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Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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TITLE: Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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Adaptive diseases intervention programme, Communicable and non-communicable dual epidemics, tuberculosis and diabetes dual epidemic, health systems, implementation methods

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1
2 55 **ABSTRACT**
3

4 56 **Introduction:** Most sub-Saharan African countries endure a high burden of communicable
5
6 57 diseases but also face a simultaneous rise of non-communicable illnesses. Interventions
7
8
9 58 targeting particular epidemics are often executed within vertical programmes. We aim to
10
11 59 develop a model that will strengthen health systems by shifting traditional vertical programmes
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13
14 60 to an adaptive diseases control approach through integrating communicable and non-
15
16 61 communicable diseases diagnosis and management using the tuberculosis (TB) and diabetes
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18
19 62 mellitus (DM) dual epidemic as a case study.
20

21 63 **Methods and analysis:** This programme will use a mixed research design, with both qualitative
22
23
24 64 and quantitative approaches. A prospective cohort design will be used in assessing integration
25
26 65 of TB and DM services that will enable early diagnosis of dual TB/DM cases. Lastly, a stepped-
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28
29 66 wedge cluster randomized trial will assess the impact of introducing individualized TB/DM
30
31 67 practices at the health care facility level. A blueprint for addressing communicable and non-
32
33 68 communicable dual epidemics will be developed using several tools and techniques such as a
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35
36 69 collection of stakeholders' views and literature reviews, monitoring of key indicators in the
37
38 70 TB/DM case study, and applying a system thinking approach to essential elements in the health
39
40
41 71 service delivery.
42

43 72 **Ethics and Dissemination:** Ethical approval was granted by The National Research Health Ethical
44
45
46 73 Committee with reference number NIMR/HQ/R.8a/Vol.IX/2988 and the implementation was
47
48 74 endorsed by the President Office Regional Administration and Local Government Authority. The
49
50
51 75 results will be proactively disseminated through peer-reviewed open access journals, policy
52
53 76 briefs, various stakeholders, public engagement activities, conference presentations, and social
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55 77 media.
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ARTICLE SUMMARY

Strengths and limitations of this study

- The study is conducted in pragmatic settings using a mixed study design to allow triangulation
- Considers all levels of service delivery while covering urban, semi-urban and rural settings
- The proposed ADEPT model outcome considers process and patient outcomes
- Lack of randomization of study settings or health facilities may introduce bias

INTRODUCTION

Tanzania like other sub-Saharan African countries endures a high burden of communicable diseases including multidrug resistant pathogens; but also a concurrent rise of non-communicable diseases (NCD) as populations urbanize, diets “westernize” and lifespans lengthen¹. The health system is largely inflexible and during various period of disease epidemics, the health management teams operate in crisis-mode with limited capacity to plan for a long-term disease prevention². Currently in Tanzania, planned interventions for several longstanding and socioeconomically draining epidemics like tuberculosis (TB) and diabetes mellitus (DM) and their associated comorbidities, are executed within disease specific or vertical programmes³. Vertical programmes operate in silos while in reality various communicable and NCDs and treatments can influence one another, and overlap in⁴⁻⁷ populations of shared genetic backgrounds or environmental exposures, and in communities with similar socioeconomic conditions or behaviours. Vertical programmes can significantly constrain health care delivery, and represent a top-down approach that is rarely efficient or cost-effective, particularly when considering health challenges⁸.

This sobering fact has been illuminated in different vertical programmes. In Tanzania, compendium of research studies uncovered a health systems gridlock for patients trying to

1
2 105 negotiate the road from diagnosis to treatment of TB^{4,7}. There was a widespread underuse of
3
4 106 the technologies mostly due to inadequate knowledge and skills on clinical application and
5
6 107 interpretation of molecular diagnostics results. Likewise, there was not only a low response to
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8
9 108 the international consensus but also absence of linkage to care for patients presenting with TB
10
11 109 but failing to be screened for DM and triaged to adequate DM services ⁹. Similarly, in Tanzania
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13
14 110 DM services are centralized at the district and referral health facilities but also front-line health
15
16 111 care providers were ill-prepared for DM management. Research studies conducted in different
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19 112 programmes to identify multimorbidity particularly the NCD have found a considerable client
20
21 113 harbouring the burden of multiple diseases. The observed increasing prevalence of dual
22
23
24 114 communicable and emerging non-communicable multimorbidity epidemics and the existing
25
26 115 systemic bottlenecks suggest modification of models of health care delivery. We developed a
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29 116 model to strengthen health systems by shifting traditional vertical programmes to an adaptive
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31 117 diseases control approach through integrating communicable and NCDs. Henceforth, we
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33
34 118 describe the strategy to establish a contemporary **Adaptive Diseases control Expert Programme**
35
36 119 in Tanzania (Figure 1) (**ADEPT**), focusing on the TB/DM co-epidemic.

37
38 120 The dual TB and DM epidemic is ideal as a case for our ADEPT model because worldwide evidence
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40
41 121 shows a 3-fold increase of active TB in populations with DM compared to those without DM while
42
43 122 the global prevalence of TB in DM populations ranges from 1% -14%^{10,11}. In Tanzania, the effect was
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45
46 123 slightly higher and estimated at nearly 4-fold¹². Indeed, stakeholders from The International
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48 124 Union Against Tuberculosis and Lung Disease and the World Diabetes Foundation outlined the
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51 125 historic Bali Initiative on TB and DM (endorsed by World Health Organization (WHO)), stating:
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53 126 “▪That TB and DM represent two of the greatest global health challenges of our time, and their
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55 127 convergence globally represents a looming co-epidemic,
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57
58 128 ▪That this looming co-epidemic threatens progress against TB,
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60 129 ▪That, based on what we have learned from past co-epidemics, particularly TB-HIV, we must act

1
2 130 early and decisively to avoid large numbers of avoidable deaths”^{13 14}.
3
4 131 We understand this urgency all too well in Tanzania. Recently, we have observed an increase in
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6
7 132 the incidence of dual diagnosed patients with TB/DM epidemic ranging from 4% of all TB patients
8
9 133 in rural areas to 17% in urban settings, resulting in a 5-fold increase of death compared to TB
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11
12 134 patients without DM^{15 16}. Importantly, our research has determined that these deaths primarily
13
14 135 occur *early*, in the first three months of TB treatment^{15 16}. We now understand that this high and
15
16 136 early mortality from TB/DM in Tanzania is due to both programmatic and biological factors¹⁷. For
17
18
19 137 example, TB and DM services are not linked and these separated service lines lead to delayed
20
21 138 interventions for both diseases¹⁸. Interestingly, targeted drug therapy of dual TB/DM disease
22
23
24 139 may also open new ways of enhancing the effect of essential drugs against either disease¹⁹. Thus,
25
26 140 data have suggested that the first-line anti-DM drug metformin could be a promising candidate
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28
29 141 for host-adjunctive anti-TB therapy, by reducing chronic inflammation and enhancing immune
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31 142 response²⁰.
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34 143 Yet, other biological factors also contribute to poor TB/DM treatment outcomes including DM-
35
36 144 related alterations in drug absorption and metabolism resulting in sub-therapeutic anti-TB drug
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38 145 serum concentrations,²¹ and altered inflammatory/anti-inflammatory host immune defences.
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41 146 Furthermore, TB disease itself may worsen control of hyperglycaemia leading to uncontrolled
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43 147 DM²². In turn, patients with uncontrolled DM also have higher bacterial burdens of *M.*
44
45
46 148 *tuberculosis* and more extensive lung disease, and therefore achieving anti-TB drug
47
48 149 concentrations at the most optimal of levels may be even more important in patients with DM²³
49
50
51 150²⁴. Yet, in our prior work in Tanzania, we found sub-therapeutic drug concentrations to occur in
52
53 151 the majority of all TB patients^{25 26}. While international standards mention therapeutic drug
54
55 152 monitoring to guide TB/DM individualized dose adjustment²⁷, few programmes from TB-endemic
56
57
58 153 settings have carried these recommendations forward²⁸. Although the Tanzania Ministry of
59
60 154 Health recognizes the challenge of the TB/DM epidemic, the vast majority of health facilities have

1
2 155 not been able to implement international standards of TB/DM care. Therefore, this research
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4 156 project will also take the opportunity to underpin implementation of the international standards
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6 157 for controlling the TB/DM in the health system and conduct applied research to answer critical
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8
9 158 scientific questions of direct patient benefit while simultaneously training the next generation
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11
12 159 of health systems scientists.

13
14 160 The overall study aim is to integrate TB/DM diagnosis and optimal management strategies in
15
16 161 client-friendly clinics as part of an adaptive disease control framework to inform future best
17
18
19 162 policies for integrating care of communicable and NCDs in Tanzania. The objectives are given
20
21 163 below, and have been divided into the following;

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24
25 164 I. Objective 1. Integrate TB, and DM services.

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27
28 165 To study how early and accurate bidirectional screening of TB, including TB-HIV, and DM can be
29
30
31 166 established in a client-friendly way while investigating how early and accurate treatment of dual
32
33 167 TB/DM or TB-HIV/DM cases can be linked to specialized care and improve outcomes, and if
34
35
36 168 feasible to sustain treatment at the primary health care level. Furthermore, investigation on how
37
38 169 quality assurance for the laboratories serving TB/DM at the primary health care level can be
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41 170 established.

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44 171 II. Objective 2. Deliver international standards of care for optimizing favourable outcomes.
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1
2 172 To study how to apply diagnostic technologies such as WHO endorsed TB diagnostics for
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4 173 susceptibility testing, therapeutic drug monitoring for anti-TB medicine and HbA1c for
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6
7 174 monitoring of DM disease severity to deliver best practice for optimizing favourable dual
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9 175 TB/DM treatment outcomes Furthermore, to estimate the incidence and associated risk
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11
12 176 factors for treatment failure during dual TB/DM treatment, including the development of *M.*
13
14 177 *tuberculosis* resistance, and whether the hypoglycaemic drug, metformin may have an
15
16 178 adjunctive anti-TB effect.

- 18
19
20 179 III. Objective 3; Capacity building for training ADEPT health care workers and implementation
21
22 180 & health system scientists

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24
25 181 To study how short-course training to the front-line health care providers in best
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27
28 182 practices for dual TB/DM and other comorbidities at varying health system levels can
29
30
31 183 be provided and be reflected in outcome of WP-1 and WP-2.

32 33 184 **METHODS AND ANALYSIS**

34 35 36 185 **Conceptual framework of the ADEPT model**

37
38 186 The ADEPT model pioneers the systems thinking methodology described by Swanson and
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40
41 187 colleagues to guide integrative changes in health practice, education, research and policy ²⁹.

42
43 188 We proposed to introduce ADEPT first to the dual TB and DM epidemic as a case study of
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45
46 189 integrating communicable (TB) and non-communicable (DM) diseases ^{30 31} to engage currently
47
48 190 siloed policy makers, researchers, and service providers ³². The proposed ADEPT model is
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50
51 191 overarching by three principles with interdependent themes; transformational leadership,
52
53 192 collaboration, and constant interactive learning. ADEPT will be evaluated using the logic
54
55 193 framework developed by the WHO/US-Centre for Diseases Control and Prevention (US-CDC)
56
57
58 194 (Figure 2) ³³. The design of input and output pillars reflect largely on the archetypical work
59
60

1
2 195 designed by Potters and Brought in 2004 for health system strengthening³⁴. This includes a four-
3
4 196 tier hierarchy with nine-interdependent elements as depicted in Figure 3.

5
6
7 197 **Role, Structural and System capacity:** ADEPT will mobilize physicians and nurse officers working
8
9 198 at TB, DM, or general clinics at the regional level regardless of facility level. The team will serve
10
11 199 as a Regional Technical Working Group (RTWG), and will be empowered to serve as mentors in
12
13
14 200 the Region to support the health system to deliver best practices in patients with dual
15
16 201 communicable and NCDs. The formed team will operate under the Regional Medical Officer
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18
19 202 (RMO), a newly formed structure that will also link with the National Technical Working Groups
20
21 203 (NTWG) (Figure 1). RTWG under the leadership of RMO will conduct regular discussion with all
22
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24 204 stakeholders supporting the communicable and or NCDs intervention and associated co-
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26 205 morbidities. The discussion emanating from the meetings will guide local decision but also
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28
29 206 communicated to the Ministries; responsible for Health and Regional Administration and Local
30
31 207 Government Authorities, and shared with responsible NTWG for prioritization (Figure 1).
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33
34 208 The ADEPT consortium will meticulously and continuously explore gaps that will progressively
35
36 209 evolve the system toward people-centred health system³⁵.

37
38 210 **Staff and Personnel Training:** ADEPT has collaborated with National Training Centres and
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41 211 hospitals/facilities that provide advanced/specialized care of patients in creating modules for
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43 212 training of the front-line healthcare providers (HCPs). Leadership and supervisory lines will be
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46 213 strengthened simultaneously with increasing accountability and establishment of a clinical
47
48 214 audit programme. ADEPT has also created local technical working groups composed of senior
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51 215 front-line HCPs currently empowered with skills and knowledge for integrating and clinical
52
53 216 management of communicable (TB) and non-communicable (DM) diseases³⁶. The
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55 217 empowerment of HPCs has been facilitated by those training modules delivered as web-based
56
57
58 218 or m-Health platforms for continuous professional development that has increased the reach
59
60 219 to all HCPs that would otherwise not be possible due to limited funds. The designed modules

1
2 220 are not only adaptive to cover HCPs with different skills (for example, clinicians and nurses) but
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4 221 modules can be updated remotely should new processes need to be introduced. Importantly,
5
6 222 the HCPs have endless access and updated alerts to their mobile numbers or emails prompting
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9 223 them to complete a new module.

10
11 224 **Tools:** Equipment and consumables for piloting the programme have been inventoried at
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13
14 225 participating facilities within the communities of study. Supplies for DM were frequently not
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16 226 available or inadequately stocked and these including glucometers, glucostrips, HbA1c devices,
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19 227 therapeutic drug monitoring supplies, recording and reporting. These tools were funded
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21 228 temporarily through the Danish International Development Agency. TB consumables, supplies
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24 229 and tools were procured through conventional channels.

25 26 230 **Study design**

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29 231 This is a mixed research design; and applies both qualitative and quantitative approaches. Cross
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31 232 sectional design will be conducted for needs assessment and bidirectional screening while,
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34 233 prospective cohort designs will be deployed for and stepped wedged cluster non-randomized
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36 234 trial will be used in different work packages.

37 38 235 **Study area**

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41 236 The research project will be conducted in three regions of Tanzania; Dar es Salaam, Iringa, and
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43 237 Kilimanjaro. Districts that will participate include Ilala and Kigamboni for Dar es Salaam, Iringa
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45
46 238 Municipal, Kilolo and Mufindi for Iringa, and Moshi Municipal, Same and Siha for Kilimanjaro.

47 48 239 **Study outline**

49 50 51 240 **Objective 1 method: Integrate TB or TB/HIV and DM services**

52
53 241 A prospective observational of the health system study will be conducted. It is recommended
54
55 242 that at least 30 health facilities are needed for reliable and accurate results therefore each region
56
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58 243 will contribute at least 10 health facilities at various levels for integrating TB or TB/HIV and DM
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60 244 services³⁷. The catchment area includes one- referral hospital, three district hospitals and at least

1
2 245 6 health centres/dispensaries. Integration will start stepwise from the referral (secondary or
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4 246 tertiary) hospitals levels towards primary health care clinics, i.e. the district hospitals followed
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6
7 247 by the health centres and dispensaries. Needs assessments have been carried to identify capacity
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9 248 of the health facility and decide whether the health facility will operate as a “one-stop shop”
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11
12 249 defined as TB and DM services provided at the same time using adjacent rooms, “partial
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14 250 integration” defined as health care providers swaps between clinics, or “remote integration”
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16 251 through cross referral of DM to TB services. Entries of TB/DM integration in TB services or TB/HIV
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19 252 services will be at the TB and DM clinics³⁸. TB diagnosed cases will receive DM testing while at
20
21 253 the DM clinics, presumed TB will be screened according to the standard national TB algorithm.
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23
24 254 An algorithm to identify cases with high potential for treatment failure including those with TB
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26 255 drug resistance and other DM co-morbidities will be identified and tabled for expert discussion.
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29 256 Participants will be managed according to the collaborative TB/DM services framework guideline
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31 257 ³⁹ as follows;

34 258 **Sub-objective 1.1. Method. Screening TB in DM patients**

36
37 259 DM cases especially those with sub-optimal control as defined by HbA_{1c}, will be screened for
38
39 260 active TB. The algorithms for active TB case findings will be applied as described elsewhere^{40 41}.

42 261 **Sub-objective 1.2. Method. Screening DM in TB patients**

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45 262 All TB cases irrespective of having “classical” symptoms (polyuria, polydipsia and polyphagia),
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47 263 cases will be screened with glucometer and Interpretation of results is as follows; if the random
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49
50 264 blood/serum glucose (RBG) \leq 7.8 mmol/L or fasting blood glucose (FBG) \leq 6.1 mmol/L without
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52 265 DM symptoms, blood or serum glucose will be considered normal. If the RBG is 7.8 – 11.0 mmol/L
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54
55 266 or FBG is 6.2 – 6.9 mmol/L, this will be considered as pre-DM. When RBG is \geq 11mmol/L or FBG is
56
57 267 \geq 7.0 mmol/L this is DM. To exclude patients with transient hyperglycaemia due to cytokine
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59
60 268 stimulation (false DM diagnosis), Hb_{1c} is used to confirm the diagnosis of DM in TB cases ²².

1
2 269 Individuals with pre-DM or DM will further be tested with HbA1c, and the interpretation of the
3
4 270 results are as follows; HbA1c of ≤ 38 mmol/mol ($\leq 5.6\%$); $39 < 48$ mmol/mol ($5.7\% < 6.5\%$), and ≥ 48
5
6 271 mmol/mol ($\geq 6.5\%$) will be reported and considered as normal, pre-DM and DM respectively⁴². TB
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9 272 cases with pre-DM will be re-evaluated in the mid-term of TB treatment and TB treatment
10
11 273 completion to identify if the condition has resolved, or progressed or remained static; if pre-DM
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13
14 274 will have advanced to DM, patients will be treatment according to the DM guideline. The TB IPC
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16 275 practice that is applicable in HIV clinics will be applied³⁸.

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19 276 **Objective 2 methods: Deliver International Standards using diagnostics for optimizing**
20
21 277 **outcomes**

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24 278 Health facilities effectively integrating dual TB/DM services will enter a next phase of delivering
25
26 279 the best practice in dual TB/DM patients (Figure 4). The implementation design will study the
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28
29 280 best clinical practice of dual TB/DM services comprising of TB diagnostics including susceptibility
30
31 281 testing, anti-TB therapeutic drug monitoring, and HbA1c for monitoring the DM and guide
32
33
34 282 selection and combination of both anti-TB and anti-DM drugs. Under sequential roll out, or
35
36 283 stepped wedge cluster trial design; facilities in each region integrating TB/DM services will be
37
38 284 stepwise allocated; (referral hospitals>>district hospitals>>>health centres/dispensaries) to
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41 285 incorporate the best clinical practice package in dual TB/DM case treatment. Three centres from
42
43 286 each region will be allocated to start the best practice of TB/DM package interventions
44
45
46 287 concurrently. A new facility level will be subsequently allocated to implement the best practice
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48 288 TB/DM package in steps of 3 months (quarterly) intervals such that a complete coverage of 30
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51 289 health facilities in WP1 will be obtained after 2 years and 9 months. In our previous observational
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53 290 study, we found 16% of TB/DM patients had unfavourable outcomes in Tanzania ¹⁶. We assume
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55 291 that the best practice package will reduce the unfavourable event rate to 8 %. To achieve 90%
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57
58 292 power to detect this difference with a significance level of 5% with a non-compliance estimated
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60 293 at 8% ⁴³, the adjusted minimum sample size of 970 TB/DM patients will be rigorously followed ⁴⁴.

