Supplementary File 4: Third draft (v.1.1) of the target product profile prepared by KP for round 2 of online expert review.

Target Product Profile

The target audience for this TPP are software/App developers. This TPP is also aimed at health programme implementers as a toolkit selection aid. The TPP does not encompass guidance for primary research nor does it provide the types of clinical validation studies for electronic clinical decision-support algorithms. Guidance by the U.S. Food and Drug Administration (FDA) and the International Medical Device Regulators Forum (IMDRF) are available online and referred to in this document for guidance and can also be found in synthesised versions in Appendices A-C.

Definitions:

For the purposes of this TPP:

- An App (mobile App) includes any of the following types: a native app, a web app, or a hybrid app
- the healthcare programme is implementing the toolkit in the intended setting

Legend: Characteristics for the toolkit components are coloured coded as below.

Electronic clinical decision-support algorithm
Point of care diagnostics and medical devices
Data and App functionality

Pellé KG, *et al. BMJ Global Health* 2020; 5:e002067. doi: 10.1136/bmjgh-2019-002067

Scope General			
CHARACTERISTIC	**MINIMAL REQUIREMENT**	**OPTIMAL REQUIREMENT**	**COMMENT**
Intended Use	The toolkit, composed of an electronic clinical decision support algorithm(s) and point of care diagnostic tests, is intended to increase **evidence-based** treatment decisions by capturing diagnostic test results, patient clinical data (e.g. exposures, signs including vital signs) and context specific data (e.g. disease incidence, seasonality) to provide treatment and care recommendations.		
Target Population	The algorithm shall define the target population. Inclusion and exclusion criteria are used at the encounter to enrol the patient.		The system can be modular i.e. composed of discrete algorithms such that one can be used for a specific population based on pre-defined criteria.
Setting (level of implementation in the healthcare system)	Defined by the algorithm		The system can be modular i.e. composed of discrete algorithms such that one can be used for a specific healthcare setting based on the infrastructure, workforce knowledge and skills, point of care tools available.
Targeted End User	Defined by the algorithm		The end user shall have the required training/skills to use the App appropriately

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Scope Toolkit Components			
CHARACTERISTIC	**MINIMAL REQUIREMENT**	**OPTIMAL REQUIREMENT**	**COMMENT**
Algorithm Access	The electronic clinical decision-support algorithm is accessible through an App downloaded on compatible target devices		The App can be a web app, a native app or a hybrid app.
Algorithm Content	Built on: — well-established clinical evidence based on WHO/international/local clinical care guidelines, peer-reviewed articles (systematic reviews, original clinical research), clinical experience/practice; **and/or** — appropriate clinical validation research*		*Refer to Appendix B section on "Clinical Validation" and guidelines on best practices such as WHO 2016 "Monitoring and Evaluation Digital Health Intervention: A practical guide to conducting research and assessment"[i].
Algorithm Treatment Recommendations	Therapeutic recommendations shall be compliant with national treatment guidelines and national EML[1] and support antimicrobial stewardship	Same and evidence based medicine to support optimal treatment recommendations	Recommendations support the appropriate selection, dosage and duration of antimicrobial and any other kind of treatment and management, causing the least harm to the patient
Compatible Point of Care Tools	POCs[2] or other relevant medical devices prompted for use by the App shall be locally relevant, i.e. recommended by EDL or relevant national equivalent, or country program	Same, plus emerging diagnostic tools and medical devices relevant to the algorithm and implementation setting	
Regulated Toolkit Components	POC diagnostic tests and medical devices are regulatory approved and compliant with local regulations	Same, and if the software is a medical device, the App shall also have regulatory approval	
Compatible Devices	The App is compatible with any device including: — Smartphones — Tablets — Computers		Computers are included as it may be necessary for health facility supervisors to access data collected at the facility level to make informed decisions (i.e. restocking medical supplies)
Compatible Operating Systems	OS agnostic	Same as Minimal	

