year.

Volume of the new product needed by quarter and year needs to be estimated considering the planned coverage, disease burden and incidence of the disease.
An estimated annual budget is then calculated for the time frame of the transition.

MoH needs to meet with the Treasury to discuss the budget needed. They need to communicate the following:

- Advantages of the new product
- Cost-benefit ratio (consider in the long term)
- Difference in costs between the old and new product
- Associated reduced morbidity and mortality.
- Reduced cost to the government due to reduced hospitalisation and disability adjusted life year (DALYs).

The treasury will have to advise the MoH if the transition to the new product is possible in the current financial year or if provision needs to be made to apply for funding through other sources e.g., donors- PEPFAR, Global Fund etc., other governments, philanthropic organisations, non-governmental organisations, disease advocacy groups, etc.

### 4.2 Resources and Tools

| Tool | Description | Tool link |
|---|---|---|
| CHAI Pediatric ARV Forecasting Simple Tool | This is a simple but useful Excel based tool for forecasting quantity of ARVs needed calculation of cost as well of the transition over a period of | https://clintonhealth.app.box.com/s/vlkz0gxlfoexrq63czccdm1welbi8zc0/folder/194975352349 |

| | | |
|---|---|---|
| | three years. There is a paediatric and an adult version of the tool. | |
| ANNEX 9“How-to” guide for forecasting drugs needs and tools for quantification and forecasting.<br><br>Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 2014. Available from: https://www.ncbi.nlm.nih.gov/books/NBK247420/ | A step-by-step guide for National Tuberculosis (TB) control programs to accurately estimate and forecast the volume of medication needed. It also discusses coordination with the public health facilities, national warehouses as well as procurement units to prevent stock outs and facilitate treatment delivery. | https://www.ncbi.nlm.nih.gov/books/NBK247441/ |
| Quantification and Budgeting for Rapid and Sustainable Access to New Pediatric Antiretroviral Therapies EGPAF/UNITAID Oct 2020 | Step by Step guide to early and accurate forecasting of new medication considering what is already available in facilities and at the national level to prevent wastage while transitioning into the new regimen | https://www.pediads.org/wp-content/uploads/2020/11/Pediatric-ARV-Quantification-Budgeting_EGPAF-Unitaid_Jan2021.pdf |

## 4.3. CASE STUDIES

### 4.3.1 Forecasting drug utilization and expenditure: ten years of experience in Stockholm

In a repeated cross-sectional study, predicted pharmaceutical expenditure was compared with actual expenditure over 2007-2018 both for overall drug usage and individual therapeutic groups. Forecasts were reasonably accurate for the same year and showed an increase between 2-8% annually. Introduction of new medications and generics, rate of uptake of new medicines and sudden changes in reimbursement policies affected the accuracy of forecasting.

https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-020-05170-0

### 4.3.2 Forecasting in a Crisis: Using Demand Planning to Prevent Medicine Stock Outs in South Africa's Public Health Supply Chain During the COVID-19 Pandemic

South Africa MoH worked closely with the Global Health Supply Chain program technical support (GHSC-TA) funded through the United States Agency for International Development (USAID) to use demand planning to estimate the country’s medicine requirements during the pandemic to meet health care demand due to increased number of cases during the COVID-19 pandemic.
The forecasts generated were continually updated using data from the technical experts, national and international research. Suppliers used the forecasts to ensure they had enough stock to supply the provinces and there was no shortage of the essential drugs.

https://ghsupplychain.org/news/forecasting-crisis-using-demand-planning-prevent-medicine-stock-outs-south-africas-public

# CHAPTER 5: QUANTIFICATION

## 5.1. INTRODUCTION

Quantification is the process to estimate the volume or quantity of the new product needed within a specified timeframe and when it should be delivered to ascertain that the transition of the new product is sustainable and there are no shortages. It is often calculated with an associated budget.
Forecasting is the procedure of estimating the quantity of new product that is needed or will be used within a specified timeframe.
Hence, quantification uses both forecasting and supply planning.

