Supplementary File 2: Second draft (v.1.0) of the target product profile prepared by KP for the first round 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:

- App (mobile app): software that houses a clinical decision-support algorithm.
- App owner: healthcare programme or the healthcare implementer using 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. temperature, respiratory rate, oxygen saturation) 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 |

| **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 | | |
| Algorithm Content | Built on:<br>— well-established clinical evidence based on WHO/international/local clinical care guidelines, peer-reviewed articles (systematic reviews, original clinical research), clinical experience/practice; **or**<br>— appropriate validation research* | | *Refer to guidelines on best practices or evidence-based medicine to conduct research activities |
| Algorithm Treatment Recommendations | Therapeutic recommendations shall be compliant with national treatment guidelines and national EML[1] | Same and the algorithm shall provide recommendations which support antimicrobial stewardship | Optimal: recommendations support the appropriate selection, dosage and duration of antimicrobial treatment, 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 App is a medical device, the App shall also have regulatory approval | |
| Compatible Devices | — Smartphones<br>— Tablets<br>— 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 | Android for smartphones and tablets, and Windows for computers | OS[3] agnostic | |

[1] EML: WHO's Model list for Essential Medicines
[2] POC : Point of Care diagnostics
[3] OS: Operating System

| **Electronic Clinical Decision-Support Algorithm** | | | |
|---|---|---|---|
| **CHARACTERISTIC** | **MINIMAL REQUIREMENT** | **OPTIMAL REQUIREMENT** | **COMMENT** |
| Content Transparency | The algorithm is "human interpretable". The App owner[4] comprehends the algorithm decision-making processes | The App owner has 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 (i.e. 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:<br>A) Analytical verification: the algorithm output is accurate and reproducible<br>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?"<br>(See FDA's SaMD Clinical Evaluation for current guidance[i], Appendices B and C) |
| Algorithm Validation | The level of validation will depend on the eCDA status as a Software as a Medical Device (SaMD).<br>Refer to upcoming rulings from regulatory bodies such as the FDA or the European Commission | | Answers the question "did I build the right model"?<br>(See FDA's SaMD Clinical Evaluation for current guidance[i], Appendices B and C) |
| Machine Learning | None. The algorithm is static | ML[5] is applied to generate data on the algorithm performance and improve content, inform healthcare system processes, etc.<br><br>Predictive model based on the cloud running in the back-end and not changing the decision logic. Gating mechanisms are in place to trigger decisions for a change in the algorithm to go live. | Optimal: A gating mechanism is in place to allow a change in the algorithm to go live.<br>Example: an alert algorithm for dengue is triggered based on historical surveillance data. The district officer approves the implementation of the change in the algorithm across the district |

[4] App owner: healthcare programme or the healthcare implementer using the toolkit in the intended setting
[5] 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 white blood cell count) | | |
| Disease Likelihood | Based on POC data or disease likelihood where POC tests are not available | Based on pre-test probability and POC positive/negative predictive values | Minimal: application of a tests is based on prevalence, patient data and assumptions on the population that increases the likelihood of having a particular disease<br>Optimal: disease likelihood is based on both pre-test probability and diagnostic positive/negative predictive values |
| 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 | | The App performance has been established under real-world conditions in the implementation setting defined by the algorithm (e.g. if the App is meant to be used by community health workers in a health facility Level 1, then the App is validated in this setting)<br><br>Performance metrics can be generated from e.g.:<br>— Clinical usability and user interface testing<br>— User acceptance testing<br>— Failure behaviour testing (test operation in specified degraded mode)<br>— Efficiency testing (rational use of resources) |
| 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[6]/HL7[7] standards are adhered to | |
| Context Configuration | — Language: UN official languages<br>— Local time<br>— Local weights and measures | — Language: option to customise to local official language<br>— Local time<br>— Local weights and measures<br>— 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 | The user can update the list of medicines, add clinics and algorithm modules | — Easy functioning, no need to contract technology support<br>— Core changes to the algorithm are done remotely with user approval | |
| User Access Rights | Appropriate data access is provided based on specific roles | | Roles may include data manager (facility supervisor) or data entry person (nurse) |

[6] HIE: Health Information Exchange
[7] HL7: Health Level Seven

| | | | |
|---|---|---|---|
| Expert Support | None | Built-in access to online/remote expert advice to assist in patient consultation via SMS[8], 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)<br>— 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[9] and HIS[10] | |
| 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 | Support multiple, simultaneous active consultations with resume capability | | Multiple active consultations in the App domain |
| 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 |
| Encounter | Multiple patient windows can be opened at a time by one user (multiple encounters are supported) | | |
| Follow up | Ability to retrieve patient information using patient registration information (i.e. anonymous patient ID) | Same and built-in function to send patient reminders via SMS or phone call | The minimal implies data recoverability, also covered below in Data Characteristics section |
| 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 | | |