[1] EML: WHO's Model list for Essential Medicines

[2] POC : Point of Care diagnostics

Electronic Clinical Decision-Support Algorithm			
CHARACTERISTIC	**MINIMAL REQUIREMENT**	**OPTIMAL REQUIREMENT**	**COMMENT**
Content Transparency	The algorithm is "human interpretable". The healthcare programme and end user can comprehend the algorithm decision-making processes	The healthcare programme and end user have access to underlying evidence and methodology used to develop the algorithm	Human interpretable: a human can understand the choices taken by the model in the decision-making process, i.e. how output variables are generated based on input variables. Visual representations (e.g.. decision trees, Principle Component Analyses, protocol charts, etc.) and performance metrics can be used to support content transparency.
Quality control	The algorithm has been A) analytically and B) semantically tested: A) Analytical verification: the algorithm output is accurate and reproducible B) Semantical verification: the algorithm doesn't deviate from expert content/evidence and there are no interactions or conflicts in the logic		A) and B) answer the question "did I build the model right?" (See FDA's SaMD Clinical Evaluation for current guidance[ii], Appendices B and C)
Algorithm Validation	The algorithm has been validated. The level of validation will depend on the eCDA status as a Software as a Medical Device (SaMD). Refer to upcoming rulings from regulatory bodies such as the FDA or the European Commission		Answers the question "did I build the right model"? (See FDA's SaMD Clinical Evaluation for current guidance[ii], Appendices B and C)
Machine Learning	None. The algorithm is static	ML[3] is applied to generate data on the algorithm performance, improve content, inform healthcare system processes, etc. Changes in the algorithm based on ML should be validated.	

[3] ML: Machine Learning

Point Of Care Tool			
CHARACTERISTIC	**MINIMAL REQUIREMENT**	**OPTIMAL REQUIREMENT**	**COMMENT**
POC Data Inputs	— Any kind of data (qualitative data such as positive/negative/invalid lateral flow test results and quantitative data such as data provided by hemoglobinometers and glucometers)		
Disease Likelihood	Based on: — pre-test probability (in the absence of POC or POC performance data); **or** — POC positive/negative likelihood ration	Based on: — pre-test probability; **and** — POC positive/negative likelihood ration	The test performance (eg. likelihood ration) is known and performance data ideally previously determined through independent studies in relevant settings. The test brand should ideally also be considered so as to account for changes between manufacturers.
POC Training	On-site training performed by local authority or implementer		

App			
CHARACTERISTIC	**MINIMAL REQUIREMENT**	**OPTIMAL REQUIREMENT**	**COMMENT**
System Validation	The App has been validated in the intended implementation setting. There is evidence demonstrating: — Valid Clinical Association (clinical output based on input data is supported by well-established or novel evidence) **and** — Analytical Validation (input data is processed correctly into expected output data)	The App has been validated in the intended setting. There is evidence demonstrating: — Valid Clinical Association (clinical output based on input data is supported by well-established or novel evidence), **and** — Analytical Validation (input data is processed correctly into expected output data), **and** — Clinical Validation (clinical safety or other meaningful outcome relevant to the intended use)	There is evidence that the system is based on evidence and working to achieve the intended use for the intended setting. See FDA guidance (See FDA's SaMD Clinical Evaluation for current guidance[ii], Appendices B)
System Access (public API)	Publicly available application programming interface (API) for data access protected by authentication and authorization. At a minimum, technical standards are adhered to	Optimally, HIE[4]/HL7[5] standards are adhered to	
Context Configuration	— Language: UN official languages — Local time — Local weights and measures	— Language: option to customise to local official language — Local time — Local weights and measures — Other country preferences	Language can be a major barrier for the proper use of the tool for patient management and can lead to errors and misinterpretation
Customization	Changes to the App, such as updates to the list of medicines and POCs available in the setting, can be made by the healthcare programme. Validation of this change should be provided.	Same as Minimal	
User Access Rights	Appropriate data access is provided based on specific roles		Roles may include data manager (facility supervisor) or data entry person (nurse)

[4] HIE: Health Information Exchange
[5] HL7: Health Level Seven

Expert Support	None	Built-in access to online/remote expert advice to assist in patient consultation via SMS[6], audio call, video conferencing	
App Training	On-site training	Same and remote training and/or remote "Train the Trainer"	
Internet Availability	— Functions offline (allows for service delivery and key workflows) — Allows automatic resynchronisation	Same and trigger alerts on user device when data has not been synchronised for a long time	Internet connection can be very unstable therefore the tool should work in offline mode so as to not disrupt the workflow of the user
Clinical Data Entry	Manual entry by the operator	Same, plus automatic upload of digital data (e.g. from biosensors, medical devices)	Optimal: This allows external integration of other App modules, built-in and third party Apps and devices
Patient Management Recommendation	Consultation data is summarised and actionable recommendations provided (e.g. treatment, referral, home care or follow up)	Same **and** recommendations are integrated in EMRs[7] and HIS[8]	
Navigation	Sequential: the user follows a strict sequence of data input to reach a final recommendation	Non-sequential: the user can move in any direction through an assessment and change input data to reach a final recommendation	
Workflow requirements to enable time delayed POC data input	Ability for a user to perform multiple, simultaneous consultations, with pause and resume capability, to allow clinical and laboratory data entry	Same as minimal plus ability to disable simultaneous workflow feature in settings with minimally skilled workers	This is particularly relevant for implementation in settings where testing and clinical consultations are performed in different locations
Task Management	Multiple algorithms can be supported simultaneously in one application against a common dataset		Can accommodate task-shifting capability i.e. multiple consultations can be opened at a time and patient profiles can be accessed using pre-set user access rights
Follow up	None	Ability to retrieve patient information using patient registration information	The optimal implies data recoverability, also covered below in Data Characteristics section