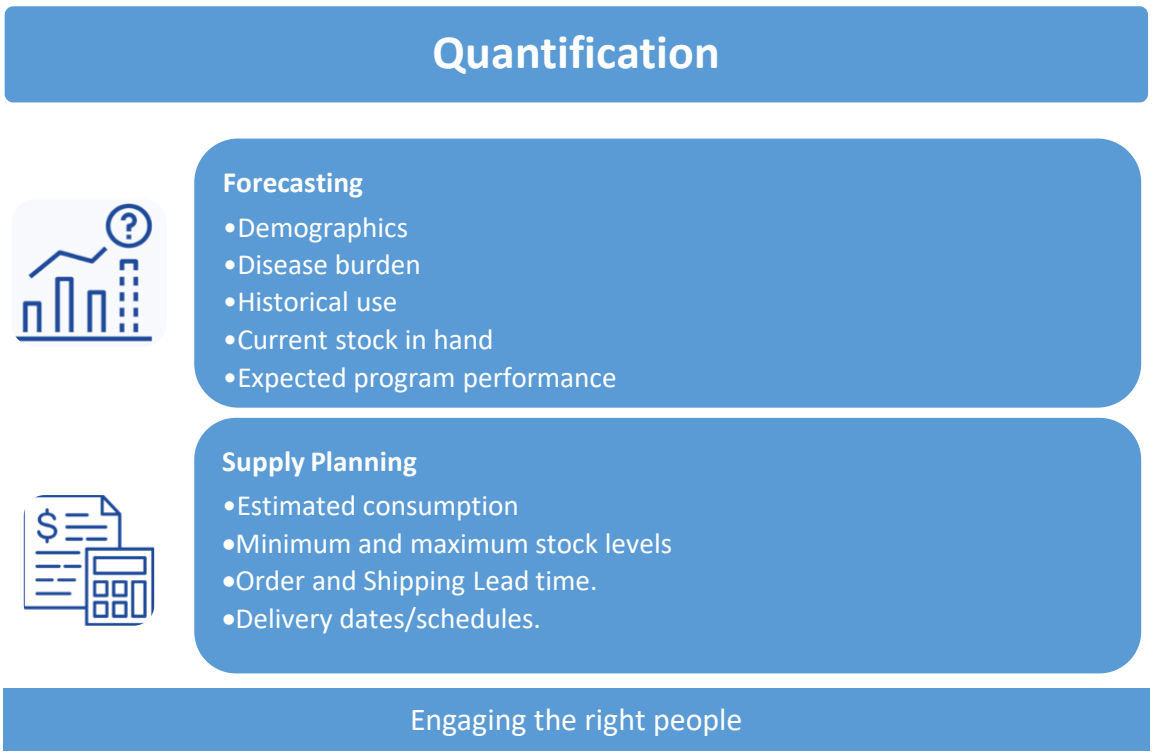


***Fig: Quantification steps***

To forecast accurately, the following need to be evaluated:

- Demographics
- Historical use of the current product by year
- Current product stock in hand, procurement pipeline, and estimated usage
- Burden of unmet need
- Expected program performance (improved diagnosis, etc.)

In addition, the inclusion of the following would be useful:

- Expected rate of roll out/uptake- demand creation.
- Calculation of quantity by age band for medications- adjusting for aging out and weight changes.
- Expected duration of the new treatment for medication

- Assumptions may be needed where data is unavailable or unreliable.

For the transition of the new product to be sustainable, it is important to have a supply plan in place.

The plan needs to include calculation of adequate quantities of the new product and budget required considering the following:

- Estimated consumption of new product.
- Minimum and maximum stock levels for both new and current product.
- Order and Shipping lead time.
- Delivery dates/schedules.

To ensure that the results from the quantification can be used purposefully, it is important to engage the right people which would include statisticians, epidemiologists, technical specialists, pharmacists, program managers, procurement managers and the logistics team at a minimum. International organisations and donors can provide additional support for this exercise, however we need to ascertain that in-country capacity is built as quantification needs to be ongoing to ensure the procurement and supply of the new product is uninterrupted.

### 5.2. RESOURCES AND TOOLS

| **Tool** | **Description** | **Tool link** |
|---|---|---|
| CHAI Pediatric ARV Forecasting Simple Tool | This is a simple but useful Excel based tool for forecasting quantity of ARVs needed calculation of cost as well of the transition over a period of three years. There is a paediatric and an adult version of the tool. | https://clintonhealth.app.box.com/s/vlkz0gxlfoexrq63czccdm1welbi8zc0/folder/194975352349 |
| Guide to forecast medicines and health supplies for reproductive, maternal and child health using different sources of data and information. Ministry of Health of Belize November 2015 | This is a step-by-step guide to ensure that the supply chain for medications for management of reproductive health, maternal and child health is maintained. It goes through which data sources to use for accurate forecasting and ensure that good quality data are used. | https://www.saludmesoamerica.org/sites/default/files/2018-06/2.%20Guide%20to%20forecast%20MCH%20supplies%20Belize_0.pdf |
| Quantification and Budgeting for Rapid and Sustainable Access to New Pediatric Antiretroviral Therapies EGPAF/UNITAID Oct 2020 | Step by Step guide to early and accurate forecasting of new medication considering what is already available in facilities and at the national level to prevent wastage while transitioning into the new regimen | https://www.pedaids.org/wp-content/uploads/2020/11/Pediatric-ARV-Quantification-Budgeting_EGPAF-Unitaid_Jan2021.pdf |

## 5.3. CASE STUDIES

### 5.3.1 Forecasting Ferrous Sulphate and Folic acid tablets for prophylaxis and treatment of anaemia amongst antenatal attendees in the Kingdom of Belize

To ensure that all antenatal attendees receive adequate prophylaxis for prevention of and treatment for anaemia where indicated in 2016, number of ferrous sulphate and folic acid combination tablets were estimated using historical antenatal attendance data and proportion of attendees presenting with mild and moderate anaemia from 2014-2015.
(Pages 11-15)
https://www.saludmesoamerica.org/sites/default/files/2018-06/2.%20Guide%20to%20forecast%20MCH%20supplies%20Belize_0.pdf

# CHAPTER 6: PROCUREMENT AND SUPPLY CHAIN

## 6.1. INTRODUCTION

. The procurement process and supply chain need to be robust for sustainability of the rollout of the new product and to ensure that there is equitable distribution of the product across the country especially where the need is.
In particular, the following need to be considered:

- Manufacturer/s- number and if any are generic.
- Capacity of the manufacturer/s
- Raw material for the product- availability, pipeline
- Manufacturing and Marketing License
- Quality assurance of the product

There is a need to implement the World Health Assembly resolution WHA 72.8 to improve equitable access to fair pricing and increase collaboration between countries for improved access to health products.

WHO/Europe with the Norwegian Ministry of Health and Care services and the Norwegian Medicines Agency have developed the 'Oslo Medicines Initiative' . "This provides a neutral platform where the public and private entities can jointly outline a vision for equitable and sustainable access to effective, innovative and affordable medicines ."

Procurement systems need to be robust to ensure that the new product is of good quality, can reach the people who need it, is affordable and sustainable. Effective procurement systems need capacitated individuals in the country who can monitor regulatory compliance and quality assurance of the product. There is also a need to work with multiple stakeholders to ensure that there is no stock out of essential medical products including test kits, medicines, vaccines etc.