1
2 294 TB/DM or TB-HIV/DM individuals will provide baseline sputum for culture and drug susceptibility
3
4 295 testing as well as smear microscopy. Patients will also test for HbA1c and renal function test to
5
6 296 assess for severity of DM. Two weeks after starting anti-TB medication, blood will be collected
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8
9 297 for therapeutic drug monitoring of anti-TB drugs. Collection of blood will be through dry blood
10
11 298 spot and transported to the Biotechnology Laboratory/Kilimanjaro Clinical Research Institute
12
13
14 299 through Expedited Mail Services. The dry blood spot collection will be processed for testing the
15
16 300 serum drug levels starting with rifampicin then isoniazid, and pyrazinamide using an assay
17
18
19 301 validated according to international guidelines⁴⁵ Results will be communicated before day 21 of
20
21 302 anti-TB treatment, and if needed the anti-TB dosage adjustment will be made. A TDM strategy
22
23
24 303 suitable for fixed dose combination regimen will be applied. In summary, the therapeutic drug
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26 304 monitoring will be performed at week 2 of TB treatment, based on plasma concentrations
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28
29 305 results, the appropriate FDC tablets can be selected^{46 47}. Serum drug exposure that differ at least
30
31 306 25% from target concentrations will be considered as clinically relevant ⁴⁸. Therefore, those
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33
34 307 below the target will be eligible for dose adjustment. Two weeks after dose adjustment, the drug
35
36 308 concentrations will be confirmed⁴⁶. In the continuation phase, the appropriate fixed drug
37
38 309 combination of rifampicin and isoniazid can be selected, based on earlier measured drug
39
40
41 310 concentrations. In addition, routine pharmaco-vigilance will complement the safety data of this
42
43 311 strategy. TB/DM cases will have monthly mycobacteriological monitoring for detection of
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46 312 microbiological treatment failure. While DM monitoring will include the assessment of
47
48 313 retinopathy, impaired wound healing (diabetic foot), and nephropathy^{49 50}. HbA1c and renal
49
50
51 314 function tests will also be followed at month 3 and 6 to enable further anti-DM regimen
52
53 315 adjustment.

316 **Objective 3 methods: Capacity building on training and applied research**

57
58 317 Training of the frontline health care providers will follow the “*classical diffusions of innovation*
59
60 318 *theory*” drawn by Dearing,2009 ⁵¹. ADEPT will change the current passive delivery of

1
2 319 international standards of care into an active approach, and the training will be delivered in a
3
4 320 step-down approach and will be implemented in phases;

- 5
6
7
8 321 ▪ Phase 1- includes a self-learning package with assessment delivered through a web-based
9
10 322 platform. The assessment will be shared to the ADEPT team prior to attending the next
11
12 323 phase.
- 13
14
15 324 ▪ Phase 2- Learners achieving > 80% of the web-based assessment will be invited to attend
16
17 325 training of the trainer (ToT) workshop. Emphasis during this phase will be to expose
18
19 326 individuals to acquire the principles, of the technology or innovations or intervention and
20
21 327 conduct practical on dual TB/DM and associated co-morbidities including HIV-coinfection,
22
23 328 malnutrition and non-communicable chronic lung diseases.
- 24
25 329 ▪ Phase 3- ToT will receive package/materials to train frontline health service providers in
26
27 330 their district. This will be the minimum package for providing dual TB and DM care with
28
29 331 short modules and directives to the task to be conducted. ToT will deliver the training to
30
31 332 the selected health facilities assigned to him/her.
- 32
33 333 ▪ Phase 4- Competency of the ToT will combine assessment of best practice portfolio
34
35 334 documented at their clinics, and also practice implemented by the trainers s/he
36
37 335 empowered.

38
39 336 Medical education modules on TB/DM and associated comorbidities will be tailored to different
40
41 337 roles and associated quality control questions for assessing the level of acquired skills for each
42
43 338 type of health care provider (clinicians, nurses, pharmacist and laboratory staff). A minimum
44
45 339 threshold of quality control pass will be included as one of the criteria to qualify the health facility
46
47 340 to integrate TB/DM services. Other criteria will be sought from the health facility needs
48
49 341 assessment tools, which will include availability, and operational infection prevention policy for
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1
2 342 TB controls and equipment for DM diagnosis and prevention of complications. Knowledge
3
4 343 comparison will be made pre and post training.
5

6 344 **Data collection**

8
9 345 Data collection will be done under routine patient care in clinics. Data management will follow
10
11 346 and adhere to the Tanzania Code of Conduct for Research Integrity. Qualitative data will be
12
13
14 347 summarized in qualitative case record forms while quantitative data will be available in the Multi-
15
16 348 Schema Information Capture database, which is a customizable format current in use in
17
18
19 349 Kilimanjaro, utilizing secure encryption services (www.mysql.com). Data collection, transfer,
20
21 350 entry, validation, queries generation, audit, archival and ownership will be detailed in specific
22
23
24 351 standard operational procedures as described elsewhere⁵².

26 352 **Data analysis plan on dual TB and DM**

27
28
29 353 Outcome measures include;

30
31 354 Bidirectional screening and diagnosis of dual TB/DM disease

- 32
33
34 355 • Proportion of facilities capable of providing best practice of TB/DM services
- 35
36
37 356 • Proportion of laboratories supporting dual TB/DM services
- 38
39
40 357 • Proportion of health care providers trained in best practice on dual TB/DM services
- 41
42 358 • Proportion of registered TB patients screened for DM
- 43
44
45 359 • Proportion of diabetes patients screened for TB
- 46
47 360 • Proportion of registered TB patients identified with presumptive DM among patients
48
49 361 and screened for DM and vice versa
- 50
51
52 362 • Proportion of registered TB patients tested for DM and vice versa.
- 53
54
55 363 • Proportion of registered TB patients diagnosed with DM and vice versa.
- 56
57 364 • Proportion of registered DM patients with TB referred to a TB clinic.
- 58
59 365 • Proportion of registered DM patients with TB started on TB treatment and vice versa.
60

1
2 366 **Dual TB/DM treatment outcomes**

3
4 367 TB treatment outcomes

- 5
6
7 368 • Proportion of TB/diabetes patients with favourable outcomes (cured, or treatment
8 complete) or unfavourable outcomes (death, lost to follow-up, treatment failure)
9 369
10
11 370 • Proportion of TB/DM recurrence of TB one year after completion TB treatment as
12 determined by sputum culture and advanced genomic technologies.
13
14 371
15
16 372 • Proportion of TB/DM acquiring DR-TB at the time of failure or TB recurrence
17
18
19 373 • Proportion of TB/DM patients with sub-optimal concentrations of first line anti-TB drugs
20 at 2nd-week of treatment
21 374
22
23
24 375 • Proportion of TB/DM with abnormal HbA1c compared to the baseline
25
26 376 • Proportion of TB/DM patients with treatment adjustment
27
28

29 377 DM complications at baseline and at the end of TB treatment

- 30
31 378 • Proportion of TB/DM with hypertension, kidney dysfunction as estimated by the
32 albuminuria/proteinuria, blood urea nitrogen and creatinine
33 379
34
35
36 380 • Proportional of TB/DM with neuropathy through assessment of bladder or erectile (male)
37 dysfunction, sensorimotor neuropathy, orthostatic hypotension, sudomotor neuropathy,
38 frequent non-infective diarrhoea or constipation
39 381
40
41 382
42
43
44 383 • Proportional of TB/DM with retinopathy as graded by severity (none, mild, moderate or
45 severe)
46 384
47

48
49 385 We will assess the pathway of patients' experience and acceptability of dual TB/DM services
50
51 386 ⁵³.Likewise we will assess the feasibility and acceptability of all steps of ADEPT model as
52 portrayed in Figure 2.
53 387
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55

56 388 **Conclusion**

57
58 389 Health systems in most of sub-Saharan Africa are fragile despite facing an enormous burden of
59 communicable diseases and NCDs. Unfortunately, resources are scare and therefore the
60

1
2 391 situation, as emblematic in the dual TB/DM epidemic in Tanzania, necessitates new thinking and
3
4 392 an approach that will eventually build resilient health systems.⁵⁴ The proposed ADEPT model will
5
6 393 challenge the status quo of the Tanzanian health system in addressing the existing systemic
7
8
9 394 bottlenecks. Yet a key element of the ADEPT model is to create and nurture a learning system,
10
11 395 teamwork, collective responsibilities, accountability, and leadership for a common favourable
12
13
14 396 future. Consequently, front line HCPs and other locals will be empowered to innovate around
15
16 397 health care delivery and changes that will be likely to have a long-term constructive effect²⁹.

18 19 398 **ETHICS AND DISSEMINATION**

20
21 399 This protocol has been approved at the local health research committee serving Kibong'oto
22
23
24 400 Infectious Diseases Hospital and National Health Research Committee with reference numbers
25
26 401 KNCHREC003 and NIMR/HQ/R.8a/Vol.IX/2988, respectively. Furthermore, the Ministries of
27
28
29 402 Health and Regional Administrative & Local Government Authority have endorsed
30
31 403 implementation of this protocol.

32 33 404 **AUTHOR CONTRIBUTIONS**

34
35
36 405 Each author has contributed significantly to and is willing to take public responsibility for one or
37
38 406 more aspects of the protocol. All authors contributed to the design and provided critical
39
40
41 407 revisions and approved the final version.

42 43 408 **FUNDING STATEMENT**

44
45
46 409 This study is fully funded by the Danish Ministry of Foreign Affairs, DFC File No. 17-03-KU.

47 48 410 **DATA STATEMENT**

49
50
51 411 The data sets that will be generated and analysed during the conduct of the study will be made
52
53 412 available according to the available laws and regulations

1
2 414 **ACKNOWLEDGEMENT**

3
4 415 The authors thank Professor Flemming Konradsen, University of Copenhagen, Denmark for his
5
6 416 valuable comments on the research study

8
9 417 **FIGURES LEGEND**

10
11 418 Figure 1: This model will break the siloed policy makers, health providers and researchers and
12
13 gradually transform the health system into a proactive self-organizing or self-repairing system.
14 419
15
16 420 Essential elements (Performance, Instance Selection, Critique, and Learning), if operated
17
18 effectively will form an adaptive learning system. The proposed TB/DM-ADEPT Model will
19 421
20
21 422 interconnect all interactive elements through: (a) Setting a regular single platform for policy
22
23 makers, researchers and service providers on TB/DM epidemic agenda (Learning element); (b)
24 423
25
26 424 Implementing international standards of dual TB and DM care through integrative TB/DM
27
28 collaborative services that will facilitate early diagnosis while providing individualized treatment
29 425
30
31 426 of patients with dual TB/DM disease (Performance element); (c) Conduct TB/DM applied
32
33 research in implementation and health system research science to determine how to deliver best
34 427
35
36 428 practices that will enable a people-centred health system (Critique element); and (d) Train PhD
37
38 429 and postdoctoral fellows to answer dual TB/DM health system challenges to strengthen applied
39
40 research capacity and hands-on skills to create a critical mass of the next generation of scientists
41 430
42
43 431 able to scale up TB/DM interventions and adapt to study other communicable/ non-
44
45 communicable disease intersections (Instance Selection element).
46 432

47
48 433 Figure 2: Logic framework model for measuring outcomes and impact

49
50 434 Figure 3: Hierarchy of needs for strengthening the health system as described by Potter &
51
52 Brough³⁴

53 435
54
55 436 Figure 4: Introduction of integration of TB/DM services thereafter stepwise introduction of
56
57 packages comprises of susceptibility, therapeutic drug monitoring, HbA1c for optimal TB/DM
58 437
59
60 438 case management at all levels of health facilities