[6] SMS : Short message service
[7] EMR : Electronic medical record
[8] HIS: Health Information System

System Malfunction protection	System malfunctions are made clear to the user	
Scalability	The App should allow high transaction volumes with complex workflows to cover primary care workforce at a national scale	
Updates and Versioning	Processes are in place to control any App change (including algorithm version updates) and provide the appropriate and correct update to the user	

Data			
CHARACTERISTIC	**MINIMAL REQUIREMENT**	**OPTIMAL REQUIREMENT**	**COMMENT**
Data Capture	Text, numeric, image, audio, video	Same, and GPS[9], barcode, biometric	
Data Validation	The system validates data entry to prevent errors that diminish value of the data or the outcome		
Data Ownership	Ownership shall be determined by the healthcare programme		The healthcare programme is responsible for compliance with any country law, policy and regulation.
Data Storage	The healthcare programme shall be able to choose the destination of the App's data	Same as Minimal	
Data Recovery	Data can be recovered or the system can be re-established to the desired state in the event of interruption or failure		
Data Flow	The flow of data shall be determined by the healthcare programme	Same as Minimal	
Data Reporting	Data export available from all target devices	Pre-built data reporting, analytics and dashboards are available with the App	The level of data manipulation, aggregation and reporting should be sensitive to the device the App is running on i.e. the computer App can be rich in functionality, the mobile App is optimised for data collection and exchange only
Data Provenance	Included	Same	Provides origin and processes applied to output data. When data is downloaded or shared, the version of the model is tagged so it is always clear how the data was obtained

[9] GPS: Global Positioning System

Data Dictionary	Available, referencing standards used (e.g. ICD[10], SNOMED[11])	Ensures indicators reported are uniform across different health programs
Data Security & Privacy	The App operates under secure connectivity, which meet data protection and regulations of individual countries to avoid loss and corruption of sensitive data, and mitigate cyber-attacks, whether data is at rest or in transmission. Conforms to national privacy laws. Includes processes such as: — Two factor authentication — Authorization/Access Control — De-identified data — Data encryption	Encourages GDPR[12] (should no national data security policies exist) to ensure a system that: — preserves data integrity — identifies & mitigates risks — provides relevant parties security processes

[10] ICD : International Classification of Diseases
[11] SNOMED: Systematized Nomenclature of Medicine
[12] GDPR: General Data Privacy Regulation

Procurement Model			
CHARACTERISTIC	**MINIMAL REQUIREMENT**	**OPTIMAL REQUIREMENT**	**COMMENT**
Procurement Model	— Individual components of the toolkit can be procured directly by a MoH[13] and through global procurement agencies — Retirement or End-of-Life services	— Toolkit components are bundled and available via global procurement agencies[14] — Retirement or End-of-Life services	

[13] MoH : Ministry of Health

[14] Examples of global procurement agencies: UNICEF Supply Division, ASRAMES DRC, and CHMP Kenya

Appendix A: Software Product Quality Characteristics [15]

The ISO 25010 standard includes eight characteristics for which software quality characteristics may be defined against and measured during software development, depending on the software's intended use[iii]. These characteristics are addressed throughout the TPP.

Functional Suitability	Degree to which a product or system provides functions that meet stated and implied needs when used under specified conditions
Performance Efficiency	Performance relative to the amount of resources used under stated conditions
Compatibility	Degree to which a product, system or component can exchange information with other products, systems or components, and/or perform its required functions, while sharing the same hardware or software environment
Usability	Degree to which a product or system can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use
Reliability	Degree to which a system, product or component performs specified functions under specified conditions for a specified period of time
Security	Degree to which a product or system protects information and data so that persons or other products or systems have the degree of data access appropriate to their types and levels of authorization
Maintainability	Degree of effectiveness and efficiency with which a product or system can be modified by the intended maintainers
Portability	Degree of effectiveness and efficiency with which a system, product or component can be transferred from one hardware, software or other operational or usage environment to another

[15] Adapted from ISO/IEC 25010 Software product quality model [iii]