Various international organisations are working to support countries globally through different mechanisms:

- Launch of the Oslo Medicines initiative
- Strengthening of in country capacity
- Pooling of resources for joint procurement

The supply chain needs to be reviewed periodically due to the various conflicts around the world to ensure that the raw material for the medication is in adequate supply and there is no stockout of the final product. This can be supported through the 'Oslo Medicines initiative'

## 6.2. RESOURCES AND TOOLS

| Tool | Description | Tool link |
|---|---|---|
| Procurement Tools | Describes tools and services that can be used to procure medication efficiently and effectively.<br>i) The 'pooled **procurement mechanism**' is described, which is a Global Fund (GF) initiative to "aggregate order volumes on behalf of their implementing partners to | https://www.theglobalfund.org/en/sourcing-management/procurement-tools/ |

| | | |
|---|---|---|
| | negotiate prices and delivery conditions with manufacturers."<br>ii) **Wambo.org** is GF's procurement platform which offers access to their implementing partners, governments, and other organisations to secure products through the pooled procurement mechanism. It is specifically for HIV, TB, malaria health programs. It allows the teams to search for quality products, submit and track orders and invoices. This helps to improve access to quality products, increase transparency around the ordering process and improves procurement lead times.<br>**iii) Private sector co-payment mechanism** This is a financing model to help improve access to Artemisinin based combination treatment for Malaria through the private retail sector distribution mechanism. This is ideal for countries where the private sector is a major provider for anti-malarial medication | |
| QuanTB | **QuanTB** is a downloadable tool which helps to quantify TB medicines to support the ordering, planning and procurement process to prevent interruptions in treatment. It is designed for any TB regimen and allows for changing needs of the TB program to support regular quantifications and stock management. | https://siapsprogram.org/tools-and-guidance/quantb/ |

## 6.3. CASE STUDIES

### 6.3.1 Introduction of New Paediatric TB Drug Formulations in Ethiopia

The Challenge TB project worked with the National TB program and other implementing partners in Ethiopia to develop a transition plan to support an update of the national guidelines, register the new treatment, perform situational and feasibility analysis, engage stakeholders, build capacity among health care workers, implement quantification, forecasting and supply plan and monitor the transition. Quantification was done using the QuanTB tool which helped to plan the transition to the new medicines to maximise resources and reduce wastage.

https://msh.org/wp-content/uploads/2019/06/2019_ctb_highlight_ethiopia_intro_new_pediatric_tb_drug_formulations.pdf

# CHAPTER 7: HEALTH CARE PROVIDER CAPACITATION

## 7.1. INTRODUCTION

The Ministry of Health supported by stakeholders need to develop a training plan to capacitate the health care providers (HCPs) on the new guidelines. The type of training is country specific and can be varied allowing the HCP to use the most suitable format.

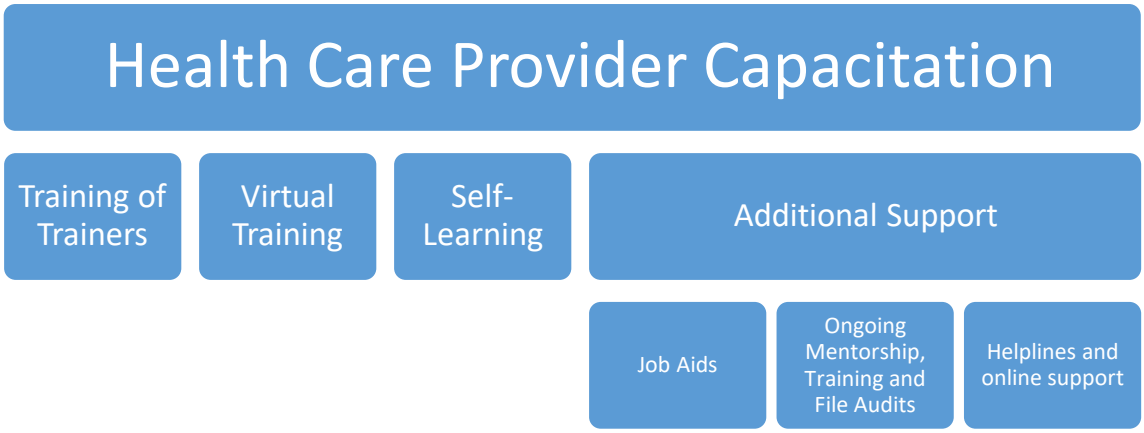


***Fig: Elements of health care provider capacitation***

**Training of trainers** from the sub-national units is used by most LMICs, the trainers disseminate the training at the sub-national level in smaller groups. They are supported by MoH program managers and stakeholders working in those communities.

**Online training** through **virtual platforms** is increasingly used as it has a wider reach allowing participation of HCPs from remote sites. These sessions can be recorded and made available to HCPs to use in their own time. Challenges such as data usage, bandwidth, and connectivity issues will need to be addressed.

**Self-learning platforms** are popular among HCPs who are unable to attend virtual or in-person sessions due to time constraints and are willing to/ prefer attending the recorded sessions in their own time.

In short-staffed clinics or those using the 'Super-Market' approach, HCPs provide care and treatment for all diseases in one place, hence it can be challenging to remember all the updates and nuances in the different disease specific treatment guidelines. **Job Aids** play an important role after the training to support adherence to the guidelines and serve as a reminder for the process flow, timing of laboratory tests and dosages for children. Job aids can be in the form of desk reference tools e.g., flow charts, check lists, abridged guidelines, posters, dosage charts etc.

Trainings should be accompanied by **ongoing mentorship**. **File audits** conducted periodically can identify gaps in the interpretation of the guidelines which can be addressed through targeted mentorship and retraining as needed.

**Toll-free and WhatsApp helplines, email, and online platforms** help to channel challenges, questions and clarifications which can be responded to by technical experts and improve understanding of the guidelines. The clarifications can be used to update the guidelines, improve future trainings and guideline development.