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4 440 **COMPETING INTEREST STATEMENT:**
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6
7 441 None declared.
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11 443 **REFERENCES**
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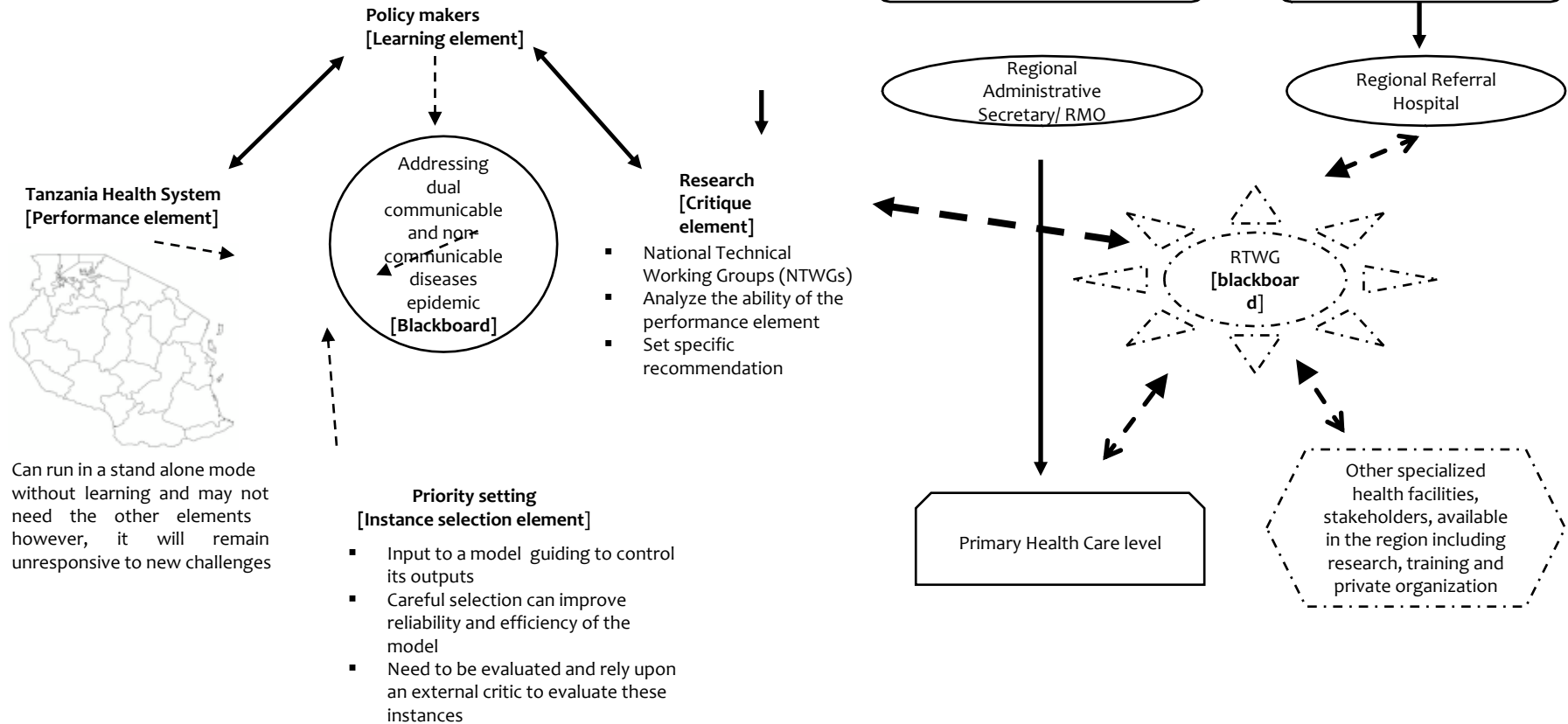
- 14 444 1. Institute for Health Metrics and Evaluation (IHME). Global Burden of Diseases (GBD)
15 445 Profile;Tanzania, 2010.
- 16 446 2. Commission on Global Health Risk Framework for the Future (GHRF). Accelerating Research and
17 447 Development to Counter the Threat of Infectious Diseases. The Neglected Dimension of
18 448 Global Security: A Framework to Counter Infectious Disease Crises. Washington (DC)2016.
- 19 449 3. Ministry of Health. Ministry of Health -Tanzania. Health Sector Strategic Plan IV (2015-2020),
20 450 2015.
- 21 451 4. Liyoyo A, Heysell SK, Kisonga RM, et al. Gridlock from diagnosis to treatment of Multidrug-
22 452 Resistant Tuberculosis (MDR-TB) in Tanzania: Illuminating Potential Factors for Possible
23 453 Intervention. *East African Health Research Journal* 2017;1(1)
- 24 454 5. Mpagama SG, Heysell SK, Ndusilo ND, et al. Diagnosis and interim treatment outcomes from the
25 455 first cohort of multidrug-resistant tuberculosis patients in Tanzania. *PLoS One*
26 456 2013;8(5):e62034. doi: 10.1371/journal.pone.0062034
- 27 457 6. Mpagama SG, Mangi E, Mbelele PM, et al. Gridlock from diagnosis to treatment of multidrug
28 458 resistant tuberculosis (MDR-TB) in Tanzania: Patients perspectives from the focus group
29 459 discussion. *bioRxiv pre print* 2018;doi: <http://dx.doi.org/10.1101/402594>. doi:
30 460 10.1101/402594
- 31 461 7. Mpagama SG, Mbelele PM, Chongolo AM, et al. Gridlock from diagnosis to treatment of
32 462 multidrug-resistant tuberculosis in Tanzania: low accessibility of molecular diagnostic
33 463 services and lack of healthcare worker empowerment in 28 districts of 5 high burden TB
34 464 regions with mixed methods evaluation. *BMC Public Health* 2019;19(1) doi:
35 465 10.1186/s12889-019-6720-6
- 36 466 8. Bryan L, Conway M, Keesmaat T, et al. Strengthening sub-Saharan Africa's health systems: A
37 467 practical approach | McKinsey & Company. *Health Systems & Services* 2010:1-11.
- 38 468 9. Harries AD, Murray MB, Jeon CY, et al. Defining the research agenda to reduce the joint burden
39 469 of disease from diabetes mellitus and tuberculosis. *Trop Med Int Health* 2010;15(6):659-63.
40 470 doi: 10.1111/j.1365-3156.2010.02523.x
- 41 471 10. Workneh MH, Bjune GA, Yimer SA. Prevalence and associated factors of tuberculosis and
42 472 diabetes mellitus comorbidity: A systematic review. *PLoS One* 2017;12(4):e0175925. doi:
43 473 10.1371/journal.pone.0175925 [published Online First: 2017/04/22]
- 44 474 11. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic
45 475 review of 13 observational studies. *PLoS Med* 2008;5(7):e152. doi:
46 476 10.1371/journal.pmed.0050152
- 47 477 12. Faurholt-Jepsen D, Range N, Praygod G, et al. Diabetes is a risk factor for pulmonary
48 478 tuberculosis: a case-control study from Mwanza, Tanzania. *PLoS One* 2011;6(8):e24215.
49 479 doi: 10.1371/journal.pone.0024215 [published Online First: 2011/09/14]
- 50 480 13. Bali Declaration on the Looming TB-Diabetes Co-epidemic. Stopping a looming Co-epidemic: A
51 481 global Summit on Diabetes and Tuberculosis; 2-3 November 2015; Bali-Indonesia.
52 482
53
54
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2 482 14. Kapur A, Harries AD, Lönnroth K, et al. Diabetes and tuberculosis co-epidemic: the Bali
3 483 Declaration. *The Lancet Diabetes & Endocrinology* 2016;4(1):8-10. doi: 10.1016/s2213-
4 484 8587(15)00461-1
- 5 485 15. Sariko ML, Mpagama SG, Gratz J, et al. Glycated hemoglobin screening identifies patients
6 486 admitted for retreatment of tuberculosis at risk for diabetes in Tanzania. *J Infect Dev Ctries*
7 487 2016;10(4):423-6. doi: 10.3855/jidc.7324
- 8 488 16. Faurholt-Jepsen D, Range N, PrayGod G, et al. Diabetes is a strong predictor of mortality during
9 489 tuberculosis treatment: a prospective cohort study among tuberculosis patients from
10 490 Mwanza, Tanzania. *Trop Med Int Health* 2013;18(7):822-9. doi: 10.1111/tmi.12120
- 11 491 17. Workneh MH, Bjune AG, Yimer SA. Diabetes mellitus is associated with increased mortality
12 492 during tuberculosis treatment: a prospective cohort study among tuberculosis patients in
13 493 South-Eastern Amahra Region, Ethiopia. *Infectious Diseases of Poverty* 2016;5(22):10. doi:
14 494 0.1186/s40249-016-0115-z
- 15 495 18. Harries AD, Kumar AMV, Satyanarayana S, et al. Addressing diabetes mellitus as part of the
16 496 strategy for ending TB. *Trans R Soc Trop Med Hyg* 2016;110:173-79. doi:
17 497 0.1093/trstmh/trv111
- 18 498 19. Singhal A, Jie L, Kumar P, et al. Metformin as adjunct antituberculosis therapy. *Sci Transl Med*
19 499 2014;6(263):263ra159. doi: 10.1126/scitranslmed.3009885 [published Online First:
20 500 2014/11/21]
- 21 501 20. Park S, Yang BR, Song HJ, et al. Metformin and tuberculosis risk in elderly patients with
22 502 diabetes mellitus. *Int J Tuberc Lung Dis* 2019;23(8):924-30. doi: 10.5588/ijtld.18.0687
23 503 [published Online First: 2019/09/20]
- 24 504 21. Heysell SK, Moore JL, Keller SJ, et al. Therapeutic drug monitoring for slow response to
25 505 tuberculosis treatment in a state control program, Virginia, USA. *Emerg Infect Dis*
26 506 2010;16(10):1546-53. doi: 10.3201/eid1610.100374
- 27 507 22. Aftab H, Christensen DL, Ambreen A, et al. Tuberculosis-Related Diabetes: Is It Reversible after
28 508 Complete Treatment? *Am J Trop Med Hyg* 2017;97(4):1099-102. doi: 10.4269/ajtmh.16-
29 509 0816 [published Online First: 2017/08/19]
- 30 510 23. Wang JY, Lee MC, Shu CC, et al. Optimal duration of anti-TB treatment in patients with
31 511 diabetes: nine or six months? *Chest* 2015;147(2):520-28. doi: 10.1378/chest.14-0918
- 32 512 24. Chiang CY, Bai KJ, Lin HH, et al. The influence of diabetes, glycemic control, and diabetes-
33 513 related comorbidities on pulmonary tuberculosis. *PLoS One* 2015;10(3):e0121698. doi:
34 514 10.1371/journal.pone.0121698
- 35 515 25. Heysell S, Mtabho C, Mpagama S, et al. Plasma drug activity assay for treatment optimization
36 516 in tuberculosis patients. *Antimicrobial agents and chemotherapy* 2011;55(12):5819-25. doi:
37 517 10.1128/AAC.05561-11 [published Online First: 2011/10/05]
- 38 518 26. Tostmann A, Mtabho CM, Semvua HH, et al. Pharmacokinetics of first-line tuberculosis drugs in
39 519 Tanzanian patients. *Antimicrob Agents Chemother* 2013;57(7):3208-13. doi:
40 520 10.1128/AAC.02599-12
- 41 521 27. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease
42 522 Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines:
43 523 Treatment of Drug-Susceptible Tuberculosis. *Clinical infectious diseases : an official*
44 524 *publication of the Infectious Diseases Society of America* 2016;63(7):e147-95. doi:
45 525 10.1093/cid/ciw376 [published Online First: 2016/08/16]
- 46 526 28. Ghimire S, Bolhuis M, Sturkenboom M, et al. Incorporating therapeutic drug monitoring into
47 527 the World Health Organization hierarchy of tuberculosis diagnostics. *The European*
48 528 *respiratory journal* 2016;47(6):1867-9. doi: 10.1183/13993003.02142-2015 [published
49 529 Online First: 2016/03/19]
- 50
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52
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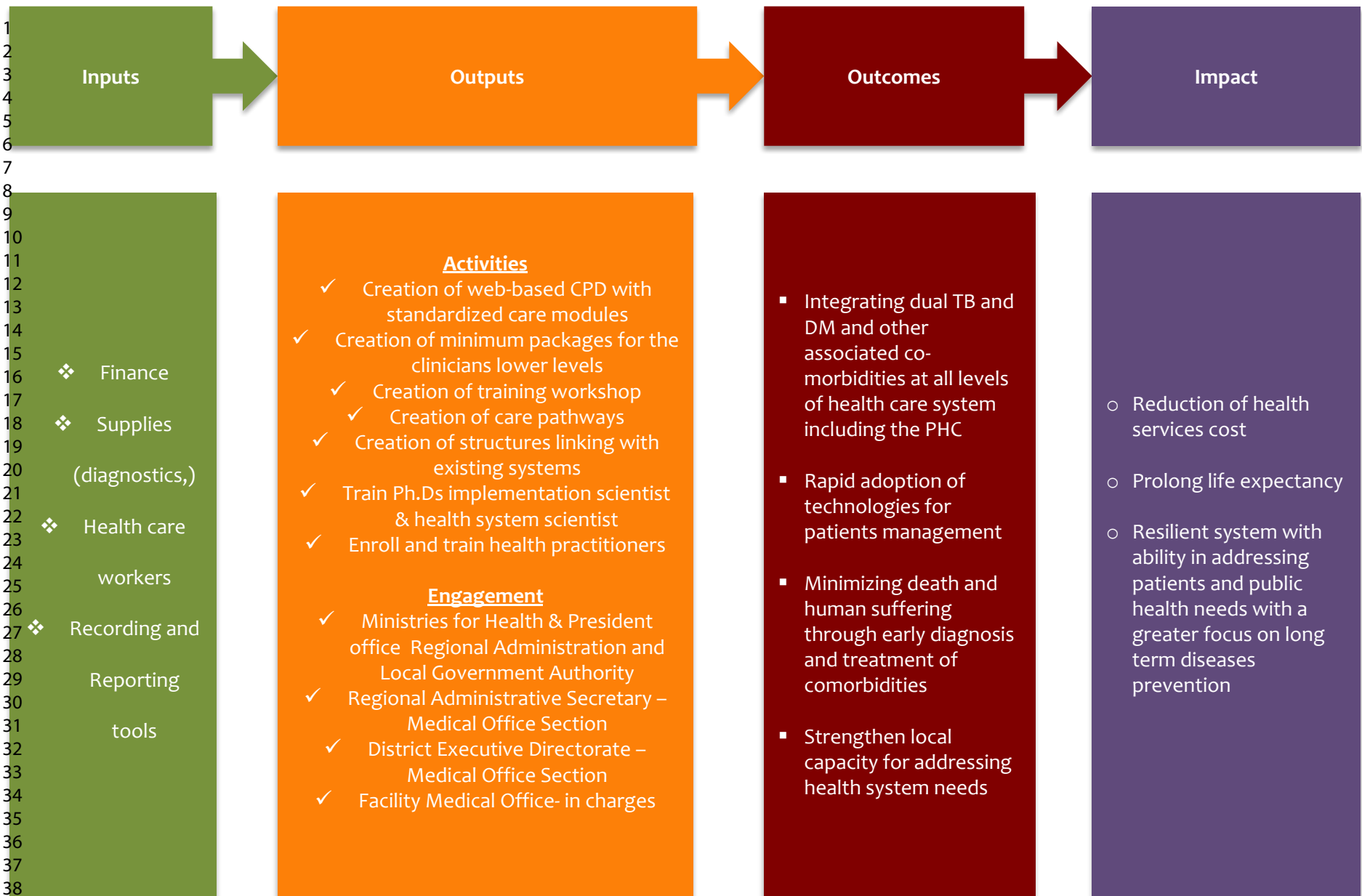
- 1
2 530 29. Swanson RC, Cattaneo A, Bradley E, et al. Rethinking health systems strengthening: key
3 531 systems thinking tools and strategies for transformational change. *Health Policy Plan*
4 532 2012;27 Suppl 4:iv54-61. doi: 10.1093/heapol/czs090 [published Online First: 2012/10/04]
5 533 30. Alkabab Y, Keller S, Dodge D, et al. Early interventions for diabetes related tuberculosis
6 534 associate with hastened sputum microbiological clearance in Virginia, USA. *BMC Infect Dis*
7 535 2017;17(1):125. doi: 10.1186/s12879-017-2226-y
8 536 31. Lo H-Y, Yang S-L, Lin HH, et al. Does enhanced diabetes management reduce the risk and
9 537 improve the outcome of tuberculosis? *Int J Tuberc Lung Dis* 2016;20(3):376-82. doi:
10 538 0.5588/ijtld.15.0654
11 539 32. Lönnroth K, Roglic G, Harries AD. Improving tuberculosis prevention and care through
12 540 addressing the global diabetes epidemic: from evidence to policy and practice. *The Lancet*
13 541 *Diabetes & Endocrinology* 2014;2(9):730-39. doi: 10.1016/s2213-8587(14)70109-3
14 542 33. De-Regil LM, Pena-Rosas JP, Flores-Ayala R, et al. Development and use of the generic
15 543 WHO/CDC logic model for vitamin and mineral interventions in public health programmes.
16 544 *Public Health Nutr* 2014;17(3):634-9. doi: 10.1017/S1368980013000554 [published Online
17 545 First: 2013/03/20]
18 546 34. Potter C, Brough R. Systemic capacity building: a hierarchy of needs. *Health Policy Plan*
19 547 2004;19(5):336-45. doi: 10.1093/heapol/czh038 [published Online First: 2004/08/18]
20 548 35. Hales S, Leshner-Trevino A, Ford N, et al. Reporting guidelines for implementation and
21 549 operational research. *Bull World Health Organ* 2016;94(1):58-64. doi:
22 550 10.2471/BLT.15.167585 [published Online First: 2016/01/16]
23 551 36. Shayo FK, Shayo SC. Availability and readiness of diabetes health facilities to manage
24 552 tuberculosis in Tanzania: a path towards integrating tuberculosis-diabetes services in a high
25 553 burden setting? *BMC Public Health* 2019;19(1):1104. doi: 10.1186/s12889-019-7441-6
26 554 [published Online First: 2019/08/16]
27 555 37. World Health Organization (WHO). How to investigate drug use in health facilities: Selected
28 556 drug use indicators. Action Programme on Essential Drugs, 1993.
29 557 38. Riza AL, Pearson F, Ugarte-Gil C, et al. Clinical management of concurrent diabetes and
30 558 tuberculosis and the implications for patient services. *The Lancet Diabetes & Endocrinology*
31 559 2014;2(9):740-53. doi: 10.1016/s2213-8587(14)70110-x
32 560 39. World Health Organization (WHO). Collaborative Framework for Care and Control of
33 561 Tuberculosis and Diabetes In: Stop TB Department and Department of Chronic Diseases
34 562 and Health Promotion WHO, Geneva, Switzerland and The International Union Against
35 563 Tuberculosis and Lung Diseases Paris France, ed., 2011.
36 564 40. Mave V, Nimkar S, Prasad H, et al. Tuberculosis screening among persons with diabetes
37 565 mellitus in Pune, India. *BMC Infect Dis* 2017;17(1):388. doi: 10.1186/s12879-017-2483-9
38 566 [published Online First: 2017/06/05]
39 567 41. Byashalira K, Mbelele P, Semvua H, et al. Clinical outcomes of new algorithm for diagnosis and
40 568 treatment of Tuberculosis sepsis in HIV patients. *International Journal of Mycobacteriology*
41 569 2019;8(4) doi: 10.4103/ijmy.ijmy_135_19
42 570 42. van Crevel R, Koesoemadinata R, Hill PC, et al. Clinical management of combined tuberculosis
43 571 and diabetes. *Int J Tuberc Lung Dis* 2018;22(12):1404-10. doi: 10.5588/ijtld.18.0340
44 572 [published Online First: 2019/01/05]
45 573 43. Sealed Envelope Ltd. Power calculator for continuous outcome superiority trial: Accessed on
46 574 2017.
47 575 44. Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for
48 576 treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *The Lancet*
49 577 *Infectious Diseases* 2016 doi: 10.1016/s1473-3099(16)30274-2
50
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58
59
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2 578 45. Capiou S, Veenhof H, Koster RA, et al. Official International Association for Therapeutic Drug
3 579 Monitoring and Clinical Toxicology Guideline. *Therapeutic Drug Monitoring* 2019;41(4):409-
4 580 30. doi: 10.1097/ftd.0000000000000643
5 581 46. van der Burgt EP, Sturkenboom MG, Bolhuis MS, et al. End TB with precision treatment! *Eur*
6 582 *Respir J* 2016;47(2):680-2. doi: 10.1183/13993003.01285-2015 [published Online First:
8 583 2016/02/02]
9 584 47. Zuur MA, Akkerman OW, Davies Forsman L, et al. Fixed-dose combination and therapeutic
10 585 drug monitoring in tuberculosis: friend or foe? *Eur Respir J* 2016;48(4):1230-33. doi:
11 586 10.1183/13993003.00833-2016 [published Online First: 2016/09/03]
13 587 48. Alffenaar JC, Gumbo T, Dooley KE, et al. Integrating Pharmacokinetics and Pharmacodynamics
14 588 in Operational Research to End Tuberculosis. *Clin Infect Dis* 2020;70(8):1774-80. doi:
15 589 10.1093/cid/ciz942 [published Online First: 2019/09/29]
16 590 49. Prada-Medina CA, Fukutani KF, Pavan Kumar N, et al. Systems Immunology of Diabetes-
17 591 Tuberculosis Comorbidity Reveals Signatures of Disease Complications. *Sci Rep*
19 592 2017;7(1):1999. doi: 10.1038/s41598-017-01767-4 [published Online First: 2017/05/19]
20 593 50. Kumar NP, Moideen K, Sivakumar S, et al. Tuberculosis-diabetes co-morbidity is characterized
21 594 by heightened systemic levels of circulating angiogenic factors. *J Infect* 2017;74(1):10-21.
22 595 doi: 10.1016/j.jinf.2016.08.021 [published Online First: 2016/10/09]
24 596 51. Dearing JW. Applying Diffusion of Innovation Theory to Intervention Development. *Res Soc*
25 597 *Work Pract* 2009;19(5):503-18. doi: 10.1177/1049731509335569 [published Online First:
26 598 2010/10/27]
27 599 52. Martin DL, Hoff JL, Gard RA, et al. Data collection, processing, validation, and verification.
28 600 *Health Phys* 2008;95(1):36-46. doi: 10.1097/01.HP.0000298817.72107.48 [published
30 601 Online First: 2008/06/12]
31 602 53. Hammarberg K, Kirkman M, de Lacey S. Qualitative research methods: when to use them and
32 603 how to judge them. *Hum Reprod* 2016;31(3):498-501. doi: 10.1093/humrep/dev334
33 604 [published Online First: 2016/01/14]
35 605 54. Bygbjerg IC. Double burden of noncommunicable and infectious diseases in developing
36 606 countries. *Science* 2012;337(6101):1499-501. doi: 10.1126/science.1223466 [published
37 607 Online First: 2012/09/22]
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- Interface between research and the performance
- Translate abstract recommendations of the critic into specific changes in the rules or parameters used by the performance element

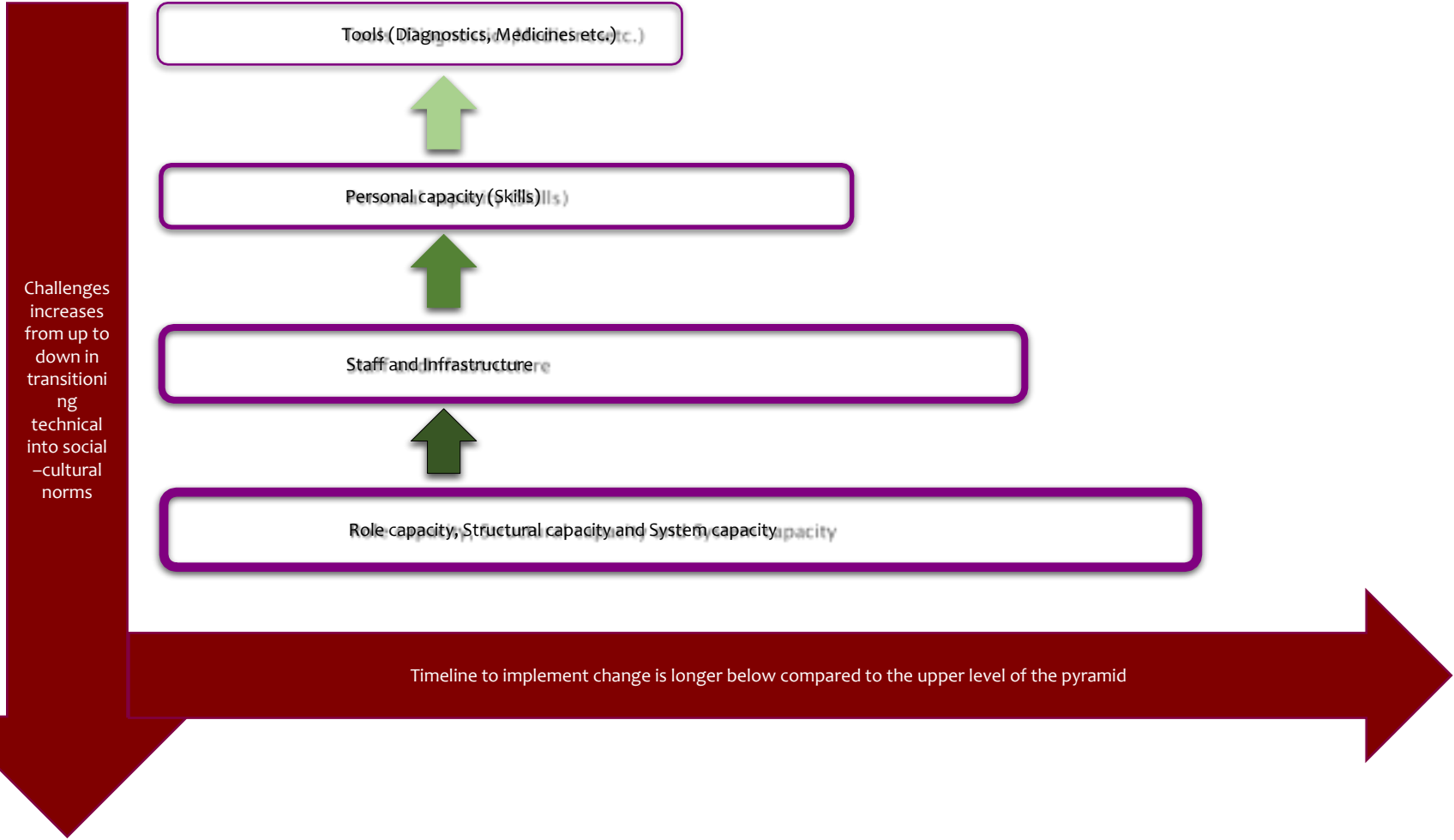


Can run in a stand alone mode without learning and may not need the other elements however, it will remain unresponsive to new challenges



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Integrating dual TB/DM services