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

| | | |
|---|---|---|
| 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[11], barcode, biometric | |
| Data Validation | The system validates data entry to prevent errors that diminish value of the data or the outcome | | |
| Data Ownership | All data collected via the App in the implementation setting is owned by the App owner (i.e. healthcare programme) | | |
| Data Storage | Data is stored in a server/cloud accessible to high-level country authority on a web interface | Data can be stored in a server within the country | |
| 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 | De-identified output data can be exchanged with different authorities with authorization by local authorities | De-identified output data can be exchanged with different authorities | |
| 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 |
| Data Dictionary | Available, referencing standards used (e.g. ICD[12], SNOMED[13]) | | Ensures indicators reported are uniform across different health programs |

[11] GPS: Global Positioning System
[12] ICD : International Classification of Diseases
[13] SNOMED: Systematized Nomenclature of Medicine

| | | |
|---|---|---|
| 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.<br><br>Conforms to national privacy laws. Includes processes such as:<br>— Two factor authentication<br>— Authorization/Access Control<br>— De-identified data<br>— Data encryption | Encourages GDPR[14] (should no national data security policies exist) to ensure a system that:<br>— preserves data integrity<br>— identifies & mitigates risks<br>— provides relevant parties security processes |

[14] 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[15] and through global procurement agencies<br>— Retirement or End-of-Life services | — Toolkit components are bundled and available via global procurement agencies[16]<br>— Retirement or End-of-Life services | |

[15] MoH : Ministry of Health

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

## Appendix A: Software Product Quality Characteristics [17]

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[ii]. 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 |

[17] Adapted from ISO/IEC 25010 Software product quality model [ii]

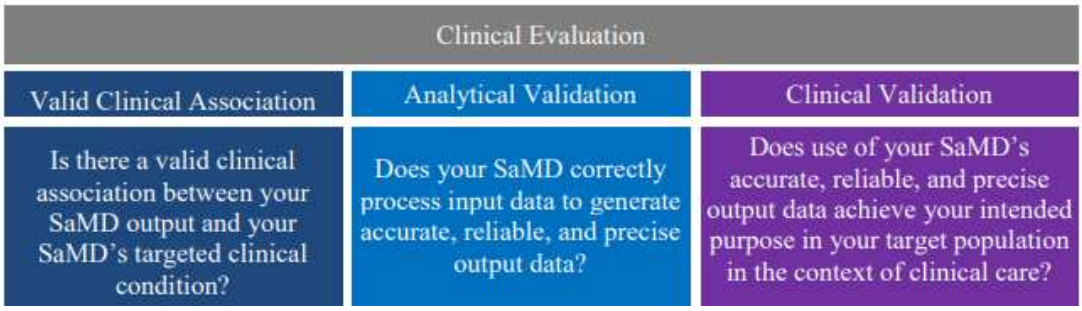
## Appendix B: Software as a Medical Device (SaMD) Clinical Evaluation Process[18]

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

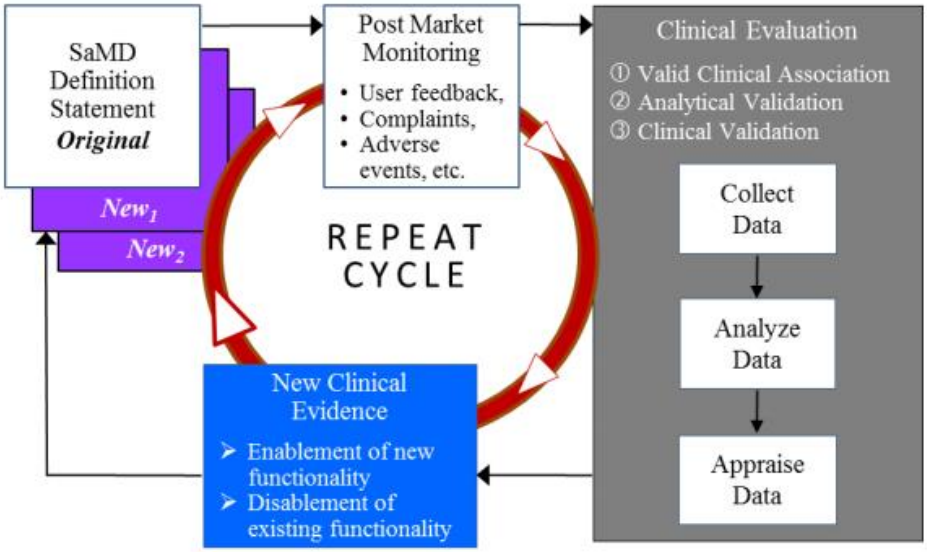
3. **Clinical Validation**: Generate evidence to ensure the algorithm produces clinically relevant outputs. This steps provides assurance that the algorithm is safe for use in the target population and users achieve clinical meaningful outcomes. Clinical can be demonstrated by either:
    a. Referencing 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




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

## Appendix C: Pathway for Continuous Learning – Use of Real World SaMD Performance Data in Ongoing SaMD Clinical Evaluation [19]

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.




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

## References

[i] 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

[ii] 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