### 7.2. Resources and Tools

| Tool | Description | Tool link |
|---|---|---|
| WHO and JHPIEGO. Effective teaching: a guide for educating healthcare providers. WHO (2005), ISBN: 9241593806 | This is a training package developed by WHO and JHPIEGO to help trainers and health care educators to effectively train health care practitioners. It includes a reference manual, learner and facilitator guides. Exercises are included to test knowledge and skills competency after the training. There is also provision to effectively use feedback to review and improve the training. | https://www.who.int/publications/i/item/9241593806 |
| ITECH. Training Toolkit | This has a collection of resources for developing, delivering and evaluating training on HIV related topics and skills for health care providers.<br>It is divided into seven sections, the first six cover the necessary steps to create a training course (coordination, needs assessment, design, development, delivery and evaluation) and the seventh contains sample curricula which can be used as models to develop the provider's own training. Each section has a 'In the field' example that demonstrates how the tools can be used to produce and deliver training. | https://www.go2itech.org/HTML/TT06/toolkit.html |
| Supporting Vaccination: A toolkit for CHWs | Community Health Workers (CHWs) are trusted members of the community and are often the 'go to' resource for health information for millions of people around the world. They therefore need to be equipped with adequate training and knowledge so that they can support and advance accurate information. The digital toolkit has several sessions from describing the role of the CHW, the importance of vaccines, how they work, what are their side effects and adverse events, how to address beliefs and values and special concerns, be empathetic, share information to counter misbeliefs or fake information, supporting those who are ready, other prevention methods, and lastly and most importantly self-care for the CHWs. It has been translated in several languages including English, Spanish, French, Xhosa and Sepedi. | https://www.gavi.org/vaccineswork/supporting-vaccination-toolkit-community-health-workers<br><br>https://digitalmedic.stanford.edu/our-work/vaccine-ed/ |

| | | |
|---|---|---|
| WHO 2014. Childhood TB Training Toolkit<br><br>ISBN 978 92 4 150778 3 | A toolkit to train health care providers on childhood TB was developed by WHO and the International Union against Tuberculosis and Lung Disease.<br>The objectives of the toolkit were to increase detection and improve management of TB, increase contact tracing and preventive treatment, and provide more accurate TB data for better monitoring and evaluation amongst children.<br>The toolkit is formed of ten modules ranging from epidemiology, diagnosis, treatment and managing childhood TB in the community. | https://iris.who.int/bitstream/handle/10665/134387/9789241507783_eng.pdf?sequence=1 |

## 7.3. CASE STUDIES

### 7.3.1 COVID-19 Vaccination training for health care workers in South Africa

The National Department of Health (NDoH) of South Africa worked closely with the South African Vaccination and Immunisation Centre at Sefako Makgatho Health Sciences University and other partners to prepare a short course with tools to train the vaccinators to roll out the COVID-19 vaccine. The course was free and could be accessed online without any cost to the user.
The vaccine roll-out was a success as it involved all possible clinical staff and involved community doctors, nurses, clinical associates, and pharmacists at the grassroots.
https://knowledgehub.health.gov.za/course/covid-19-vaccination-training-health-workers

# CHAPTER 8: DEMAND CREATION

## 8.1. INTRODUCTION

Demand creation is defined as the process to increase demand for a product or service using marketing techniques .
**Health Literacy** is the extent to which an individual can access or understand health information, treatment options and services available to make an informed decision about their own health or for a child/family member that is being cared for by them.
**Treatment literacy** is health literacy but specific to a disease condition.
Increasing health literacy in the community builds trust and improves information sharing, health seeking behaviour, adherence to preventative measures and treatment, and uplifts the health of the community.
Communication material should be easy to understand and retain.
The **'P Process'** is a tool developed in 1982 that is used for planning social and behaviour change communication (SBCC) programs. It has five steps: Inquire; Design your strategy; Create and test; Mobilize and monitor; and Evaluate and evolve. It is based on three cross-cutting concepts: SBCC theory, stakeholder participation and continuous capacity strengthening. The authors caution the reader not to assume they know the audience and to engage stakeholders as much as possible when developing communication material. A monitoring and evaluation plan  is essential for continuous strengthening of the program.

The following methods are commonly used to provide Health Literacy:

- In facility: Health care provider health talks, group sessions, one-on- one sessions
- In the community: group sessions, community health days
- Mass media: radio, television
- Information, education, and communication (IEC) material: pamphlets, videos, etc.
- Social media: WhatsApp messages, Facebook platform
- Edutainment: Using plays and games

An excellent example of using **lived experiences** to generate demand is from ICAP (International Center for AIDS Care and Treatment Program) who have developed a video series 'The Power of PrEP' of testimonials from individuals in the Democratic Republic of Congo, Kenya and Nigeria who have used PrEP (pre-exposure prophylaxis) and benefitted from it. These are being shared in facility waiting rooms to help with demand creation for PrEP and to train health care providers.

**Community led monitoring** is a collaborative method where the members of the community collect, analyse and use information from health care facilities to improve their understanding of the program and identify any gaps. This data is used to advocate for better management and/or resources. It assists the MoH at the ground level by identifying facilities where the new product is not yet available, experiencing stockout or is available but not being dispensed for e.g., due to a gap in training or understanding of the guidelines. MoH can use these reports to improve the program and service delivery and focus on making the program client centred.

## 8.2. RESOURCES AND TOOLS

| Tool | Description | Tool Link |
|---|---|---|
| The SHARE Approach—Using the Teach-Back | This describes a very useful and collaborative technique to | https://www.ahrq.gov/health-literacy/professional- |