Implementing Best Practice Package

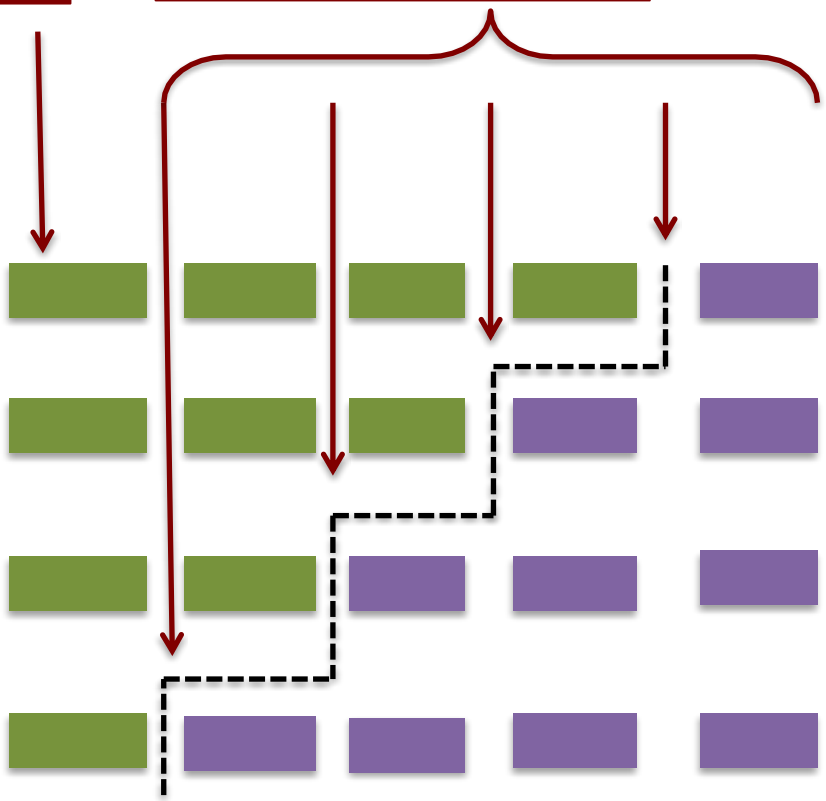
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Control Condition



Intervention with best practice package



Cluster

BMJ Open

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TITLE: Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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Keywords

Adaptive diseases intervention programme, Communicable and non-communicable dual epidemics, tuberculosis and diabetes dual epidemic, health systems, implementation science

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1
2 55 **ABSTRACT**

3
4 56 **Introduction:** Most sub-Saharan African countries endure a high burden of communicable
5
6 57 diseases but also face a rise of non-communicable illnesses. Interventions targeting particular
7
8 58 epidemics are often executed within vertical programmes. We aim to develop a model that will
9
10 59 strengthen health systems by shifting traditional vertical programmes to an adaptive diseases
11
12 60 management approach through integrating communicable and non-communicable diseases
13
14 61 diagnosis and management using the tuberculosis (TB) and diabetes mellitus (DM) dual epidemic
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16 62 as a case study.
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21 63 **Methods and analysis:** This programme will use a mixed research design, with both qualitative
22
23 64 and quantitative approaches. Qualitative approach will explore patients with dual TB/DM
24
25 65 experiences they encountered during health care seeking in health facilities and their
26
27 66 perspectives centering on integration. A prospective cohort design will be used in assessing
28
29 67 integration of TB and DM services to enable early diagnosis of dual TB/DM cases. Lastly, a
30
31 68 stepped-wedge cluster randomized trial will assess the impact of introducing individualized
32
33 69 TB/DM practices at the health care facility providing clinical management services level. A
34
35 70 blueprint for addressing communicable and non-communicable dual epidemics will be
36
37 71 developed using several tools and techniques such as a collection of stakeholders' views and
38
39 72 literature reviews, monitoring of key indicators in the TB/DM case study, and applying a system
40
41 73 thinking approach to essential elements in the health service delivery.
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48 74 **Ethics and Dissemination:** Ethical approval was granted by The National Research Health Ethical
49
50 75 Committee (reference number NIMR/HQ/R.8a/Vol.IX/2988) and the implementation was
51
52 76 endorsed by the President Office Regional Administration and Local Government Authority. The
53
54 77 results will be proactively disseminated through peer-reviewed open access journals, policy
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56 78 briefs, engagement with various stakeholders and community advisory boards, public
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58 79 engagement activities, conference presentations, and social media.
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ARTICLE SUMMARY

Strengths and limitations of this study

- The study is conducted in pragmatic settings using a mixed study design to allow triangulation
- Considers service delivery at varying health facilities levels while covering urban, semi-urban and rural settings
- The proposed ADEPT model outcome considers process and patient-centered outcomes
- Lack of randomization of study settings or health facilities may introduce bias

INTRODUCTION

Tanzania like other sub-Saharan African countries endures a high burden of communicable infections including multidrug resistant pathogens; but also a concurrent rise of non-communicable diseases (NCD) as populations urbanize, diets “westernize” and lifespans lengthen ¹. The health system is largely inflexible and during various periods of disease epidemics, the health management teams operate in crisis-mode with limited capacity to plan for long-term disease prevention ². Currently in Tanzania, planned interventions for several longstanding and socioeconomically draining epidemics like tuberculosis (TB) and diabetes mellitus (DM) and their associated comorbidities, are executed within disease specific or vertical programmes ³. Vertical programmes operate in silos while in reality various communicable and NCDs and treatments can influence one another, and overlap in populations of shared genetic backgrounds or environmental exposures, and in communities with similar socioeconomic determinants of health. Vertical programmes can significantly constrain health care delivery, and represent a top-down approach that is rarely efficient or cost-effective, particularly when considering prevailing regional health challenges ⁴.

This sobering fact has been illuminated in recent study of different vertical programmes in

1
2 105 Tanzania. We recently completed a compendium of research studies that uncovered a health
3
4 106 system gridlock for patients trying to negotiate the road from diagnosis to treatment of TB⁵⁻⁸.
5
6 107 There was a widespread underuse of the technologies mostly due to inadequate dissemination
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8
9 108 of healthcare provider knowledge and skills on clinical application and interpretation of
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11 109 molecular diagnostics despite clear patient preference for onsite rapid results and moving assays
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14 110 to meet patients where they were at along the care continuum ⁹. Likewise, there was not only
15
16 111 minimal resources to implement international consensus diagnostics, but also an absence of
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19 112 linkage to care for patients presenting with TB and with need to triage to adequate DM services
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21 113 ¹⁰. Similarly, in Tanzania DM services are centralized at the district and referral health facilities
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23
24 114 but also front-line health care providers were ill-prepared for DM management¹¹. Research
25
26 115 studies conducted in different programmes to identify multi-morbidity, particularly the NCDs,
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28
29 116 have found a considerable burden of people harbouring multiple common diseases¹². The
30
31 117 observed increasing prevalence of dual communicable and emerging non-communicable
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33
34 118 multimorbidity epidemics and the existing systemic bottlenecks suggest the urgent need for
35
36 119 modification of models of health care delivery. We developed a model to strengthen health
37
38 120 systems by shifting traditional vertical programmes to a patient-centred adaptive diseases
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41 121 control approach through integrating communicable and NCDs. Henceforth, we describe the
42
43 122 strategy to establish a contemporary **Adaptive Diseases control Expert Programme in Tanzania**
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45 123 (Figure 1) (**ADEPT**), focusing on the TB/DM co-epidemic.
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48 124 The dual TB/DM epidemic is ideal as a case for our ADEPT model because worldwide evidence
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50
51 125 shows a 3-fold increase of active TB in populations with DM compared to those without DM,
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53 126 while the global prevalence of TB in DM populations ranges from 1% -14%^{13,14}. In Tanzania, the
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55 127 effect was slightly higher and estimated at nearly 4-fold increase of active TB in DM population¹⁵.
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58 128 Indeed, stakeholders from The International Union Against Tuberculosis and Lung Disease and
59
60 129 the World Diabetes Foundation outlined the historic Bali Initiative on TB and DM (endorsed by

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2 130 World Health Organization (WHO)), stating:
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4 131 “▪That TB and DM represent two of the greatest global health challenges of our time, and their
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6 132 convergence globally represents a looming co-epidemic,
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9 133 ▪That this looming co-epidemic threatens progress against TB,
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11 134 ▪That, based on what we have learned from past co-epidemics, particularly TB-HIV, we must act
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14 135 early and decisively to avoid large numbers of avoidable deaths”^{16,17}.

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16 136 We understand this urgency all too well in Tanzania. Recently, we have observed an increase in
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18
19 137 the incidence of dual diagnosed patients with TB/DM ranging from 4% of all TB patients in rural
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21 138 areas to 17% in urban settings, resulting in a 5-fold increase of death compared to TB patients
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23
24 139 without DM^{18,19}. Importantly, our research has determined that these deaths primarily occur
25
26 140 early, in the first three months of TB treatment^{18,19}. We now understand that this high and early
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28
29 141 mortality from TB/DM in Tanzania is due to both programmatic and biological factors²⁰. For
30
31 142 example, TB and DM services are not linked and these separated service lines lead to delayed
32
33
34 143 interventions for both diseases²¹. Interestingly, targeted drug therapy of dual TB/DM disease
35
36 144 may also open new ways of enhancing the effect of essential drugs against either disease²². Thus,
37
38 145 data have suggested that the first-line anti-DM drug metformin could be a promising candidate
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40
41 146 for host-adjunctive anti-TB therapy, by reducing chronic inflammation and enhancing immune
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43 147 response²³.

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46 148 Yet, other biological factors also contribute to poor TB/DM treatment outcomes including DM-
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48 149 related alterations in drug absorption and metabolism resulting in sub-therapeutic anti-TB drug
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50
51 150 serum concentrations,²⁴ and altered inflammatory/anti-inflammatory host immune defences.
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53 151 Furthermore, TB disease itself may worsen control of hyperglycaemia leading to uncontrolled
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55 152 DM²⁵. In turn, patients with uncontrolled DM also have higher bacterial burdens of *M.*
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57
58 153 *tuberculosis* and more extensive lung disease, and therefore achieving anti-TB drug
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60 154 concentrations at the most optimal of levels may be even more important in patients with DM

1
2 155 ^{26,27}. Yet, in our prior work in Tanzania, we found sub-therapeutic drug concentrations to occur
3
4 156 in the majority of all TB patients ^{28,29}. While international standards mention therapeutic drug
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6 157 monitoring to guide TB/DM individualized dose adjustment³⁰, few programmes from TB-endemic
8
9 158 settings have carried these recommendations forward³¹. Although the Tanzania Ministry of
10
11 159 Health recognizes the challenge of the TB/DM epidemic, the vast majority of health facilities have
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14 160 not been able to implement international standards of TB/DM care. Therefore, this research
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16 161 project will also take the opportunity to underpin implementation of the international standards
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19 162 for controlling the TB/DM in the health system and conduct applied research to answer critical
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21 163 scientific questions of direct patient benefit while simultaneously training the next generation
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23
24 164 of health systems scientists.

25
26 165 The overall aims of developing an ADEPT model is to strengthen the health systems by shifting
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29 166 traditional vertical programmes to a patient-centred adaptive diseases control approach
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31 167 through integrating communicable and non-communicable diseases using the TB and DM dual
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34 168 epidemic as a case study in Tanzania. Integration of the TB/DM diagnosis and optimal
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36 169 management strategies will be conducted in client-friendly clinical space near to patient's entry
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38 170 into the health systems, as part of an adaptive disease control framework to inform future best
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41 171 policies for integrating care of communicable and NCDs in Tanzania.

42 43 172 **Overview of the ADEPT Model**

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45
46 173 The ADEPT model has three components considered as vital to re-orient the health system to
47
48 174 address dual communicable and NCDs. Each component is described as follows;

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51
52 175 **I. A Step-wise Training approach: The objective is to improve knowledge, skills and**
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54 176 **resource acquisition for the frontline health care providers to integrate communicable**
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56 177 **and NCDs at varying health system levels.**

1
2 178 This model follows the “classical diffusions of innovation theory” described elsewhere³² and
3
4 179 organised on-job training in two clusters that will stepwise deliver a logically related set of
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6 180 international standards of patients with communicable and NCDs. The first cluster consisting of
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8
9 181 mentors that train to integrate communicable and non-communicable diseases. The potential
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11 182 mentors will be selected by the health managers at the respective health facilities, preferably
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13
14 183 working in either a general clinic or TB or DM clinic but also a minimum of undergraduate
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16 184 training. This cluster will also then serve as subsequent mentors. The initial training is through
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18
19 185 the e-learning methodology and pre-defined proceeding criterion (score > 80% of the online
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21 186 training) to the next phase which is a face-to-face workshop. The aim of the workshop is to
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23
24 187 expose individuals to acquire hands-on skills and conduct practical exercises related to clinical
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26 188 services focusing on algorithms of management or nursing care and new endorsed technologies.
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29 189 The second cluster will receive training and mentorship from the first cluster. The first cluster
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31 190 receives package/materials to train the second cluster working at the same level or at primary
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34 191 health care facilities.

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37 192 **II. Adaptive service delivery. The objective is to integrate communicable and NCDs at**
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39 193 **varying health system levels**

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43 194 Clinics delivering communicable or NCDs at varying levels of health facilities will receive training
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45 195 using a step-wise model. Considerations of infection prevention control will guide a service
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47
48 196 delivery approach while considering patient-centred recommendations. The first clinic will be
49
50 197 applicable to clients with TB with or without other co-morbidities. Recognizing individuals with
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52
53 198 non-communicable lung diseases (CLDs) presenting with features akin of TB, a separate clinic
54
55 199 may need to be organized. For the TB and CLD clinics, although potentially operating separately,
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57
58 200 it is important to maintain the link of these clinics as an important component of practical
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60 201 approach of lung health. The third clinic will encompass all non-TB-non-CLD with or without other

1
2 202 comorbidities including HIV, DM, and Hypertension. A multimorbidity team within a health
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4 203 facility will facilitate mechanisms for screening communicable and NCDs.
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5 206 **III. Learning system model: The objective is to create a platform for reviewing data and**
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7 **information generated during implementation, and create a ‘self-repairing’ mechanism**
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11 208 The mentors or first cluster of trainees will have regular meetings at the Regional Medical
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13 Officer with attendance of District Medical Officers and different programme coordinators;
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15 including TB & Leprosy, NCDs, HIV, Malaria and Neglected Tropical Diseases. The meeting will
16 210
17 review the clinical audit and quality improvement reports from health facilities focusing on
18 211
19 health service delivery and identify the gaps for actions. Likewise, the coordinators will share
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21 212
22 on the expected national targets in their local context. The meeting report will be submitted
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24 to the higher authorities responsible for health. Currently the report will be submitted to the
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27 Ministry of Health Community Development Gender Elderly and Children and the President
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29 Office Regional Administration and Local Government Authority. The report will be included
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31 216
32 in the respective national technical working groups (TWG) for incorporation in the general
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34 provision of technical direction and advice. The relay mechanisms from the TWG to regions
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37 will also be established.
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42 220 **ADEPT Model Research Questions Component**
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45 221 Implementation research
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48 222 1. What patients did with dual TB and DM experience and what were their perspectives on
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50 223 services they received in the health facilities?
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52 224 2. What is/are the most effective approach/es to de-implement health facility practices
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54 that do not support effective integration of proposed service delivery model using TB
55 225
56 and DM as a case study?
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3. What is the best approach to deliver on-job training and facilitate delivery of integration of TB and DM in a patient-centred approach?
4. What is the feasibility, acceptability and fidelity of the implemented designed models?
5. Where is the best place in the HCS system to implement (or initiate) integration of TB and DM?

Operational research in TB and DM

1. How many additional dual TB and DM patients will be identified during bi-directional screening of TB and DM services who would otherwise not have been identified?
2. What are the treatment outcomes of patients with dual TB and DM with or without HIV compared to other patients without DM?
3. What are the effects of therapeutic drug monitoring on dose adjustment and subsequently on treatment outcomes?

METHODS AND ANALYSIS FOR ADEPT MODEL

Conceptual framework of the ADEPT model

The ADEPT model pioneers the systems thinking methodology described by Swanson and colleagues to guide integrative changes in health practice, education, research and policy³³.

We proposed to introduce ADEPT first to the dual TB/DM epidemic as a case study of integrating communicable and non-communicable diseases^{34,35} to engage currently siloed policy makers, researchers, and service providers³⁶. The proposed ADEPT model is supported by three principles with interdependent themes; transformational leadership, collaboration, and a constant interactive learning process prompting to self-repairing mechanisms. ADEPT will be evaluated using the logic framework developed by the WHO/US-Center for Diseases Control and Prevention (US-CDC) (Figure 2)³⁷. The design of input and output pillars reflect largely on the archetypical work designed by Potters and Brought in 2004 for health system strengthening³⁸. This includes a four-tier hierarchy with nine-interdependent elements as depicted in Figure 3.

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2 254 **Role, Structural and System capacity:** ADEPT will mobilize physicians and nurse officers working
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4 255 at TB, DM, or general clinics at the regional level regardless of the facility level. The team will
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6 256 serve as a Regional Technical Working Group (RTWG), and will be empowered to serve as
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9 257 mentors in the Region to support the health system to deliver best practices in patients with
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11 258 dual communicable and NCDs. The formed team will operate under the Regional Medical Officer
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14 259 (RMO), a newly formed structure that will also link with the National Technical Working Groups
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16 260 (NTWG) (Figure 1). RTWG under the leadership of RMO will conduct regular discussion with all
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19 261 stakeholders supporting the communicable and or NCDs intervention and associated co-
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21 262 morbidities. The discussion emanating from the meetings will guide local decision but will also
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24 263 be communicated to the Ministries responsible for Health and Regional Administration and Local
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26 264 Government Authorities, and shared with responsible NTWG for prioritization (Figure 1).
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29 265 The ADEPT consortium will meticulously and continuously explore gaps that will progressively
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31 266 evolve the system toward people-centred health system³⁹.
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34 267 **Staff and Personnel Training:** ADEPT has collaborated with National Training Centres and
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36 268 hospitals/facilities that provide advanced/specialized care of patients in creating modules for
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38 269 training of the front-line healthcare providers (HCPs). Leadership and supervisory lines will be
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41 270 strengthened simultaneously with increasing accountability and establishment of a clinical
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43 271 audit programme. ADEPT has also created local technical working groups composed of senior
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46 272 front-line HCPs currently empowered with skills and knowledge for integrating and clinical
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48 273 management of communicable (TB) and non-communicable (DM) diseases¹¹. The
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51 274 empowerment of HPCs has been facilitated by those training modules delivered as web-based
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53 275 or m-Health platforms for continuous professional development that has increased the reach
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55 276 to all HCPs that would otherwise not be possible due to limited funds. The designed modules
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58 277 are not only adaptive to cover HCPs with different skills (for example, clinicians and nurses) but
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60 278 modules can be updated remotely should new processes need to be introduced for instance

1
2 279 emerging epidemics like COVID-19. Importantly, the HCPs have endless access and updated
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4 280 alerts to their mobile numbers or emails prompting them to complete a new module.
5

6 281 **Tools:** Equipment and consumables for piloting the programme have been inventoried at
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9 282 participating facilities within the communities of study. Supplies for DM were frequently not
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11 283 available or inadequately stocked and these including glucometers, glucostrips, HbA1c devices,
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14 284 therapeutic drug monitoring supplies, recording and reporting. These tools were funded
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16 285 temporarily through the Danish International Development Agency, subsequently health
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19 286 facilities will take over. TB consumables, supplies and tools were procured through conventional
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21 287 channels including the cost sharing and implementing partners.
22

23 288 **METHODS AND ANALYSIS FOR TB AND DM**

24 289 **Study design**

25
26 289 This is a mixed research design and applies both qualitative and quantitative approaches. A cross
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28
29 290 sectional design will be conducted for needs assessment and bidirectional screening and
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31 291 bidirectional screening of TB and DM while a prospective cohort design will be deployed for
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33 292 assessing the treatment outcomes of patients with dual TB/DM. A stepped wedged cluster non-
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35
36 293 randomized trial design will be for assessing effect of therapeutic drug monitoring for dose
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38 294 adjustment and subsequent treatment outcome of patients with dual TB/DM. Stepped-wedged
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41 295 methodology is a design that is preferably used when implementation and research go hand in
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43 296 hand, especially with complex medical procedures this is a preferred approach.
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48 298 A stepped wedge cluster randomised trial design is the most robust design that is logistically
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51 299 feasible whilst providing the level of evidence of efficacy and effectiveness to support further
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53 300 implementation in health care^{40,41}. This design helps to minimise ethical issues related to
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55 301 withholding the optimized care in a traditional individual randomized trial design and can be
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58 302 considered of low or negligible risk.
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2 304 **Study area**

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4 305 The research project will be conducted in three regions of Tanzania; Dar es Salaam, Iringa, and
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6 306 Kilimanjaro. Districts that will participate include Ilala and Kigamboni for Dar es Salaam, Iringa
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8
9 307 Municipal, Kilolo and Mufindi for Iringa, and Moshi Municipal, Same and Siha for Kilimanjaro. We
10
11 308 selected areas to affiliate with the workplaces of the current consortium's Tanzanian expertise
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13
14 309 and to reflect representative population types. Dar es Salaam is largely a metropolitan while
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16 310 Iringa and Kilimanjaro selected areas cover rural (Kilolo and Siha), semi-urban (Mufindi and
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18
19 311 Same) and urban settings (Iringa Municipal and Moshi Municipal). According to the National TB
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21 312 survey of 2012, the TB prevalence is high in Dar es Salaam and in rural settings⁴². The burden of
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23
24 313 DM is 9% in Tanzania but is more common in urban settings⁴³.