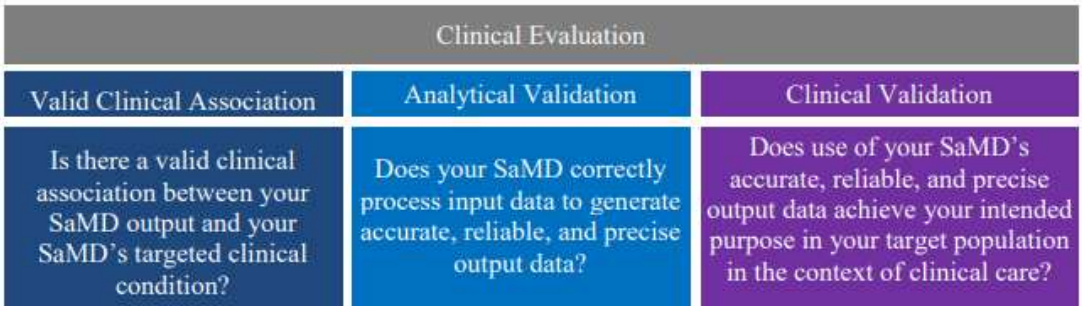
Appendix B: Software as a Medical Device (SaMD) Clinical Evaluation Process[16]

Guidance on the process of Clinical Evaluation of SaMDs:

1. **Valid Clinical Association**: Generate evidence to ensure the clinical association between the SaMD output and the targeted SaMD condition is supported by evidence. Evidence can be based on literature review, clinical care guidelines, clinical experience, etc. For algorithms that include novel clinical associations, evidence should be collected in the form of secondary data analyses, randomised clinical trials, cohort studies, etc.

2. **Analytical Validation**: Generate evidence that the algorithm has been designed correctly to represent the specific intended use. The algorithm is validated internally to show input data is processed correctly into expected output data. Previously collected curated databases (i.e. adjudicated clinical datasets where patient outcome is known) can be used for this purpose

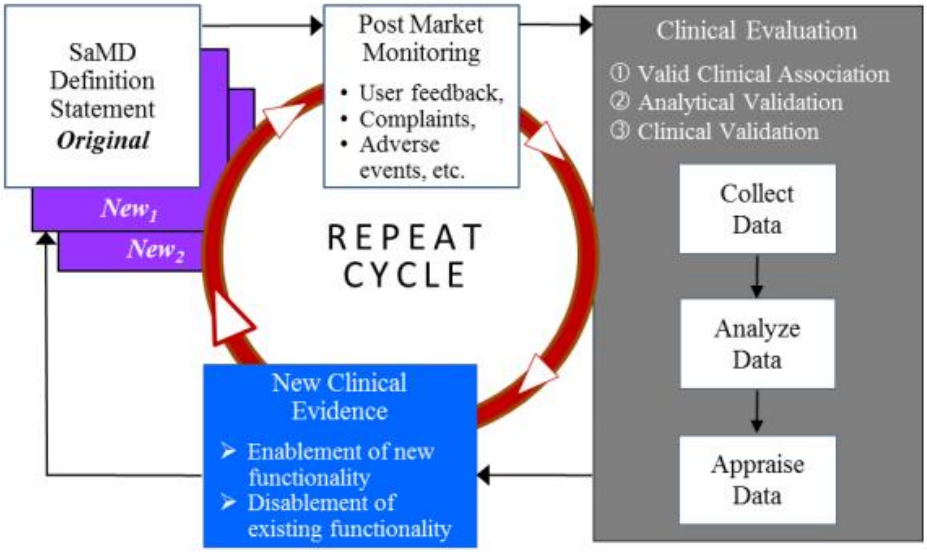
3. **Clinical Validation**: Generate evidence to ensure the algorithm produces clinically relevant outputs. This steps provides assurance that the algorithm is safe for use in the target population and users achieve clinical meaningful outcomes. Clinical can be demonstrated by either:
    a. Referencing existing data from studies conducted for the same intended use;
    b. Referencing existing data from studies conducted for a different intended use, where extrapolation of such data can be justified; or
    c. Generating new clinical data for a specific intended use



[16] Adapted from FDA's Software as a Medical Device (SAMD): Clinical Evaluation[ii]

Appendix C: Pathway for Continuous Learning – Use of Real World SaMD Performance Data in Ongoing SaMD Clinical Evaluation [17]

Clinical evaluation within the continuous learning loop of SaMDs. The SaMD can change to incorporate new inputs, target new populations, etc. New data may need to be collected and analysed to modify the SaMD to fit the new definition.



[17] Adapted from FDA's Software as a Medical Device (SAMD): Clinical Evaluation[ii]

References

[i] World Health Organization. (2016). Monitoring and evaluating digital health interventions: a practical guide to conducting research and assessment. World Health Organization. http://www.who.int/iris/handle/10665/252183. License: CC BY-NC-SA 3.0 IGO

[ii] U.S. Food & Drug Administration. "Software as a Medical Device (SAMD): Clinical Evaluation. Guidance for Industry and Food and Drug Administration Staff". December 8, 2017. Accessed December 1 2018. https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM524904.pdf

[iii]ISO 25000 Software Product Quality, ISO/IEC 25010. Accessed December 5, 2018. https://iso25000.com/index.php/en/iso-25000-standards/iso-25010?limit=3&limitstart=0