| | | |
|---|---|---|
| Technique: A Reference Guide for Health Care Providers | communicate with the patient and/or the caregiver.<br>The health care provider describes the clinical care information, options, treatment dosages etc. to the patient/caregiver. The patient/caregiver has to repeat what was shared in their own words. This helps to ensure that the patient/caregiver has understood what was being said, increases collaboration between the health care provider and the patient, improves patient satisfaction and helps to gain trust. | training/shared-decision/tool/resource-6.html |
| The P Process Tool | The P Process is a tool that is used for planning social and behaviour change communication programs. It has five steps: Inquire; design your strategy; create and test; mobilize and monitor; and evaluate and evolve. It has been used by several programs to develop communication materials for the community. | Health Communication Capacity Collaborative (November 2013). The P Process. Five Steps to Strategic Communication. Baltimore: Johns Hopkins Bloomberg School of Public Health Center for Communication Programs. https://www.healthcommcapacity.org/wp-content/uploads/2014/04/P-Process-Brochure.pdf |
| CDC. PrEP demand creation toolkit | This toolkit was designed for implementing partners to use to increase demand and uptake of pre-exposure prophylaxis (PrEP) for HIV among those whose who need it. It is based on the P process tool. It has various sample templates that can be used to develop the country's own demand creation messaging. Several countries have used this toolkit to develop their own demand creation materials. | https://www.prepwatch.org/wp-content/uploads/2022/08/CDC-PrEP-Demand-Creation-Toolkit_FINAL.pdf |
| EGPAF Children Treatment Literacy Booklet for Caregivers | Comprehensive booklet for caregivers providing information on HIV, antiretrovirals, adherence, viral load etc. It guides the caregivers on how to administer treatment to children, the different ways to access health services and when to access health services. | https://www.pedaids.org/wp-content/uploads/2021/06/2021CaregiversGuideIEC19.pdf |

## 8.3. CASE STUDIES

### 8.3.1 Demand Creation of PrEP in South Africa

The MoH worked with civil society, non-governmental organisations, academia, research institutions, implementing partners and donors to develop demand creation tools for PrEP. These included a PrEP factsheet, brochure addressing frequently asked questions, posters for health care workers to introduce PrEP to clients, an online risk assessment tool allowing clients to choose an avatar and

assess their own risk for acquiring HIV, HIV prevention material and information for youth as well as videos, and radio jingles. The information about the website was spread through social media and through the different stakeholders participating in the development of the material.
https://myprep.co.za/users/users/

8.3.2 **Co-Development of literacy material by the community and researchers led to successful enrolment**

Community engagement strategies were introduced in the Greater Mekong subregion of Cambodia to reduce the exposure through use of chemo-prophylaxis with anti-malarial artemether-lumefantrine (AL) versus a control multivitamins (MV). Key messages and literacy material was developed jointly with the community leading to a 92% enrolment rate.

Conradis-Jansen, F., Tripura, R., Peto, T.J. *et al.* Community engagement among forest goers in a malaria prophylaxis trial: implementation challenges and implications. *Malar J* **22**, 178 (2023). https://doi.org/10.1186/s12936-023-04610-6

# CHAPTER 9: PHARMACOVIGILANCE

### 9.1. Introduction

While randomised clinical trials (RCTs) are the gold standard for collection of information on efficacy, safety, and risks of a new medical product, they are unable to provide information of drug usage in a real-world setting.

Changes in regulation to allow rapid access to treatment by patients e.g., the 21st Century Cres Act signed into law on December 2016, make it necessary to pro-actively conduct pharmacovigilance and post marketing surveillance to strengthen the safety and efficacy data on the new product and to support its continued use.


Fig: Pharmacovigilance
(adapted from WHO)

Pharmacovigilance is defined by WHO as 'the science and activities related to detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems'. WHO recommends that every country should have a pharmacovigilance system which allows them to conduct these activities at a local and national level and collate the information for reporting into a global platform.

Post Market surveillance is defined as "active, systematic and scientifically valid collection, analysis and interpretation of data or other information about a marketed device".

It is crucial that there is in country capacitation and development of electronic pharmacovigilance systems. Training and ongoing mentorship should be provided to health care providers to perform routine pro-active ongoing safety and toxicity monitoring of both new and previously approved medical products as this will improve the quality of care provided to our patients. National regulatory authorities should also be capacitated to evaluate the reported adverse events to determine causality and inform the global database on the new product usage, safety and risk profile.

The FDA collects **real world data** (RWD) from different sources including electronic medical records, medical claims data, data from product and disease registries etc., to create **real world evidence** (RWE) which includes usage, safety, and risk information to support regulatory oversight of medical products after they have been registered as well as to advance the development of better treatment. In 2018, they established a framework to strengthen the evaluation of RWE to support additional indications for the already approved product as well as to support the ongoing monitoring and evaluation of the new product's usage, side effects and risk profile.

The European union requires every new medicinal product to have a **risk management plan** (RMP) as part of its licensing and approval process. RMPs contain the product's safety profile, measures to minimise and prevent risk in patients, measurement of the effectiveness of risk minimisation procedures as well as plans to collect additional data for safety and effiicacy of the medication. They need to updated throughout the lifetime of the product and submitted to the EMA whenever the risk management profile is altered due to new information.

Post-authorization safety studies (PASS) can be designed to allow prospective collection of additional safety and risk information and help plan for risk minimising management and prove the effectiveness of such measures.

The specialist cohort event monitoring (SCEM) methods used in the UK and EU are an excellent example of how routine use of such methods in clinical practice can help inform safety and risk information for new and existing products.

### 9.2. RESOURCES AND TOOLS

| Tool | Description | Tool Link |
|---|---|---|
| Standard reporting form for adverse events following immunization (AEFI) | Has a downloadable form for documenting adverse events following immunization | https://www.who.int/publications/m/item/reporting-form-aefi |
| VigiMobile | Application used on any handheld device allows health care workers to submit adverse events related to immunization from anywhere even when offline | https://who-umc.org/pv-products/vigiflow-for-aefi/vigimobile-for-aefi/ |
| USAID Pharmacovigilance Monitoring System (PViMS) | Web based application used to monitor the safety of medicines by health care practitioners, regulatory bodies and implementing partners. It enables data collection, analysis, and reporting for active surveillance in LMICs. It is a comprehensive pharmacovigilance tool as it offers both active monitoring and spontaneous reporting options. | https://www.ghsupplychain.org/pharmacovigilance-monitoring-system-pvims |

| | | |
|---|---|---|
| Specialist Cohort Event Monitoring (SCEM) studies: a new study method for risk management in pharmacovigilance. | The authors Deborah Layton and Saad Shakir describe the use of the SCEM method in clinical practice to prospectively collect safety information on a new product as well as to compare two products | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4328122/pdf/40264_2014_Article_260.pdf |
| Guidelines for Market surveillance of medicines | Guidelines and tools to support post market surveillance of medicines in South Africa. It guides the user on sample plan, training of the sample collectors and monitoring. | https://www.sahpra.org.za/wp-content/uploads/2022/06/SAHPGL-INSP-RC-01-Guidelines-for-Market-Surveillance-of-Medicines.pdf |