25
26 314 **Study outline**

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29 315 **Objective 1 method: Integrate TB or TB/HIV and DM services**

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31 316 A prospective cohort study of the health system will be conducted to observe the effect of the
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33 317 step-down approach and integration of services. It is recommended that at least 30 health
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35
36 318 facilities are needed for reliable and accurate results therefore each region will contribute at
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38 319 least 10 health facilities at various levels for integrating TB or TB/HIV and DM services ⁴⁴. The
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41 320 catchment area includes one- referral hospital, three district hospitals and at least 6 health
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43 321 centres/dispensaries. Integration will start stepwise from the referral (secondary or tertiary)
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45
46 322 hospitals levels; corresponding with the stepwise training model towards primary health care
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48 323 clinics, i.e. the district hospitals followed by the health centres and dispensaries. Needs
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51 324 assessments have been carried to identify capacity of the health facility and decide whether the
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53 325 health facility will operate as a "one-stop shop" defined as TB and DM services provided at the
54
55 326 same time using adjacent rooms, "partial integration" defined as health care providers swaps
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57
58 327 between clinics, or "remote integration" through cross referral of DM to TB services. Entries of
59
60 328 TB/DM integration in TB services or TB/HIV services will be at the TB and DM clinics ⁴⁵. People

1
2 329 diagnosed with TB diagnosed will receive DM testing while at the DM clinics, presumed TB will
3
4 330 be screened according to the standard national TB algorithm. An algorithm to identify people
5
6 331 with active TB and high potential for treatment failure, including those with TB drug resistance
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8
9 332 and other DM co-morbidities, will be identified and tabled for expert discussion of additional
10
11 333 support mechanisms that can be mobilized. Participants will be managed according to the
12
13
14 334 collaborative TB/DM services framework guideline⁴⁶ as follows;

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16
17 335 **Sub-objective 1.1. Method. Screening TB in DM patients**

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19
20 336 People with DM, especially those with sub-optimal control as defined by HbA1c, will be screened
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22 337 for active TB. The algorithms for active TB will be applied as described elsewhere^{47 48}.

23
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25 338 **Sub-objective 1.2. Method. Screening DM in TB patients**

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28 339 All people with active TB irrespective of having “classical” symptoms (polyuria, polydipsia and
29
30 340 polyphagia) will be screened with glucometer and interpretation of results is as follows; if the
31
32 341 random blood/serum glucose (RBG) ≤ 7.8 mmol/L or fasting blood glucose (FBG) ≤ 6.1 mmol/L
33
34
35 342 without DM symptoms, blood or serum glucose will be considered normal. If the RBG is 7.8 – 11.0
36
37 343 mmol/L or FBG is 6.2 – 6.9 mmol/L, this will be considered as pre-DM. When RBG is ≥ 11 mmol/L or
38
39
40 344 FBG is ≥ 7.0 mmol/L this is DM⁴⁹. To exclude patients with transient hyperglycaemia due to
41
42 345 cytokine stimulation (false DM diagnosis), Hb1Ac will be performed in follow-up²⁵. Individuals
43
44
45 346 with pre-DM or DM further tested with HbA1c, interpretation of the results will be as follows;
46
47 347 HbA1c of ≤ 38 mmol/mol ($\leq 5.6\%$); $39 < 48$ mmol/mol ($5.7\% < 6.5\%$), and ≥ 48 mmol/mol ($\geq 6.5\%$) will
48
49
50 348 be reported and considered as normal, pre-DM and DM respectively⁵⁰. People with active TB and
51
52 349 pre-DM will be re-evaluated in the mid-term of TB treatment and TB treatment completion to
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54
55 350 identify if the condition has resolved, progressed, or remained static; if pre-DM will have
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57 351 advanced to DM, patients will be treated according to the DM guideline. The TB Infection
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59
60 352 Prevention Control practice that is applicable in HIV clinics will be applied⁴⁵.

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2 353 **Objective 2 methods: Determine effect of diagnostics (HbA1c and therapeutic drug monitoring)**
3
4 354 **for regimen and dosage selection for optimizing treatment outcomes of patients with dual**
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6
7 355 **TB/DM**

8
9 356 Health facilities effectively integrating dual TB/DM services will enter a next phase of using
10
11 357 therapeutic drug monitoring for personalized dose adjustment to optimize dual TB/DM patient
12
13 management (Figure 4). The implementation study design will describe the outcomes of patients
14 358 with dual TB/DM tested with diagnostics comprising of susceptibility testing, anti-TB therapeutic
15
16 359 drug monitoring, and HbA1c for monitoring the DM and guide selection and combination of both
17
18 360 anti-TB and anti-DM drugs. The stepped wedge trial design will be used for assessing the effect
19
20 361 of therapeutic drug monitoring will have 3-phases: pre-enrolment phases where prior to
21
22 362 implementation of all facilities will serve as controls; roll-out period when health facilities cross-
23
24 363 over from control to active implementing the therapeutic drug monitoring (TDM); post-rollout
25
26 364 when all selected health facilities will be implementing TDM.

27
28 366 Health facilities in each region integrating TB/DM services will be allocated; to incorporate the
29
30 367 therapeutic drug monitoring in optimizing anti-TB drug dosages. In our previous observational
31
32 368 study, we found 16% of TB/DM patients had unfavourable outcomes in Tanzania ¹⁹. We assume
33
34 369 that the therapeutic drug monitoring will reduce the unfavourable event rate to 8%. To achieve
35
36 370 90% power to detect this difference with a significance level of 5% with a non-compliance
37
38 371 estimated at 8% ⁵¹, the adjusted minimum sample size of 970 TB/DM patients will be rigorously
39
40 372 followed ⁵². TB/DM or TB-HIV/DM individuals will provide baseline sputum for culture and drug
41
42 373 susceptibility testing as well as smear microscopy. Patients will also test for HbA1c and renal
43
44 374 function test to assess for severity of DM. Two weeks after starting anti-TB medication, blood
45
46 375 will be collected for therapeutic drug monitoring of anti-TB drugs. Collection of blood will be
47
48 376 through dry blood spot and transported to the Biotechnology Laboratory/Kilimanjaro Clinical
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60 377 Research Institute through Expedited Mail Services. The dry blood spot collection will be

1
2 378 processed for testing the serum drug levels starting first with rifampicin using an assay validated
3
4 379 according to international guidelines⁵³ Results will be communicated before day 21 of anti-TB
5
6 380 treatment, and if needed the anti-TB dosage adjustment will be made. A TDM strategy suitable
7
8
9 381 for a fixed dose combination regimen will be applied. In summary, the therapeutic drug
10
11 382 monitoring will be performed at week 2 of TB treatment, and based on plasma concentrations
12
13 383 results, the appropriate FDC tablets can be selected^{54,55}. Serum drug exposure that differs by at
14
15
16 384 least 25% from target concentrations will be considered as clinically relevant ⁵⁶. Therefore, those
17
18
19 385 below the target will be eligible for dose adjustment. Two weeks after dose adjustment, the new
20
21 386 drug concentrations will be assayed and determined if having met target⁵⁴. In the continuation
22
23 387 phase, the appropriate fixed drug combination of rifampicin and isoniazid can be selected, based
24
25
26 388 on earlier measured drug concentrations. In addition, routine pharmaco-vigilance will
27
28
29 389 complement the safety data of this strategy. TB/DM cases will have monthly mycobacteriological
30
31 390 monitoring for detection of microbiological treatment failure. While DM monitoring will include
32
33 391 the assessment of retinopathy, impaired wound healing (diabetic foot), and nephropathy^{57,58}.
34
35
36 392 HbA1c and renal function tests will also be followed at month 3 and 6 to enable further anti-DM
37
38 393 regimen adjustment.

41 394 **Objective 3 methods: Capacity building on training and applied research**

42
43 395 Training of the frontline health care providers will follow the “*classical diffusions of innovation*
44
45 396 *theory*” drawn by Dearing (2009) [REF]. ADEPT will change the current passive delivery of
46
47
48 397 international standards of care into an active approach, and the training will be delivered in a
49
50
51 398 step-wise approach and will be implemented in phases;

- 52
53
54 399 ▪ Phase 1- includes a self-learning package for TB and DM and associated comorbidities
55
56 400 contents with assessment delivered through a web-based platform. The assessment will
57
58
59 401 be shared to the ADEPT team prior to attending the next phase.
60

- 1
2 402 ▪ Phase 2- Learners achieving > 80% of the web-based assessment will be invited to attend
3
4 403 training of the trainer (ToT) workshop. Emphasis during this phase will be to expose
5
6 404 individuals to acquire the principles, of the technology or innovations or intervention and
7
8
9 405 conduct practical on dual TB/DM and associated co-morbidities including HIV-coinfection,
10
11 406 malnutrition and non-communicable chronic lung diseases.
- 12
13
14 407 ▪ Phase 3- ToT will receive package/materials to train frontline health service providers in
15
16 408 their district. This will be the minimum package for providing dual TB and DM care with
17
18
19 409 short modules and directives to the task to be conducted. ToT will deliver the training to
20
21 410 the selected health facilities assigned to him/her.
- 22
23
24 411 ▪ Phase 4- Competency of the ToT will combine assessment of best practice portfolio
25
26 412 documented at their clinics, and also practice implemented by the trainers s/he
27
28
29 413 empowered.

30
31
32 414 Medical education modules on TB/DM and associated comorbidities will be tailored to different
33
34
35 415 roles and associated quality control questions for assessing the level of acquired skills for each
36
37 416 type of health care provider (clinicians, nurses, pharmacist and laboratory staff). A minimum
38
39
40 417 threshold of quality control pass will be included as one of the criteria to qualify the health facility
41
42 418 to integrate TB/DM services. Other criteria will be sought from the health facility needs
43
44
45 419 assessment tools, which will include availability, and operational infection prevention policy for
46
47 420 TB controls and equipment for DM diagnosis and prevention of complications. Knowledge
48
49 421 comparison will be made pre- and post-training.

50 51 422 **Data collection**

52
53
54 423 Data collection will be done under routine patient care in clinics. Data management will follow
55
56
57 424 and adhere to the Tanzania Code of Conduct for Research Integrity. Qualitative data will be
58
59 425 summarized in qualitative case record forms while quantitative data will be available in the Multi-
60
426 Schema Information Capture database, which is a customizable format current in use in

1
2 427 Kilimanjaro, utilizing secure encryption services (www.mysql.com). Data collection, transfer,
3
4 428 entry, validation, queries generation, audit, archival and ownership will be detailed in specific
5
6
7 429 standard operational procedures as described elsewhere⁵⁹.

9 430 **Data analysis plan on dual TB and DM**

10
11 431 Outcome measures include;

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13
14 432 Bidirectional screening and diagnosis of dual TB/DM disease

- 15
16
17
18 433 • Proportion of health facilities capable of providing best practice of TB/DM services at
19
20 434 varying levels
- 21
22 435 • Proportion of laboratories supporting dual TB/DM services
- 23
24
25 436 • Proportion of health care providers trained in best practice on dual TB/DM services
- 26
27 437 • Proportion of registered TB patients screened for DM
- 28
29
30 438 • Proportion of diabetes patients screened for TB
- 31
32 439 • Proportion of registered TB patients identified with presumptive DM among patients
33
34
35 440 and screened for DM and vice versa
- 36
37 441 • Proportion of registered TB patients tested for DM and vice versa.
- 38
39
40 442 • Proportion of registered TB patients diagnosed with DM and vice versa.
- 41
42 443 • Proportion of registered DM patients with TB referred to a TB clinic.
- 43
44
45 444 • Proportion of registered DM patients with TB started on TB treatment and vice versa.

46 47 48 445 **Dual TB/DM treatment outcomes**

49 50 51 446 TB treatment outcomes

- 52
53 447 • Proportion of TB/diabetes patients with favourable outcomes (cured, or treatment
54
55 448 complete) or unfavourable outcomes (death, lost to follow-up, treatment failure)
- 56
57
58 449 • Proportion of TB/DM recurrence of TB one year after completion TB treatment as
59
60 450 determined by sputum culture and advanced genomic technologies.

- 1
2 451 • Proportion of TB/DM acquiring DR-TB at the time of failure or TB recurrence
3
4 452 • Proportion of TB/DM patients with sub-optimal concentrations of first line anti-TB drugs
5
6
7 453 at 2nd-week of treatment
8
9 454 • Proportion of TB/DM with abnormal HbA1c compared to the baseline
10
11
12 455 • Proportion of TB/DM patients with treatment adjustment
13

14 456 DM complications at baseline and at the end of TB treatment
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- 16
17 457 • Proportion of TB/DM with hypertension, kidney dysfunction as estimated by the
18
19 458 albuminuria/proteinuria, blood urea nitrogen and creatinine
20
21
22 459 • Proportional of TB/DM with neuropathy through assessment of bladder or erectile (male)
23
24 460 dysfunction, sensorimotor neuropathy, orthostatic hypotension, sudomotor neuropathy,
25
26 461 frequent non-infective diarrhoea or constipation
27
28
29 462 • Proportional of TB/DM with retinopathy as graded by severity (none, mild, moderate or
30
31 463 severe)
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33

34 464 We will assess the pathway of patients' experience and acceptability of dual TB/DM services
35
36 465 ⁶⁰.Likewise we will assess the feasibility and acceptability of all steps of ADEPT model as
37
38
39 466 portrayed in Figure 2.
40

41 467 **PATIENT AND PUBLIC INVOLVEMENT**
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43
44 468 Development of this protocol was informed by series of research studies that included one study
45
46 469 that examined patients experience of health services in the health facilities⁹. Findings from the
47
48
49 470 described research objectives will be shared with patients' organizations subsequently
50
51 471 contribute in shaping the agenda of effective integration of communicable and non-
52
53 472 communicable diseases
54

55
56 473 **ETHICS AND DISSEMINATION**
57

58 474 This protocol has been approved at the local health research committee serving Kibong'oto
59
60
475 Infectious Diseases Hospital and National Health Research Committee with reference numbers

1
2 476 KNCHREC003 and NIMR/HQ/R.8a/Vol.IX/2988, respectively. Furthermore, the Ministries of
3
4 477 Health and Regional Administrative & Local Government Authority have endorsed
5
6
7 478 implementation of this protocol.

8 9 479 **AUTHOR CONTRIBUTIONS**

10
11 480 SGM, DLC, KR and ICB conceptualized and designed the model and proposal. TL, SH, JWA and
12
13
14 481 MSB contributed in the design of the concept particularly in TB/DM research component
15
16 482 including Mycobacteriology, TDM and mHealth respectively. DLC obtained the funding for the
17
18
19 483 ADEPT project from the Ministry of Foreign Affairs of Denmark. SGM lead the implementation of
20
21 484 the protocol in Tanzania while KR, and MSB lead implementation of the stepwise model. NEN
22
23
24 485 co-lead the implementation in Iringa. BTM co-lead implementation of the TDM in Tanzania
25
26 486 together with SH and JWA. All authors provided technical inputs in the proposal. SGM wrote the
27
28
29 487 manuscript with input from all the authors. All authors have approved the final version and
30
31 488 agreed to be accountable for all aspects of the work related to accuracy and integrity.

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34
35
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37 38 491 **DATA STATEMENT**

39
40
41 492 The data sets that will be generated and analysed during the conduct of the study will be made
42
43 493 available according to the available laws and regulations
44
45
46 494

1
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3
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5
6 497 valuable comments on the research study

8
9 498 **FIGURES LEGEND**

10
11 499 Figure 1: This model will break the siloed policy makers, health providers and researchers and
12
13 gradually transform the health system into a proactive self-organizing or self-repairing system.
14 500
15
16 501 Essential elements (Performance, Instance Selection, Critique, and Learning), if operated
17
18 effectively will form an adaptive learning system. The proposed TB/DM-ADEPT Model will
19 502
20
21 503 interconnect all interactive elements through: (a) Setting a regular single platform for policy
22
23 makers, researchers and service providers on TB/DM epidemic agenda (Learning element); (b)
24 504
25
26 505 Implementing international standards of dual TB and DM care through integrative TB/DM
27
28 collaborative services that will facilitate early diagnosis while providing individualized treatment
29 506
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31 507 of patients with dual TB/DM disease (Performance element); (c) Conduct TB/DM applied
32
33 research in implementation and health system research science to determine how to deliver best
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35
36 509 practices that will enable a people-centred health system (Critique element); and (d) Train PhD
37
38 510 and postdoctoral fellows to answer dual TB/DM health system challenges to strengthen applied
39
40 research capacity and hands-on skills to create a critical mass of the next generation of scientists
41 511
42
43 512 able to scale up TB/DM interventions and adapt to study other communicable/ non-
44
45 communicable disease intersections (Instance Selection element).

46 513
47
48 514 Figure 2: Logic framework model for measuring outcomes and impact

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50 515 Figure 3: Hierarchy of needs for strengthening the health system as described by Potter &
51
52 Brough³⁴

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54
55 517 Figure 4: Introduction of integration of TB/DM services thereafter stepwise introduction of
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57 packages comprises of susceptibility, therapeutic drug monitoring, HbA1c for optimal TB/DM
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60 519 case management at all levels of health facilities

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COMPETING INTEREST STATEMENT:

None declared.

REFERENCES

- 1 Institute for Health Metrics and Evaluation (IHME). Global Burden of Diseases (GBD) Profile;Tanzania, 2010.
- 2 Commission on Global Health Risk Framework for the Future (GHRF). Accelerating Research and Development to Counter the Threat of Infectious Diseases. The Neglected Dimension of Global Security: A Framework to Counter Infectious Disease Crises. Washington (DC)2016.
- 3 Ministry of Health. Ministry of Health -Tanzania. Health Sector Strategic Plan IV (2015-2020), 2015.
- 4 Bryan, L., Conway, M., Keesmaat, T., McKenna, S. & Richardson, B. Strengthening sub-Saharan Africa's health systems: A practical approach | McKinsey & Company. *Health Systems & Services*, 1-11 (2010).
- 5 Mpagama, S. G. *et al.* Diagnosis and interim treatment outcomes from the first cohort of multidrug-resistant tuberculosis patients in Tanzania. *PLoS One* **8**, e62034, doi:10.1371/journal.pone.0062034 (2013).
- 6 Liyoyo, A. *et al.* Gridlock from diagnosis to treatment of Multidrug-Resistant Tuberculosis (MDR-TB) in Tanzania: Illuminating Potential Factors for Possible Intervention. *East African Health Research Journal* **1** (2017).
- 7 Mpagama, S. G. *et al.* Gridlock from diagnosis to treatment of multidrug resistant tuberculosis (MDR-TB) in Tanzania: Patients perspectives from the focus group discussion. *bioRxiv pre print* doi: <http://dx.doi.org/10.1101/402594> , doi:10.1101/402594 (2018).
- 8 Mpagama, S. G. *et al.* Gridlock from diagnosis to treatment of multidrug-resistant tuberculosis in Tanzania: low accessibility of molecular diagnostic services and lack of healthcare worker empowerment in 28 districts of 5 high burden TB regions with mixed methods evaluation. *BMC Public Health* **19**, doi:10.1186/s12889-019-6720-6 (2019).
- 9 Mpagama, S. G. *et al.* Gridlock from diagnosis to treatment of multidrug resistant tuberculosis (MDR-TB) in Tanzania: patients' perspectives from a focus group discussion. *BMC Public Health* **20**, 1667, doi:10.1186/s12889-020-09774-3 (2020).
- 10 Harries, A. D. *et al.* Defining the research agenda to reduce the joint burden of disease from diabetes mellitus and tuberculosis. *Trop Med Int Health* **15**, 659-663, doi:10.1111/j.1365-3156.2010.02523.x (2010).
- 11 Shayo, F. K. & Shayo, S. C. Availability and readiness of diabetes health facilities to manage tuberculosis in Tanzania: a path towards integrating tuberculosis-diabetes services in a high burden setting? *BMC Public Health* **19**, 1104, doi:10.1186/s12889-019-7441-6 (2019).
- 12 Chang, A. Y. *et al.* Chronic multimorbidity among older adults in rural South Africa. *BMJ Glob Health* **4**, e001386, doi:10.1136/bmjgh-2018-001386 (2019).
- 13 Workneh, M. H., Bjune, G. A. & Yimer, S. A. Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review. *PLoS One* **12**, e0175925, doi:10.1371/journal.pone.0175925 (2017).