## 9.3. CASE STUDIES

### 9.3.1 Post-Marketing Surveillance of Dolutegravir in HIV-1 positive patients

An open label study was conducted in Korea to examine data from patients (≥12 years) receiving Dolutegravir as per national guidelines. Dolutegravir was found to be safe and effective among the 139 individuals studied for the safety analysis and the 75 studied for the effectiveness analysis.

Kwon S, Cho JE, Lee EB, Kim YS, Sohn JW. A Korean Post-Marketing Surveillance Study of Dolutegravir Single-Agent Tablets in Patients with HIV-1. Infect Chemother. 2022 Dec;54(4):711-721. doi: 10.3947/ic.2022.0058. PMID: 36596681; PMCID: PMC9840956.

### 9.3.2 Post-Marketing surveillance for the safety of human papillomavirus 16/18 AS04-adjuvanted vaccine

A multicentre prospective cohort study was conducted among 3013 Chinese girls and women aged 9-45 years between May 2018-December 2020 who received 8839 doses of the Cervarix vaccine. Adverse events following immunization (AEFIs), potential immune-mediated diseases (pIMDs) &pregnancy related outcomes were collected upto 12 months from the third immunization or 24 months from the first immunization, whichever came first. Overall, no safety concerns were identified.
Wu Q, Qian M, Welby S, Guignard A, Rosillon D, Gopala K, Xu Y, et al. Prospective, multi-center post-marketing surveillance cohort study to monitor the safety of the human papillomavirus-16/18 AS04-adjuvanted vaccine in Chinese girls and women aged 9 to 45 years, 2018-2020. Hum Vaccin Immunother. 2023;19(3):2283912. doi: 10.1080/21645515.2023.2283912. Epub 2023 Dec 1. PMID: 38038626.

# CHAPTER 10: TRACKING AND IMPACT

### 10.1. Introduction

New clinical products can enhance the quality of life through reducing morbidity and mortality while also reducing costs for the individual and health system and workdays lost. Lichtenburg conducted an econometric analysis of the impact of new drug launches on longevity in 52 countries from 1982-2001, and found that the launch of new chemical entities accounted for nearly 2 years increase in life expectancy across the 52 countries from 1986-2000.

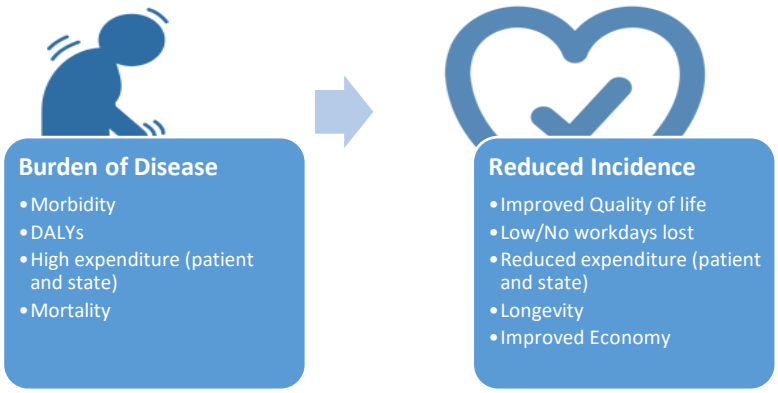


***Fig: Impact of optimal treatment***

Once a new product has been rolled out, it is important to have a monitoring and evaluation plan in place that not only assesses the robustness of the procurement and supply chain processes but also to ensure there is demand for the new product and uptake. This should be accompanied by an assessment of the impact of the product in the management of the disease- early diagnostics, impact on disease prognosis and eventually the disease burden in the region.

In a retrospective cohort analysis in South Africa between July 2014 and March 2016, it was noted that the introduction of Bedaquiline reduced all-cause mortality among patients with multi drug resistant TB or rifampicin resistant TB (hazard ratio 0.35; 95%CI 0.28-0.46) and with extensively drug resistant TB (hazard ratio 0.26; 95% CI 0.18-0.38) compared with standard regimens.

Amongst 9419 HIV positive children and adolescents 0-19 years of age (CALHIV) on treatment in six Eastern and Southern African countries, it was noted in a retrospective analysis that 93.4% of the CALHIV using Dolutegravir (DTG) were virally suppressed, and among those who were previously unsuppressed, 79.8% achieved viral suppression once transitioned to DTG.

The impact of prevention of mother to child transmission of HIV (PMTCT) programs with the implementation of “treat all” on the burden of disease among children has been well established. Despite South Africa having the largest HIV burden among children globally, and sub-optimal treatment coverage, it has seen the among the largest declines in both mother to child transmission of HIV and AIDS deaths from 2017-2018.

## 10.2. Resources and Tools

| Tool | Description | Tool Link |
|---|---|---|
| Tools for measuring antimalarial efficacy | WHO has developed tools for use in the country to monitor antimalarial efficacy, effective case management and detection of resistance | https://www.who.int/teams/global-malaria-programme/case-management/drug-efficacy-and-resistance/tools-for-monitoring-antimalarial-drug-efficacy |
| Post-authorisation safety studies (PASS) | Describes studies conducted post authorisation of the medical product to collect and validate safety information, risk information, measure the effectiveness of risk minimisation/prevntion measures. | https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/post-authorisation-safety-studies-pass |

## 10.3. Case studies

### 10.3.1 Quality of selected anti-retroviral medicines in Tanzania

Antiretroviral samples were collected from 20 regions in Tanzania mainland and were screened using the Global Pharma Health Fund® Mini-Lab Kits to assess the quality of the circulating medication. Quality of majority of antiretrovirals in the Tanzania Mainland market was good, however there were significant deficiencies in labelling and packaging. This highlights the importance of continuous monitoring of quality of medicines.

Mziray, S., Maganda, B.A., Mwamwitwa, K. *et al.* Quality of selected anti-retroviral medicines: Tanzania Mainland market as a case study. *BMC Pharmacol Toxicol* 22, 46 (2021). https://doi.org/10.1186/s40360-021-00514-w https://bmcpharmacoltoxicol.biomedcentral.com/articles/10.1186/s40360-021-00514-w

### 10.3.2 Impact of Dolutegravir based treatment in six countries among children and adolescents living with HIV

Retrospective analysis among children and adolescents living with HIV (CALHIV) 0-19 years 20kg and above who received Dolutegravir from 2017-2020 at sites in Eswatini, Botswana, Lesotho, Malawi, Tanzania, and Uganda to assess effectiveness, safety, and predictors of viral suppression. CALHIV with single drug substitutions with Dolutegravir were included. Dolutegravir was found to be safe and effective among 9419 CALHIV initiated on Dolutegravir including single dose substitutions in a real-world setting. Viral suppression was 93% among the 7898 CALHIV who had a viral load done post DTG initiation/substitution.

Bacha JM, Dlamini S, Anabwani F, Gwimile J, Kanywa JB, Farirai J, et al. Realizing the Promise of Dolutegravir in Effectively Treating Children and Adolescents Living With HIV in Real-world Settings in 6 Countries in Eastern and Southern Africa. Pediatr Infect Dis J. 2023 Jul 1;42(7):576-581. doi: 10.1097/INF.0000000000003878. Epub 2023 Feb 14. PMID: 36795586; PMCID: PMC10259212.https://pubmed.ncbi.nlm.nih.gov/36795586/

# Annex 1

**Worksheets**

Note: These worksheets were developed to serve as a practical guide for each step. They are for your consideration and are not prescriptive as each country may have their own processes.

**Step 1: Community and Stakeholder Engagement**

1. Have you mapped the stakeholders? ☐

2. Mapping exercise: Type the stakeholders in the table below and start documenting their priorities to support the introduction of the new product.

| Stakeholder group | Example | Strategic Importance | Priorities | Roles and Responsibility during scale-up |
|---|---|---|---|---|
| Example: Community | Traditional leaders | Recognized and respected community leadership. | Helping the community/ could also be personal | Help to engage community and get buy in for the new product |
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3. Has a stakeholder engagement plan been developed? ☐

4. Has a timeline been developed for the process of adoption of the product from engagement to when it is available in the public health facilities? ☐

5. Have you discussed availability with the stakeholders for the initial meeting to introduce the new product? ☐

6. Meetings scheduled with the different groups depending on availability to go through the following: ☐

- Community and other Stakeholder Engagement
- Country Registration
- Revision of National Guidelines
- Planning and Budgeting
- Quantification
- Procurement and Supply Chain
- Health care provider capacitation
- Demand Creation
- Pharmacovigilance
- Tracking and Impact

**Step 2: In Country Registration**

1. Has the product dossier been submitted with the NRA?
   (In some countries, the originator needs to submit and get approval before the generic can apply) ☐
2. Are there any generic manufacturers for the new product if applicable? ☐
3. If applicable, how many generic manufacturers are there for the new product?

   _____
4. Have any of the generic manufacturers submitted dossiers to the NRA? ☐
5. If yes, how many: _____
6. Confirm with NRA if all information and appropriate forms have been received and there is no missing information. ☐
7. Confirm with NRA if any product samples have been received for quality assurance ☐
8. Where appropriate apply for registration waiver or expedited review process while national registration is pending ☐
9. Regular meetings requested with NRA to monitor progress and address any bottlenecks ☐
10. Discuss process to include new product in the essential medicines list ☐
11. Discuss inclusion of new product in the national clinical management guidelines for the disease ☐

Note: Countries can access the WHO CRP to accelerate the registration of prequalified finished pharmaceutical products.

**Step 3: Revision of the National Clinical Management Guidelines**

Stage 1

1. Has the scope of the revision been discussed/decided by the MoH? ☐
2. Is there a timeline for the revision of the national guidelines? ☐
3. Is there a budget for costs to be incurred during the revision and subsequent training including job aids and demand creation material? ☐
4. Has a chair been appointed for the guidelines committee/technical working group? ☐
5. Has a guidelines committee /technical working group been appointed? ☐
6. Are relevant community members included in the committee? ☐
7. Has all the material for the new product been identified e.g., WHO guidelines, WHO Prequalification, FDA/EMA approvals, trial data, research papers, any relevant literature etc.? ☐
8. Has the material been sent to the committee for their perusal before the meeting to discuss the revision? ☐

Stage 2

9. Have any meetings been held to discuss the revision? ☐
10. Is there consensus among the committee members with regards to the revision? ☐
11. Has a set of review questions been developed? ☐
12. Has a set of recommendations been developed for the new guidelines ☐
13. Are there any specific recommendations stemming from the national strategic plan that need to be included? ☐

Stage 3

14. Has a draft been developed? ☐
15. Has the committee reviewed the draft? ☐
16. Have the edits /questions been reviewed and discussed? ☐

**Step 4: Planning and Budgeting**

1. Has a decision been made if the new product will be transitioned in phases, or will the new product be rolled out nationally at the same time? ☐
2. If being phased in, has a decision been made on which populations will be prioritized? ☐
3. Is there a timeframe for the transition in terms of coverage by time? ☐
4. Has the volume of product needed by a timeframe been calculated? ☐
5. Has the budget been calculated for the transition/implementation? ☐
6. Has there been a discussion with the treasury with regards to the required budget? ☐
7. Is an alternative source of funding needed? ☐
8. If yes, have any discussions been held with potential donors? ☐
9. Will the timeline need to be revised if funding is not available? ☐