- 1
2 563 14 Jeon, C. Y. & Murray, M. B. Diabetes mellitus increases the risk of active tuberculosis: a
3 564 systematic review of 13 observational studies. *PLoS Med* **5**, e152,
4 565 doi:10.1371/journal.pmed.0050152 (2008).
- 5 566 15 Faurholt-Jepsen, D. *et al.* Diabetes is a risk factor for pulmonary tuberculosis: a case-
6 567 control study from Mwanza, Tanzania. *PLoS One* **6**, e24215,
8 568 doi:10.1371/journal.pone.0024215 (2011).
- 9 569 16 Bali. in *Stopping a looming Co-epidemic: A global Summit on Diabetes and Tuberculosis*.
10 570 17 Kapur, A., Harries, A. D., Lönnroth, K., Wilson, P. & Sulistyowati, L. S. Diabetes and
11 571 tuberculosis co-epidemic: the Bali Declaration. *The Lancet Diabetes & Endocrinology* **4**, 8-
12 572 10, doi:10.1016/s2213-8587(15)00461-1 (2016).
- 14 573 18 Sariko, M. L. *et al.* Glycated hemoglobin screening identifies patients admitted for
15 574 retreatment of tuberculosis at risk for diabetes in Tanzania. *J Infect Dev Ctries* **10**, 423-426,
16 575 doi:10.3855/jidc.7324 (2016).
- 18 576 19 Faurholt-Jepsen, D. *et al.* Diabetes is a strong predictor of mortality during tuberculosis
19 577 treatment: a prospective cohort study among tuberculosis patients from Mwanza,
20 578 Tanzania. *Trop Med Int Health* **18**, 822-829, doi:10.1111/tmi.12120 (2013).
- 21 579 20 Workneh, M. H., Bjune, A. G. & Yimer, S. A. Diabetes mellitus is associated with increased
22 580 mortality during tuberculosis treatment: a prospective cohort study among tuberculosis
23 581 patients in South-Eastern Amahra Region, Ethiopia. *Infectious Diseases of Poverty* **5**, 10,
25 582 doi:10.1186/s40249-016-0115-z (2016).
- 26 583 21 Harries, A. D. *et al.* Addressing diabetes mellitus as part of the strategy for ending TB. *Trans*
27 584 *R Soc Trop Med Hyg* **110**, 173-179, doi:10.1093/trstmh/trv111 (2016).
- 29 585 22 Singhal, A. *et al.* Metformin as adjunct antituberculosis therapy. *Sci Transl Med* **6**,
30 586 263ra159, doi:10.1126/scitranslmed.3009885 (2014).
- 31 587 23 Park, S. *et al.* Metformin and tuberculosis risk in elderly patients with diabetes mellitus. *Int*
32 588 *J Tuberc Lung Dis* **23**, 924-930, doi:10.5588/ijtld.18.0687 (2019).
- 33 589 24 Heysell, S. K., Moore, J. L., Keller, S. J. & Houpt, E. R. Therapeutic drug monitoring for slow
34 590 response to tuberculosis treatment in a state control program, Virginia, USA. *Emerg Infect*
36 591 *Dis* **16**, 1546-1553, doi:10.3201/eid1610.100374 (2010).
- 37 592 25 Aftab, H. *et al.* Tuberculosis-Related Diabetes: Is It Reversible after Complete Treatment?
38 593 *Am J Trop Med Hyg* **97**, 1099-1102, doi:10.4269/ajtmh.16-0816 (2017).
- 39 594 26 Wang, J. Y. *et al.* Optimal duration of anti-TB treatment in patients with diabetes: nine or
40 595 six months? *Chest* **147**, 520-528, doi:10.1378/chest.14-0918 (2015).
- 42 596 27 Chiang, C. Y. *et al.* The influence of diabetes, glycemic control, and diabetes-related
43 597 comorbidities on pulmonary tuberculosis. *PLoS One* **10**, e0121698,
44 598 doi:10.1371/journal.pone.0121698 (2015).
- 46 599 28 Heysell, S. *et al.* Plasma drug activity assay for treatment optimization in tuberculosis
47 600 patients. *Antimicrobial agents and chemotherapy* **55**, 5819-5825, doi:10.1128/AAC.05561-
48 601 11 (2011).
- 49 602 29 Tostmann, A. *et al.* Pharmacokinetics of first-line tuberculosis drugs in Tanzanian patients.
50 603 *Antimicrob Agents Chemother* **57**, 3208-3213, doi:10.1128/AAC.02599-12 (2013).
- 52 604 30 Nahid, P. *et al.* Official American Thoracic Society/Centers for Disease Control and
53 605 Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment
54 606 of Drug-Susceptible Tuberculosis. *Clinical infectious diseases : an official publication of the*
55 607 *Infectious Diseases Society of America* **63**, e147-195, doi:10.1093/cid/ciw376 (2016).
- 56 608 31 Ghimire, S. *et al.* Incorporating therapeutic drug monitoring into the World Health
57 609 Organization hierarchy of tuberculosis diagnostics. *The European respiratory journal* **47**,
59 610 1867-1869, doi:10.1183/13993003.02142-2015 (2016).
- 60 611 32 Dearing, J. W. Applying Diffusion of Innovation Theory to Intervention Development. *Res*
612 *Soc Work Pract* **19**, 503-518, doi:10.1177/1049731509335569 (2009).

- 1
2 613 33 Swanson, R. C. *et al.* Rethinking health systems strengthening: key systems thinking tools
3 614 and strategies for transformational change. *Health Policy Plan* **27 Suppl 4**, iv54-61,
4 615 doi:10.1093/heapol/czs090 (2012).
- 5 616 34 Alkabab, Y. *et al.* Early interventions for diabetes related tuberculosis associate with
6 617 hastened sputum microbiological clearance in Virginia, USA. *BMC Infect Dis* **17**, 125,
8 618 doi:10.1186/s12879-017-2226-y (2017).
- 9 619 35 Lo, H.-Y. *et al.* Does enhanced diabetes management reduce the risk and improve the
10 620 outcome of tuberculosis? *Int J Tuberc Lung Dis* **20**, 376-382, doi:0.5588/ijtld.15.0654
11 621 (2016).
- 13 622 36 Lönnroth, K., Roglic, G. & Harries, A. D. Improving tuberculosis prevention and care through
14 623 addressing the global diabetes epidemic: from evidence to policy and practice. *The Lancet*
15 624 *Diabetes & Endocrinology* **2**, 730-739, doi:10.1016/s2213-8587(14)70109-3 (2014).
- 16 625 37 De-Regil, L. M., Pena-Rosas, J. P., Flores-Ayala, R. & del Socorro Jefferds, M. E.
17 626 Development and use of the generic WHO/CDC logic model for vitamin and mineral
18 627 interventions in public health programmes. *Public Health Nutr* **17**, 634-639,
20 628 doi:10.1017/S1368980013000554 (2014).
- 21 629 38 Potter, C. & Brough, R. Systemic capacity building: a hierarchy of needs. *Health Policy Plan*
22 630 **19**, 336-345, doi:10.1093/heapol/czh038 (2004).
- 24 631 39 Hales, S. *et al.* Reporting guidelines for implementation and operational research. *Bull*
25 632 *World Health Organ* **94**, 58-64, doi:10.2471/BLT.15.167585 (2016).
- 26 633 40 Martson, A. G. *et al.* How to design a study to evaluate therapeutic drug monitoring in
27 634 infectious diseases? *Clin Microbiol Infect* **26**, 1008-1016, doi:10.1016/j.cmi.2020.03.008
28 635 (2020).
- 30 636 41 Hemming, K., Haines, T. P., Chilton, P. J., Girling, A. J. & Lilford, R. J. The stepped wedge
31 637 cluster randomised trial: rationale, design, analysis, and reporting. *BMJ* **350**, h391,
32 638 doi:10.1136/bmj.h391 (2015).
- 33 639 42 Senkoro, M. *et al.* Prevalence of pulmonary tuberculosis in adult population of Tanzania: a
34 640 national survey, 2012. *Int J Tuberc Lung Dis* **20**, 1014-1021, doi:10.5588/ijtld.15.0340
36 641 (2016).
- 37 642 43 Ministry of Health. Tanzania Non Communicable Diseases (NCD) Prevention and Control
38 643 Program. Guidance on provision of NCD and mental health services in the context of
39 644 COVID-19 outbreak in Tanzania. (2020).
- 41 645 44 WHO. in *Action Programme on Essential Drugs* Vol. WHO/DAP/93.1 (1993).
- 42 646 45 Riza, A. L. *et al.* Clinical management of concurrent diabetes and tuberculosis and the
43 647 implications for patient services. *The Lancet Diabetes & Endocrinology* **2**, 740-753,
44 648 doi:10.1016/s2213-8587(14)70110-x (2014).
- 46 649 46 WHO. (ed World Health Organization Stop TB Department and Department of Chronic
47 650 Diseases and Health Promotion, Geneva, Switzerland and The International Union Against
48 651 Tuberculosis and Lung Diseases Paris France) (2011).
- 49 652 47 Mave, V. *et al.* Tuberculosis screening among persons with diabetes mellitus in Pune, India.
50 653 *BMC Infect Dis* **17**, 388, doi:10.1186/s12879-017-2483-9 (2017).
- 52 654 48 Byashalira, K. *et al.* Clinical outcomes of new algorithm for diagnosis and treatment of
53 655 Tuberculosis sepsis in HIV patients. *International Journal of Mycobacteriology* **8**,
54 656 doi:10.4103/ijmy.ijmy_135_19 (2019).
- 55 657 49 The United Republic of Tanzania:Ministry of Health, Community Development, Gender,
56 658 Elderly and Children:National Guidelines for Collaborative Care and Control of Tuberculosis
58 659 and Diabetes. (2016).
- 59 660 50 van Crevel, R., Koesoemadinata, R., Hill, P. C. & Harries, A. D. Clinical management of
60 661 combined tuberculosis and diabetes. *Int J Tuberc Lung Dis* **22**, 1404-1410,
662 doi:10.5588/ijtld.18.0340 (2018).

- 1
2 663 51 Sealed Envelope Ltd. Power calculator for continuous outcome superiority trial: Accessed
3 664 on 2017. <https://www.sealedenvelope.com/power/continuous-superiority/> [Accessed Wed
4 665 Dec 21 2016].) (2012).
- 5 666 52 Boeree, M. J. *et al.* High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis:
6 667 a multi-arm, multi-stage randomised controlled trial. *The Lancet Infectious Diseases*,
8 668 doi:10.1016/s1473-3099(16)30274-2 (2016).
- 9 669 53 Capiou, S. *et al.* Official International Association for Therapeutic Drug Monitoring and
10 670 Clinical Toxicology Guideline. *Therapeutic Drug Monitoring* **41**, 409-430,
11 671 doi:10.1097/ftd.0000000000000643 (2019).
- 13 672 54 van der Burgt, E. P. *et al.* End TB with precision treatment! *Eur Respir J* **47**, 680-682,
14 673 doi:10.1183/13993003.01285-2015 (2016).
- 15 674 55 Zuur, M. A. *et al.* Fixed-dose combination and therapeutic drug monitoring in tuberculosis:
16 675 friend or foe? *Eur Respir J* **48**, 1230-1233, doi:10.1183/13993003.00833-2016 (2016).
- 18 676 56 Alffenaar, J. C. *et al.* Integrating Pharmacokinetics and Pharmacodynamics in Operational
19 677 Research to End Tuberculosis. *Clin Infect Dis* **70**, 1774-1780, doi:10.1093/cid/ciz942 (2020).
- 20 678 57 Prada-Medina, C. A. *et al.* Systems Immunology of Diabetes-Tuberculosis Comorbidity
21 679 Reveals Signatures of Disease Complications. *Sci Rep* **7**, 1999, doi:10.1038/s41598-017-
22 680 01767-4 (2017).
- 24 681 58 Kumar, N. P. *et al.* Tuberculosis-diabetes co-morbidity is characterized by heightened
25 682 systemic levels of circulating angiogenic factors. *J Infect* **74**, 10-21,
26 683 doi:10.1016/j.jinf.2016.08.021 (2017).
- 27 684 59 Martin, D. L. *et al.* Data collection, processing, validation, and verification. *Health Phys* **95**,
28 685 36-46, doi:10.1097/01.HP.0000298817.72107.48 (2008).
- 30 686 60 Hammarberg, K., Kirkman, M. & de Lacey, S. Qualitative research methods: when to use
31 687 them and how to judge them. *Hum Reprod* **31**, 498-501, doi:10.1093/humrep/dev334
32 688 (2016).
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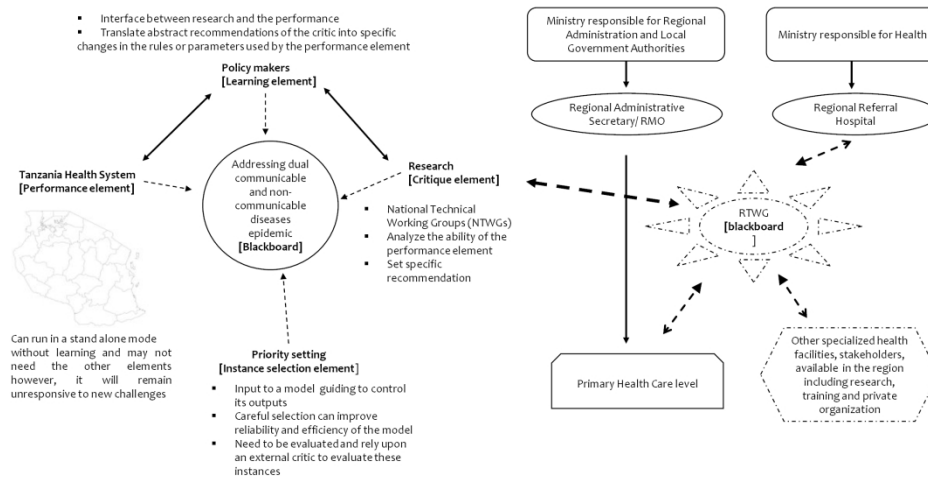
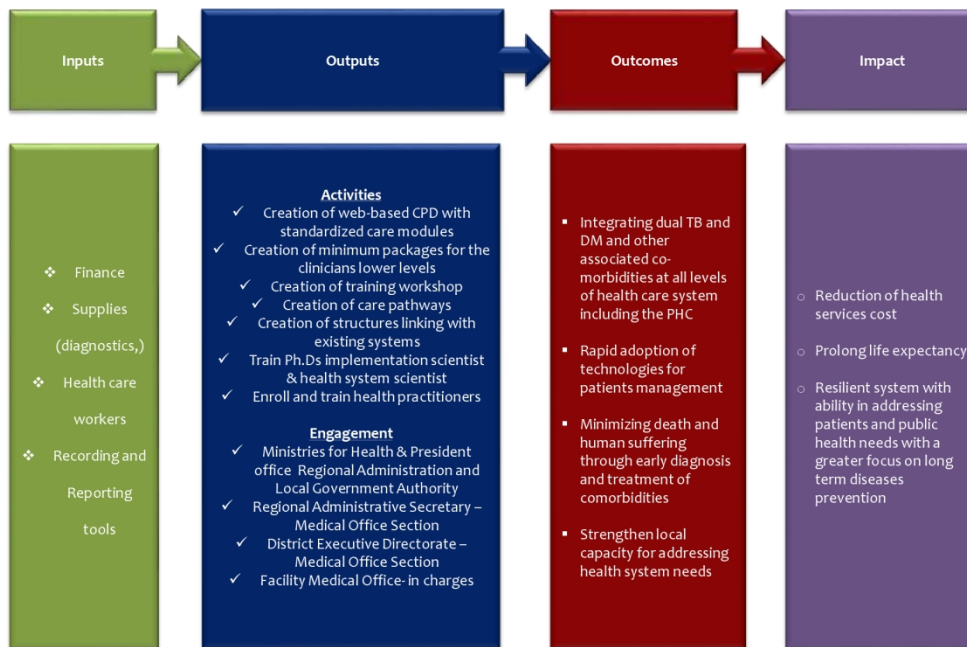


Figure 1: This model will break the siloed policy makers, health providers and researchers and gradually transform the health system into a proactive self-organizing or self-repairing system. Essential elements (Performance, Instance Selection, Critique, and Learning), if operated effectively will form an adaptive learning system. The proposed TB/DM-ADEPT Model will interconnect all interactive elements through: (a) Setting a regular single platform for policy makers, researchers and service providers on TB/DM epidemic agenda (Learning element); (b) Implementing international standards of dual TB and DM care through integrative TB/DM collaborative services that will facilitate early diagnosis while providing individualized treatment of patients with dual TB/DM disease (Performance element); (c) Conduct TB/DM applied research in implementation and health system research science to determine how to deliver best practices that will enable a people-centred health system (Critique element); and (d) Train PhD and postdoctoral fellows to answer dual TB/DM health system challenges to strengthen applied research capacity and hands-on skills to create a critical mass of the next generation of scientists able to scale up TB/DM interventions and adapt to study other communicable/ non-communicable disease intersections (Instance Selection element).