**Step 5: Quantification**

1. Have program managers and technical specialists been engaged to develop the forecasting and supply plan? ☐
2. Has the burden of unmet need been calculated for the disease (children who are undiagnosed/not on treatment)? ☐
3. Is the historical use of the current product being used to manage the disease available? ☐
4. Is the volume of current stock on hand available? ☐
5. Are there targets for disease coverage for the current financial year? ☐
6. Are there any plans to scale up testing and diagnosis of the disease? ☐

7. Has the estimated consumption been calculated keeping in mind the unmet need, expected program performance, and existing cases? ☐

8. Have the minimum and maximum stock levels been calculated for the current product, keeping in mind the transition plans? ☐

9. Have the minimum and maximum stock levels including buffer stock been calculated for the new product, keeping in mind the transition plans and existing stock of the current product? ☐

10. Has there been a discussion with the manufacturer of the new product with regards to the capacity and lead time to manufacture once the product is registered? ☐

11. Have the delivery dates and schedule for the transitioning to the new product been discussed with the manufacturer? ☐

12. Has there been a discussion with the manufacturer of the current product with regards to the change in guidance and plans to transition out of current treatment. ☐

**Step 6: Procurement and Supply Chain**

1. Has there been an assessment of the capacity of the manufacturers in comparison to quantity required? ☐

2. Are there any concerns with regards to the supply of raw material required to produce the required quantity of the new product, e.g. impact of any conflict/disease outbreak/natural disaster? ☐

3. Do all the manufacturers have their manufacturing and marketing license in place? ☐

4. Does the MoH need additional support for procurement, e.g. capacity building etc.? ☐

5. Does the MoH need support for pooled procurement or fair pricing negotiation to reduce cost of the medication? ☐

**Step 7: Health Care Provider Capacitation**

1. Is there a training plan to capacitate health care providers on the new product? ☐

2. Is there a timeline for the training to ensure a smooth rollout of the new product? ☐

3. Has the MoH decided on the type of training/s to be provided? ☐

4. Is there a budget to support the type of training required? ☐

5. If no, does there need to be any adjustment to the format of the training proposed? ☐

6. Outline the type of training/s to be provided: _____

   _____

7. Has an outline been made of the training materials and job aids that would be needed? ☐

8. Specify the materials required: _____

_____

_____

9. Has the development of training material been delegated to program managers /technical specialists/consultants/community members? ☐

10. Has the timeline been communicated to the delegated colleagues with regards to the development of the material? ☐

11. Is there a meeting planned to review the training material with the MoH, technical working group, program managers and civil society? ☐

**Step 8: Demand Creation**

1. Is the MoH planning any demand creation activities e.g. campaign to increase awareness of the disease and new product? ☐

2. Has there been a discussion with appropriate community leaders, patient advocacy groups with regards to dissemination of information? ☐

3. Has a plan been developed for information sharing? ☐

4. What methods are planned to be used for information sharing?

   Facility: _____

   Community:
   _____

   Mass media:
   _____

   Other methods:
   _____

5. Is there a plan to monitor the new product roll out by the community? ☐

6. Has the plan been presented to the MoH and program managers? ☐

7. Is there a system in place to report gaps/challenges to the district and provincial levels? ☐

8. Are there any major concerns identified by community members and program managers in terms of usage of the new product? ☐

9. Outline the challenges/concerns identified?

| Concern/ challenge identified | Possible remediation |
|---|---|
| | |
| | |
| | |
| | |

**Step 9: Pharmacovigilance**

1. Does the country have a tool for active surveillance of safety and toxicity monitoring of drugs in use and new drugs? ☐
2. If no, is there a plan to actively monitor safety and toxicity of the new product? **(note: it is a critical element)** ☐
3. Does the MoH require any support to develop a pharmacovigilance system? ☐
4. Is there a plan to request support from international partners (e.g., WHO) to capacitate the MoH to develop such a system? ☐
5. Does the NRA require a risk management plan for the new product? ☐
6. Is there a plan to report ongoing safety and toxicity data to the NRA and to the applicable global network? ☐

Strong recommendation to develop an ongoing safety and toxicity monitoring plan and reporting. If support is needed to please reach out to the appropriate network to develop a reporting system.

**Step 10: Tracking and Impact**

1. Is there a monitoring plan in place to assess the rollout? ☐
2. What data elements are included in the monitoring?

Note: This could cover drug stockout, treatment coverage, morbidity, success/failure of the new product among other indicators. A few examples are described below:

| Data element | Sub-national unit | Time interval | Reason | Data Source |
|---|---|---|---|---|
| *Drug Stockout* | | | | |
| Reported Drug shortage | District/Province | Weekly/Monthly | Identify any bottlenecks in the ordering, forecasting, procurement, supply chain etc. | |
| *Estimated Coverage of new product* | | | | |
| Treatment Coverage for new product | District/Province | Monthly/quarterly | Ensure that the rollout is going as planned (expected coverage by month/quarter). Could also be an indicator of poor compliance to guidelines at the HCP level, patient refusal, or drug stockout among others. | |
| *Morbidity* | | | | |
| Number of clinic visits due to the disease | District/Province | Monthly/quarterly | To assess if the new product is having the desired impact | |
| Number of Hospitalizations due to disease | District/Province | Monthly/quarterly | To assess if the new product is having the desired impact | |
| *Success/Failure* | | | | |
| Lab indicator e.g. VL suppression for HIV, negative cultures, cure rates, remission rates, etc. | District/Province | Monthly/quarterly | To assess if the new product is having the desired impact | |

3. Are there any remediation plans in place for gaps/challenges identified through the monitoring? ☐

4. Outline the following:

| Expected gaps/challenges | Planned remediation |
|---|---|
| | |
| | |
| | |