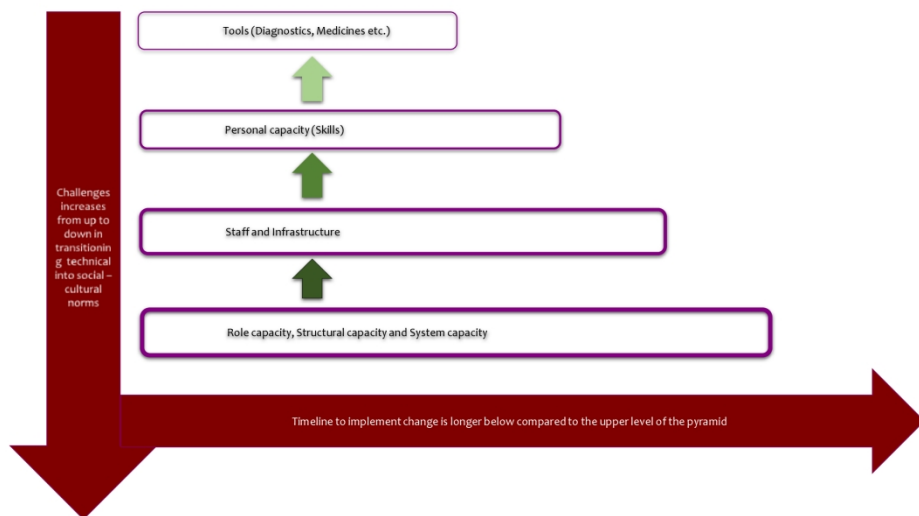
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Logic framework model for measuring outcomes and impact

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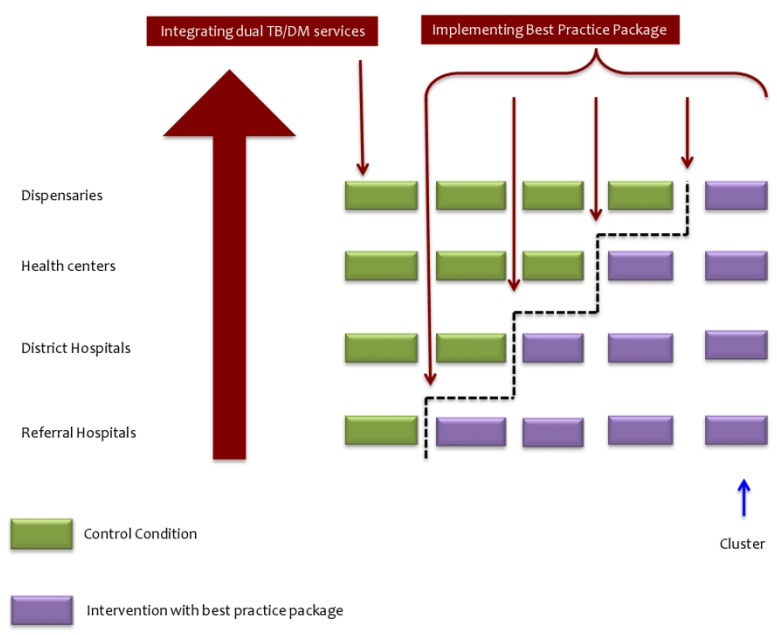
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Hierarchy of needs for strengthening the health system as described by Potter & Brough³⁴

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Introduction of integration of TB/DM services thereafter stepwise introduction of packages comprises of susceptibility, therapeutic drug monitoring, HbA1c for optimal TB/DM case management at all levels of health facilities

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BMJ Open

Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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TITLE: Protocol for establishing an Adaptive Diseases control Expert Programme in Tanzania (ADEPT) for integrating care of communicable and non-communicable diseases using tuberculosis and diabetes as a case study.

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46 44 **Keywords**

47
48 45 Adaptive diseases intervention programme, Communicable and non-communicable dual
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50 46 epidemics, tuberculosis and diabetes dual epidemic, health systems, implementation science
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53 47 **Main manuscript words count = 3707**
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51 ABSTRACT

52 **Introduction:** Most sub-Saharan African countries endure a high burden of communicable
53 infections but also face a rise of non-communicable diseases (NCDs). Interventions targeting
54 particular epidemics are often executed within vertical programmes. We establish an **Adaptive**
55 **Diseases control Expert Programme in Tanzania (ADEPT)** model with three domains; step-wise
56 training approach, integration of communicable and NCDs and a learning system and. The model
57 aims to shift traditional vertical programmes to an adaptive diseases management approach
58 through integrating communicable and NCDs using the tuberculosis (TB) and diabetes mellitus
59 (DM) dual epidemic as a case study. We aim to describe the ADEPT protocol with underpinned
60 implementation and operational research on TB/DM.

61 **Methods and analysis:** The model implement a collaborative TB and DM services protocol as
62 endorsed by the World Health Organization in Tanzania. Evaluation of the process and outcomes
63 will follow the logic framework. A mixed research design with both qualitative and quantitative
64 approaches will be used in applied research action. Anticipated implementation research
65 outcomes include at the health facilities level for organizing TB/DM services, pathways of TB/DM
66 patients seeking care in different health facilities, factors in service delivery that need de-
67 implementation, and the ADEPT model implementation feasibility, acceptability and fidelity.
68 Expected operational research outcomes include additional identified patients with dual TB/DM,
69 the prevalence of comorbidities like hypertension in TB/DM patients and final treatment
70 outcomes of TB/DM including treatment related complications. Findings will inform the future
71 policies and practices for integrating communicable and NCDs services.

72 **Ethics and Dissemination:** Ethical approval was granted by The National Research Health Ethical
73 Committee (Ref-No. NIMR/HQ/R.8a/Vol.IX/2988) and the implementation endorsed by the
74 Government authorities. Findings will be proactively disseminated through multiple mechanisms

1
2 75 including peer-reviewed journals, and engagement with various stakeholders' example in
3
4 76 conferences and social media.

6 77 **ARTICLE SUMMARY**

9 78 **Strengths and limitations of this study**

- 11 79 • The ADEPT model implementation underpins pragmatic research using a mixed study
12
13 design to allow triangulation
- 14 80
- 15
- 16 81 • Considers service delivery at varying health facilities levels while covering urban, semi-urban
17
18 and rural settings
- 19 82
- 20
- 21 83 • The proposed ADEPT model outcome considers process and patient-centered outcomes
- 22
23
- 24 84 • Lack of randomization of study settings or health facilities may introduce bias
- 25

26 85 **INTRODUCTION**

28
29 86 Tanzania like other sub-Saharan African countries endures a high burden of communicable
30
31 87 infections including multidrug resistant pathogens; but also a concurrent rise of non-
32
33 communicable diseases (NCD) as populations urbanize, diets “westernize” and lifespans
34 88
35 lengthen [1]. The health system is largely inflexible and during various periods of disease
36 89
37 epidemics, the health management teams operate in crisis-mode with limited capacity to plan
38 90
39 for long-term disease prevention [2]. Currently in Tanzania, planned interventions for several
40 91
41 longstanding and socioeconomically draining infectious diseases epidemics like tuberculosis (TB)
42 92
43 or human immunodeficiency virus (HIV), are executed within disease specific or vertical
44 93
45 programmes [3]. Vertical programmes operate in silos while in reality various communicable and
46 94
47 NCDs and treatments can influence one another, and overlap in populations of shared genetic
48 95
49 backgrounds or environmental exposures, and in communities with similar socioeconomic
50 96
51 determinants of health. Furthermore, vertical programmes significantly constrain health care
52 97
53 delivery, and are rarely efficient or cost-effective, particularly when considering prevailing
54 98
55 regional health challenges [4]. This sobering fact has been illuminated in Tanzanian research
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1
2 100 studies that uncovered a health system gridlock largely contributed by limited resources and
3
4 101 skills-training for front-line health care providers, and weak linkage to other health services with
5
6 102 the subsequent effect of underuse of technologies [5-10].

8
9 103 Likewise, the prevalence of dual communicable and NCD epidemics is increasing, yet
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11 104 communicable clinics are unprepared to deal with dual services [11, 12]. For instance, the
12
13
14 105 prevalence of DM ranged 4 – 17 % and hypertension ranged 7 – 25 % in people leaving with HIV
15
16 106 attending clinics in Tanzania cities, while, in other settings within Tanzania, the prevalence of DM
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18
19 107 ranged 4 – 5% and hypertension ranged 22 – 30% [13, 14]. Likewise, the incidence of dual
20
21 108 diagnosed patients with TB/DM ranges from 4% of all TB patients in rural areas to 17% in urban
22
23
24 109 settings. [15, 16]. Evidence has shown that TB/DM death is 5-fold higher compared to TB patients
25
26 110 without DM and that death primarily occurred early, in the first three months of TB treatment
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28
29 111 [15, 16]. This high and early mortality from TB/DM in Tanzania is due to both programmatic and
30
31 112 biological factors [17]. The TB and DM services are not linked and these separated service lines
32
33
34 113 lead to delayed interventions for both diseases [18]. Biological factors contributing to poor
35
36 114 TB/DM treatment outcomes includes DM-related alterations in drug absorption and metabolism
37
38 115 resulting in sub-therapeutic anti-TB drug serum concentrations, altered inflammatory/anti-
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41 116 inflammatory host immune defences and worsened control of hyperglycaemia leading to
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43 117 uncontrolled DM [19] [20]

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46 118 The existing systemic bottlenecks hinder optimal service delivery particularly in individuals with
47
48 119 dual communicable and NCDs, thus suggesting the urgent need for modification of models of
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50
51 120 health care delivery. We developed a model to strengthen health systems by shifting traditional
52
53 121 vertical programmes to a patient-centred adaptive diseases control approach through
54
55 122 integrating communicable and NCDs. The model intention is to integrate technologies and
56
57
58 123 innovations to personalize treatment and increase impact on quality care through novel
59
60 124 strategies while facilitating the interruption of the cycle of transmission, and mortality in

1
2 125 communities.
3
4 126 Henceforth, we describe the strategy to establish a contemporary **Adaptive Diseases control**
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6
7 127 **Expert Programme in Tanzania (ADEPT)**. The ADEPT model is likely to pioneer the systems
8
9 128 thinking methodology described by Swanson and colleagues to guide integrative changes in the
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11
12 129 health system [21], and it includes three interdependent domains; (i) step-wise training approach
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14 130 for knowledge and skills improvement of the frontline health care providers, (ii) adaptive service
15
16 131 delivery through integration of communicable and NCD and (iii) continuous learning and
17
18
19 132 integration of dual communicable and NCD (Figure 1).

20
21 133 The objective of this protocol is to describe the implementation of ADEPT model using the TB
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23
24 134 and DM dual epidemic as a case study in Tanzania with underpinned applied research questions
25
26 135 (both operational and implementation research) to answer critical scientific questions of direct
27
28
29 136 patient and public benefit. The protocol will generate evidence that will subsequently inform the
30
31 137 forthcoming best policies for integrating care of communicable and NCDs in the country.

32 33 138 **Overview of the ADEPT Model**

34
35
36 139 The ADEPT model has three components considered as vital to re-orient the health system to
37
38 140 efficiently address dual communicable and NCDs. Each component is described as follows;

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41
42 141 **I. A Step-wise Training approach: The objective is to improve knowledge, skills-training and**
43
44 142 **resource acquisition for the frontline health care providers to integrate communicable and**
45
46
47 143 **NCDs at varying health system levels.**

48
49
50 144 This approach follows the “classical diffusions of innovation theory” described elsewhere [22]
51
52
53 145 and organised on-job training in two clusters that will stepwise deliver a logically related set of
54
55 146 international standards of patients with communicable and NCDs. The first cluster consisting of
56
57
58 147 mentors that train to integrate communicable and non-communicable diseases. The potential
59
60 148 mentors will be selected by the health managers at the respective health facilities, preferably

1
2 149 working in either a general clinic or TB or DM clinic. This cluster will also then serve as subsequent
3
4 150 mentors. The initial training is through the e-learning methodology and pre-defined proceeding
5
6 151 criterion (score > 80% of the online training) to the next phase which is a face-to-face workshop.
8
9 152 The aim of the workshop is to expose individuals to acquire hands-on skills and conduct practical
10
11 153 exercises related to clinical services focusing on algorithms of management or nursing care and
13
14 154 new endorsed technologies. The second cluster will receive training and mentorship from the
15
16 155 first cluster. The first cluster receives package/materials to train the second cluster working at
17
18 156 the same level or at primary health care facilities.
20
21

22 157 **II. Adaptive service delivery. The objective is to integrate communicable and NCDs at varying**
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24
25 158 **health system levels**
26

27
28 159 Clinics delivering communicable or NCDs at varying levels of health facilities will receive training
29
30 160 using a step-wise model. Considerations of infection prevention control will guide a service
31
32 161 delivery approach while considering patient-centred recommendations. The first clinic will be
33
34 162 applicable to clients with TB with or without other co-morbidities. Recognizing individuals with
35
36 163 non-communicable lung diseases (CLDs) such as chronic obstructive pulmonary diseases
37
38 164 presenting with features akin of TB, a separate clinic may need to be organized. For the TB and
39
40 165 CLD clinics, although potentially operating separately, it is important to maintain the link of these
41
42 166 clinics as an important component of practical approach of lung health. The third clinic will
43
44 167 encompass all non-TB-non-CLD with or without other comorbidities including HIV, DM, and
45
46 168 Hypertension. A multimorbidity team within a health facility will facilitate mechanisms for
47
48 169 screening communicable and NCDs.
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56 170 **III. Learning system: The objective is to create a platform for reviewing data and information**
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59 171 **generated during implementation, and create a 'self-repairing' mechanism**
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1
2 172 The mentors or first cluster of trainees will have regular meetings at the Regional Medical Officer
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4 173 with attendance of District Medical Officers and different programme coordinators; including TB
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6 174 & Leprosy, NCDs, HIV, Malaria and Neglected Tropical Diseases. The meeting will review the
7
8
9 175 clinical audit and quality improvement reports from health facilities focusing on health service
10
11 176 delivery and identify the gaps for actions. Likewise, the coordinators will share on the expected
12
13
14 177 national targets in their local context. The meeting report will be submitted to the higher
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16 178 authorities responsible for health. Currently the report will be submitted to the Ministry of
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18
19 179 Health Community Development Gender Elderly and Children and the President Office Regional
20
21 180 Administration and Local Government Authority. The report will be included in the respective
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24 181 national technical working groups (TWG) for incorporation in the general provision of technical
25
26 182 direction and advice. The relay mechanisms from the TWG to regions will also be established.
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30 183 **ADEPT Model Research Questions Component**

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33 184 The proposed research questions focus on integration of TB and DM services. The proposed
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35
36 185 questions cover the scope of implementation and operational research sciences.

37 38 186 Implementation research

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41 187 1. Where is the best place in the HCS system to implement (or initiate) integration of TB and
42
43 188 DM?
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45 189 2. What is the best approach to deliver on-job training and facilitate delivery of integration
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47
48 190 of TB and DM in a patient-centred approach?
- 49
50 191 3. What did patients with dual TB and DM experience and what were their perspectives on
51
52
53 192 services they received in the health facilities?
- 54
55 193 4. What is/are the most effective approach/es to *de-implement* health facility practices
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58 194 that do not support effective integration of proposed service delivery model using TB
59
60 195 and DM as a case study?

- 1
2 196 5. What is the feasibility, acceptability and fidelity of the implemented designed models on
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4 197 TB/DM?
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6 198 6. What are the effects of therapeutic drug monitoring on personalized dose adjustment
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9 199 and subsequently on treatment outcomes?
10

11 200 Operational research in TB and DM

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14 201 1. How many additional dual TB and DM patients will be identified during bi-directional
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16 202 screening of TB and DM services who would otherwise not have been identified?
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18
19 203 2. What are the treatment outcomes of patients with dual TB and DM with or without HIV
20
21 204 compared to other patients without DM?
22

23 205 **METHODS AND ANALYSIS FOR ADEPT MODEL**

24
25
26 206 The protocol deploys the International Union Against Tuberculosis and Lung Disease and the
27
28
29 207 World Diabetes Foundation outlined Bali Initiative on TB and DM collaborative services that was
30
31 208 endorsed by World Health Organization (WHO) [23, 24]. The model will be evaluated using the
32
33
34 209 logic framework developed by the WHO/US-Center for Diseases Control and Prevention (US-
35
36 210 CDC) (Figure 2) [25]. The design of input and output pillars reflect largely on the archetypical
37
38
39 211 work designed by Potters and Brought in 2004 for health system strengthening [26]. This
40
41 212 includes a four-tier hierarchy with nine-interdependent elements as depicted in Figure 3.

42
43 213 **Staff and Personnel Training:** The ADEPT consortium collaborates with the National Training
44
45
46 214 Centres and hospitals/facilities that provide advanced/specialized care of patients for executing
47
48 215 the stepwise training approach on TB/DM and associated co-morbidities. Training includes
49
50
51 216 modules delivered as web-based or m-Health platforms, covering different skills (for example,
52
53 217 clinicians and nurses) and can be updated remotely should new processes need to be
54
55
56 218 introduced. Health care providers will have endless access and updated alerts to their mobile
57
58 219 numbers or emails prompting them to complete a new module.
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60

1
2 220 **Role, Structural and System capacity:** Mentors spawned in the step-wise training approach
3
4 221 form a team under the Regional Medical Officer (RMO). Together with implementing partners
5
6 222 or stakeholders will conduct regular review on TB/DM services. The clinical audit programme is
7
8
9 223 built-in to increase accountability but also as a one of the learning system components [12].
10
11 224 The goal is to guide local decision but will also be communicated to the Ministries responsible
12
13
14 225 for Health and Regional Administration and Local Government Authorities.

15
16 226 **Tools:** Supplies for DM were frequently not available or inadequately stocked and these
17
18 including glucometers, glucostrips, HbA1c devices, therapeutic drug monitoring supplies,
19 227 recording and reporting. These tools were funded temporarily through the Danish International
20
21 228 Development Agency, subsequently health facilities will take over. TB consumables, supplies and
22
23 229 tools were procured through conventional channels.

24 230 25 26 231 **METHODS AND ANALYSIS FOR TB AND DM RESEARCH**

27 232 **Study design**

28 233 (i) **Set of Implementation research questions**

29 234 A set of implementation research questions will deploy a mixed research design, both qualitative
30
31 235 and quantitative approaches. A cross sectional design will be conducted for the needs
32
33 236 assessment to identify where to provide clinical management of dual TB/DM and exploring the
34
35 237 patient's perspective and experience on dual TB/DM services using in-dept interviews of patients
36
37 238 with TB/DM. A prospective cohort design will be deployed to identify factors hindering
38
39 239 appropriate integration, feasibility, acceptability and fidelity.

40
41 240 A stepped wedged cluster non-randomized trial design will be for assessing effect of therapeutic
42
43 241 drug monitoring for dose adjustment and subsequent treatment outcome of patients with dual
44
45 242 TB/DM. Stepped-wedged methodology is a design that is preferably used when implementation
46
47 243 and research go hand in hand, especially with complex medical procedures this is a preferred
48
49 244 approach. A stepped wedge cluster randomised trial design is the most robust design that is

1
2 245 logistically feasible whilst providing the level of evidence of efficacy and effectiveness to support
3
4 246 further implementation in health care[27, 28]. This design helps to minimise ethical issues related
5
6
7 247 to withholding the optimized care in a traditional individual randomized trial design and can be
8
9 248 considered of low or negligible risk.

11 12 249 **(ii) Set of operational research question**

13
14 250 Cross sectional and prospective cohort design will be conducted through reviewing patients'
15
16 251 registries that receive bidirectional screening and treatment outcomes of dual TB/DM
17
18
19 252 respectively.

21 253 **Study area**

22
23
24 254 The research project will be conducted in three regions of Tanzania; Dar es Salaam, Iringa, and
25
26 255 Kilimanjaro. Districts that will participate include Ilala and Kigamboni for Dar es Salaam, Iringa
27
28
29 256 Municipal, Kilolo and Mufindi for Iringa, and Moshi Municipal, Same and Siha for Kilimanjaro. We
30
31 257 selected areas to affiliate with the workplaces of the current consortium's Tanzanian expertise
32
33
34 258 and to reflect representative population types. Dar es Salaam is largely a metropolitan while
35
36 259 Iringa and Kilimanjaro selected areas cover rural (Kilolo and Siha), semi-urban (Mufindi and
37
38 260 Same) and urban settings (Iringa Municipal and Moshi Municipal). According to the National TB
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40
41 261 survey of 2012, the TB prevalence is high in Dar es Salaam and in rural settings[29]. The burden
42
43 262 of DM is 9% in Tanzania but is more common in urban settings[30].

45 46 263 **Study outline: Set of the implementation Research Objectives**

47
48 264 At least 30 health facilities are needed for reliable and accurate results therefore each region will
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50
51 265 contribute at least 10 health facilities at various levels for integrating TB or TB/HIV and DM
52
53 266 services [31]. The catchment area includes one- referral hospital, three district hospitals and at
54
55
56 267 least 6 health centres/dispensaries. Using the WHO service availability and readiness assessment,
57
58 268 the identified capacity of the health facility will guide decisions on whether the health facility will
59
60 269 operate as a "one-stop shop" defined as TB and DM services provided at the same time using

1
2 270 adjacent rooms, “partial integration” defined as health care providers swaps between clinics, or
3
4 271 “remote integration” through cross referral of DM to TB services. Operational infection
5
6
7 272 prevention policy for TB controls and equipment for monitoring DM to prevent complications
8
9 273 are vital for decision. Entries of TB/DM integration in TB services or TB/HIV services will be at the
10
11
12 274 TB and DM clinics [32].

13
14 275 In the step-wise training approach, the online course will have a pre- and post-courses
15
16 276 assessment using the standard questions. Knowledge comparison will be made pre- and post-
17
18
19 277 training. During integration of dual TB/DM, patients receiving services for at least 3 months will
20
21 278 be invited for interview using a guide. Discussion will focus on identifying the pathway the
22
23
24 279 patients have experienced or encountered of receiving dual TB/DM services. Patients will be
25
26 280 asked to provide suggestions on pathways and service provision.

27
28
29 281 Information collected from the need’s assessment and in-depth interview of participants’
30
31 282 pathways of care will identify practices that need to be de-implemented. Discussion with the
32
33
34 283 health managers and responsible authorities will be conducted to reinforce *de*-implementation
35
36 284 of those practices. Pilot of clinical audit focused on de-implementing those practices will
37
38 285 complement the processes.

39
40
41 286 Health facilities effectively integrating dual TB/DM services will enter a next phase of using
42
43 287 therapeutic drug monitoring for personalized dose adjustment to optimize dual TB/DM patient
44
45
46 288 management (Figure 4). The implementation study design will describe the outcomes of patients
47
48 289 with dual TB/DM tested with diagnostics comprising of susceptibility testing, anti-TB therapeutic
49
50
51 290 drug monitoring, and HbA1c for monitoring the DM and guide selection and combination of both
52
53 291 anti-TB and anti-DM drugs. The stepped wedge trial design will be used for assessing the effect
54
55
56 292 of therapeutic drug monitoring will have 3-phases: pre-enrolment phases where prior to
57
58 293 implementation of all facilities will serve as controls; roll-out period when health facilities cross-
59
60

1
2 294 over from control to active implementing the therapeutic drug monitoring; post-rollout when all
3
4 295 selected health facilities will be implementing therapeutic drug monitoring.
5
6 296 TB/DM or TB-HIV/DM individuals will provide baseline sputum for culture and drug susceptibility
7
8
9 297 testing as well as smear microscopy. Patients will also test for HbA1c and renal function test to
10
11 298 assess for severity of DM. Two weeks after starting anti-TB medication, blood will be collected
12
13
14 299 for therapeutic drug monitoring of anti-TB drugs. Collection of blood will be through dry blood
15
16 300 spot and transported to the Biotechnology Laboratory/Kilimanjaro Clinical Research Institute
17
18
19 301 through Expedited Mail Services. The dry blood spot collection will be processed for testing the
20
21 302 serum drug levels starting first with rifampicin using an assay validated according to international
22
23
24 303 guidelines[33] Results will be communicated before day 21 of anti-TB treatment, and if needed
25
26 304 the anti-TB dosage adjustment will be made. A TDM strategy suitable for a fixed dose
27
28
29 305 combination regimen will be applied. In summary, the therapeutic drug monitoring will be
30
31 306 performed at week 2 of TB treatment, and based on plasma concentrations results, the
32
33
34 307 appropriate FDC tablets can be selected[34, 35]. Serum drug exposure that differs by at least 25%
35
36 308 from target concentrations will be considered as clinically relevant [36]. Therefore, those below
37
38
39 309 the target will be eligible for dose adjustment. Two weeks after dose adjustment, the new drug
40
41 310 concentrations will be assayed and determined if having met target [34]. In the continuation
42
43 311 phase, the appropriate fixed drug combination of rifampicin and isoniazid can be selected, based
44
45
46 312 on earlier measured drug concentrations. In addition, routine pharmaco-vigilance will
47
48 313 complement the safety data of this strategy. TB/DM cases will have monthly mycobacteriological
49
50
51 314 monitoring for detection of microbiological treatment failure. While DM monitoring will include
52
53 315 the assessment of retinopathy, impaired wound healing (diabetic foot), and nephropathy [37,
54
55 316 38]. HbA1c and renal function tests will also be followed at month 3 and 6 to enable further anti-
56
57
58 317 DM regimen adjustment.
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1
2 318 Key elements of the ADEPT model (step-wise training approach, integration of communicable &
3
4 319 NCDs and learning system) will be assessed for the coverage to estimate feasibility, acceptability
5
6
7 320 of different stakeholders on various stages of the model. Adherence of different algorithms and
8
9 321 steps described will be assessed and estimate the fidelity.

10
11 322 The data collection and analysis will be summarized in qualitative case record forms while
12
13
14 323 quantitative data will be available in the Multi-Schema Information Capture database, which is
15
16 324 a customizable format current in use in Kilimanjaro, utilizing secure encryption services
17
18
19 325 (www.mysql.com). Data collection, transfer, entry, validation, queries generation, audit,
20
21 326 archival and ownership will be detailed in specific standard operational procedures as
22
23
24 327 described elsewhere[39]. Outcome measures include

- 25
26 328 • Proportion of health facilities capable of providing dual TB/DM bidirectional screening
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28
29 329 with or without clinical management at varying levels
30
- 31 330 • Pathway of patients' experience and acceptability of dual TB/DM services [40]
32
- 33
34 331 • Effect of stepwise training on integration of dual TB/DM services at varying levels
35
- 36 332 • Systemic factors hindering optimal integration of TB/DM services at varying levels
37
- 38
39 333 • The ADEPT model implementation feasibility, acceptability of health care providers &
40
41 334 health managers and fidelity focusing on proportion of registered TB patients screened
42
43 335 for DM and vice versa as portrayed in Figure 2.
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- 45
46 336 • Treatment outcomes of patients with TB/DM adjusted for dosages with results from
47
48 337 TDM compared to those without TDM
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51 338

52
53 339 **Study outline: Set of the Operation Research Objective**

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55
56 340 People with DM, especially those with sub-optimal control as defined by HbA1c, will be screened
57
58 341 for active TB. The algorithms for active TB will be applied as described elsewhere[41] [42].
59

60
342 All people with active TB irrespective of having “classical” symptoms (polyuria, polydipsia and

polyphagia) will be screened with glucometer and interpretation of results is as follows; if the random blood/serum glucose (RBG) ≤ 7.8 mmol/L or fasting blood glucose (FBG) ≤ 6.1 mmol/L without DM symptoms, blood or serum glucose will be considered normal. If the RBG is 7.8 – 11.0 mmol/L or FBG is 6.2 – 6.9 mmol/L, this will be considered as pre-DM. When RBG is ≥ 11 mmol/L or FBG is ≥ 7.0 mmol/L this is DM[43]. To exclude patients with transient hyperglycaemia due to cytokine stimulation (false DM diagnosis), Hb1Ac will be performed in follow-up [19]. Individuals with pre-DM or DM further tested with HbA1c, interpretation of the results will be as follows; HbA1c of ≤ 38 mmol/mol ($\leq 5.6\%$); $39 < 48$ mmol/mol ($5.7\% < 6.5\%$), and ≥ 48 mmol/mol ($\geq 6.5\%$) will be reported and considered as normal, pre-DM and DM respectively[44]. People with active TB and pre-DM will be re-evaluated in the mid-term of TB treatment and TB treatment completion to identify if the condition has resolved, progressed, or remained static; if pre-DM will have advanced to DM, patients will be treated according to the DM guideline. The TB Infection Prevention Control practice that is applicable in HIV clinics will be applied[32].

An algorithm to identify people with active TB and high potential for treatment failure, including those with TB drug resistance and other DM co-morbidities, will be identified and tabled for expert discussion of additional support mechanisms that can be mobilized. Participants will be managed according to the collaborative TB/DM services framework guideline [45].

The data collection will be done under routine patient care in clinics. The outcome measures include;

- Incremental value of bidirectional screening in diagnosis of patients with dual TB/DM
- Proportion of TB/diabetes patients with favourable outcomes (cured, or treatment complete) or unfavourable outcomes (death, lost to follow-up, treatment failure)
- Proportion of TB/DM with additional comorbidities such as hypertension, kidney dysfunction, and retinopathy

PATIENT AND PUBLIC INVOLVEMENT

1
2 368 Development of this protocol was informed by a series of research studies that included one
3
4 369 study that examined patients' experience of health services in the health facilities [9]. Findings
5
6
7 370 from the described research objectives will be shared with patients' organizations for further
8
9 371 refinement before subsequently contributing in shaping the agenda of effective integration of
10
11
12 372 communicable and non-communicable diseases for policy makers.

13 14 373 **ETHICS AND DISSEMINATION**

15
16 374 This protocol has been approved at the local health research committee serving Kibong'oto
17
18
19 375 Infectious Diseases Hospital and National Health Research Committee with reference numbers
20
21 376 KNCHREC003 and NIMR/HQ/R.8a/Vol.IX/2988, respectively. Furthermore, the Ministries of
22
23
24 377 Health and Regional Administrative & Local Government Authority have endorsed
25
26 378 implementation of this protocol.

27 28 29 379 **AUTHOR CONTRIBUTIONS**

30
31 380 SGM, DLC, KR and ICB conceptualized and designed the model and proposal. TL, SH, JWA and
32
33
34 381 MSB contributed in the design of the concept particularly in TB/DM research component. DLC
35
36 382 obtained the funding for the ADEPT project from the Ministry of Foreign Affairs of Denmark.
37
38
39 383 SGM lead the implementation of the protocol in Tanzania while KR, and MSB lead
40
41 384 implementation of the stepwise model. NEN co-lead the implementation in Iringa. BTM co-lead
42
43 385 implementation of the TDM in Tanzania together with SH and JWA. All authors provided
44
45
46 386 technical inputs in the proposal. SGM wrote the manuscript with input from all the authors. All
47
48 387 authors have approved the final version and agreed to be accountable for all aspects of the work
49
50
51 388 related to accuracy and integrity.

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54
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56 57 58 391 **DATA STATEMENT**

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1
2 392 The data sets that will be generated and analysed during the conduct of the study will be made
3
4 393 available according to the available laws and regulations
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1
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3
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5
6 396 valuable comments on the research study

8
9 397 **FIGURES LEGEND**

10
11 398 Figure 1: The ADEPT model includes three essential domains. The performance domain is
12
13 identified as integration of communicable and non-communicable diseases. For effective
14 399 delivery of adaptive service, the performance domain requires support by the second and third
15
16 400 domains called a stepwise training approach and learning systems. The stepwise training
17
18 approach will ensure the frontline health care providers acquire knowledge and skills necessary
19 401 for integrating communicable and NCDs. The learning system domain should be continuously
20
21 402 operating by including processes like implementation research and clinical audits which serves
22
23 as a system lens to continuously inform the operation of the performance domain. Information
24 403 flow including clinical guidelines and new practices will go through the stepwise training
25
26 404 approach. The three functioning domains create an adaptive service delivery model for the
27
28 health system.
29 405

30
31 406 Figure 2: Logic framework model for measuring outcomes and impact

32
33 407 Figure 3: Hierarchy of needs for strengthening the health system as described by Potter &
34
35 Brough³⁴

36 408 Figure 4: Introduction of integration of TB/DM services thereafter stepwise introduction of
37
38 packages comprises of susceptibility, therapeutic drug monitoring, HbA1c for optimal TB/DM
39
40 case management at all levels of health facilities
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55 416 **COMPETING INTEREST STATEMENT:**

56
57 417 None declared.

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2 419 **REFERENCES**
3

- 4 420 1. Institute for Health Metrics and Evaluation (IHME). Global Burden of Diseases (GBD)
5 421 Profile;Tanzania, 2010.
- 6 422 2. Commission on Global Health Risk Framework for the Future (GHRF). Accelerating
7 423 Research and Development to Counter the Threat of Infectious Diseases. The Neglected
8 424 Dimension of Global Security: A Framework to Counter Infectious Disease Crises.
9 425 Washington (DC)2016
- 10 426 3. Ministry of Health and Social Welfare of Tanzania. **Health Sector Strategic Plan IV (2015-**
11 427 **2020)**. In.; 2015.
- 12 428 4. Bryan L, Conway M, Keesmaat T, McKenna S, Richardson B: **Strengthening sub-Saharan**
13 429 **Africa's health systems: A practical approach | McKinsey & Company.** *Health Systems &*
14 430 *Services* 2010:1-11.
- 15 431 5. Mpagama SG, Heysell SK, Ndusilo ND, Kumburu HH, Lekule IA, Kisonga RM, Gratz J, Boeree
16 432 MJ, Houpt ER, Kibiki GS: **Diagnosis and interim treatment outcomes from the first cohort**
17 433 **of multidrug-resistant tuberculosis patients in Tanzania.** *PLoS One* 2013, **8**(5):e62034.
- 18 434 6. Liyoyo A, Heysell SK, Kisonga RM, Lyimo JJ, Mleoh LJ, Mutayoba BK, Lekule IA, Mmbaga BT,
19 435 Kibiki GS, Mpagama SG: **Gridlock from diagnosis to treatment of Multidrug-Resistant**
20 436 **Tuberculosis (MDR-TB) in Tanzania: Illuminating Potential Factors for Possible**
21 437 **Intervention.** *East African Health Research Journal* 2017, **1**(1).
- 22 438 7. Mpagama SG, Mangi E, Mbelele PM, Chongolo AM, Kibiki GS, Heysell SK: **Gridlock from**
23 439 **diagnosis to treatment of multidrug resistant tuberculosis (MDR-TB) in Tanzania: Patients**
24 440 **perspectives from the focus group discussion.** *bioRxiv pre print* 2018, doi:
25 441 <http://dx.doi.org/10.1101/402594>.
- 26 442 8. Mpagama SG, Mbelele PM, Chongolo AM, Lekule IA, Lyimo JJ, Kibiki GS, Heysell SK:
27 443 **Gridlock from diagnosis to treatment of multidrug-resistant tuberculosis in Tanzania: low**
28 444 **accessibility of molecular diagnostic services and lack of healthcare worker**
29 445 **empowerment in 28 districts of 5 high burden TB regions with mixed methods**
30 446 **evaluation.** *BMC Public Health* 2019, **19**(1).
- 31 447 9. Mpagama SG, Ezekiel MJ, Mbelele PM, Chongolo AM, Kibiki GS, de Guex KP, Heysell SK:
32 448 **Gridlock from diagnosis to treatment of multidrug resistant tuberculosis (MDR-TB) in**
33 449 **Tanzania: patients' perspectives from a focus group discussion.** *BMC Public Health* 2020,
34 450 **20**(1):1667.
- 35 451 10. Harries AD, Murray MB, Jeon CY, Ottmani SE, Lonnoth K, Barreto ML, Billo N, Brostrom R,
36 452 Bygbjerg IC, Fisher-Hoch S *et al*: **Defining the research agenda to reduce the joint burden**
37 453 **of disease from diabetes mellitus and tuberculosis.** *Trop Med Int Health* 2010, **15**(6):659-
38 454 663.
- 39 455 11. Bintabara D, Ngajilo D: **Readiness of health facilities for the outpatient management of**
40 456 **non-communicable diseases in a low-resource setting: an example from a facility-based**
41 457 **cross-sectional survey in Tanzania.** *BMJ Open* 2020, **10**(11):e040908.
- 42 458 12. Shayo FK, Shayo SC: **Availability and readiness of diabetes health facilities to manage**
43 459 **tuberculosis in Tanzania: a path towards integrating tuberculosis-diabetes services in a**
44 460 **high burden setting?** *BMC Public Health* 2019, **19**(1):1104.
- 45 461 13. Kato I, Tumaini B, Pallangyo K: **Prevalence of non-communicable diseases among**
46 462 **individuals with HIV infection by antiretroviral therapy status in Dar es Salaam, Tanzania.**
47 463 *PLoS One* 2020, **15**(7):e0235542.
- 48 464 14. Kagaruki GB, Mayige MT, Ngadaya ES, Kimaro GD, Kalinga AK, Kilale AM, Kahwa AM,
49 465 Materu GS, Mfinanga SG: **Magnitude and risk factors of non-communicable diseases**
50 466 **among people living with HIV in Tanzania: a cross sectional study from Mbeya and Dar es**
51 467 **Salaam regions.** *BMC Public Health* 2014, **14**:904.

- 1
2 468 15. Sariko ML, Mpagama SG, Gratz J, Kisonga R, Saidi Q, Kibiki GS, Heysell SK: **Glycated hemoglobin screening identifies patients admitted for retreatment of tuberculosis at risk for diabetes in Tanzania.** *J Infect Dev Ctries* 2016, **10**(4):423-426.
- 3 469
4 470
5 471 16. Faurholt-Jepsen D, Range N, PrayGod G, Jeremiah K, Faurholt-Jepsen M, Aabye MG, Chungalucha J, Christensen DL, Grewal HM, Martinussen T *et al*: **Diabetes is a strong predictor of mortality during tuberculosis treatment: a prospective cohort study among tuberculosis patients from Mwanza, Tanzania.** *Trop Med Int Health* 2013, **18**(7):822-829.
- 6 472
7 473
8 474
9 475 17. Workneh MH, Bjune AG, Yimer SA: **Diabetes mellitus is associated with increased mortality during tuberculosis treatment: a prospective cohort study among tuberculosis patients in South-Eastern Amahra Region, Ethiopia.** *Infectious Diseases of Poverty* 2016, **5**(22):10.
- 10 476
11 477
12 478
13 479 18. Harries AD, Kumar AMV, Satyanarayana S, Lin Y, Zachariah R, Lonroth K, Kapur A: **Addressing diabetes mellitus as part of the strategy for ending TB.** *Trans R Soc Trop Med Hyg* 2016, **110**:173-179.
- 14 480
15 481
16 482 19. Aftab H, Christensen DL, Ambreen A, Jamil M, Garred P, Petersen JH, Nielsen SD, Bygbjerg IC: **Tuberculosis-Related Diabetes: Is It Reversible after Complete Treatment?** *Am J Trop Med Hyg* 2017, **97**(4):1099-1102.
- 17 483
18 484
19 485 20. Heysell SK, Moore JL, Keller SJ, Houpt ER: **Therapeutic drug monitoring for slow response to tuberculosis treatment in a state control program, Virginia, USA.** *Emerg Infect Dis* 2010, **16**(10):1546-1553.
- 20 486
21 487
22 488 21. Swanson RC, Cattaneo A, Bradley E, Chunharas S, Atun R, Abbas KM, Katsaliaki K, Mustafee N, Mason Meier B, Best A: **Rethinking health systems strengthening: key systems thinking tools and strategies for transformational change.** *Health Policy Plan* 2012, **27** Suppl 4:iv54-61.
- 23 489
24 490
25 491 22. Dearing JW: **Applying Diffusion of Innovation Theory to Intervention Development.** *Res Soc Work Pract* 2009, **19**(5):503-518.
- 26 492
27 493
28 494 23. Bali: **Bali Declaration on the Looming TB-Diabetes Co-epidemic.** In: *Stopping a looming Co-epidemic: A global Summit on Diabetes and Tuberculosis: 2-3 November 2015; Bali-Indonesia; 2-3 November 2015.*
- 29 495
30 496
31 497 24. Kapur A, Harries AD, Lönnroth K, Wilson P, Sulistyowati LS: **Diabetes and tuberculosis co-epidemic: the Bali Declaration.** *The Lancet Diabetes & Endocrinology* 2016, **4**(1):8-10.
- 32 498
33 499
34 500 25. De-Regil LM, Pena-Rosas JP, Flores-Ayala R, del Socorro Jefferds ME: **Development and use of the generic WHO/CDC logic model for vitamin and mineral interventions in public health programmes.** *Public Health Nutr* 2014, **17**(3):634-639.
- 35 501
36 502
37 503 26. Potter C, Brough R: **Systemic capacity building: a hierarchy of needs.** *Health Policy Plan* 2004, **19**(5):336-345.
- 38 504
39 505
40 506 27. Martson AG, Sturkenboom MGG, Stojanova J, Cattaneo D, Hope W, Marriott D, Patanwala AE, Peloquin CA, Wicha SG, van der Werf TS *et al*: **How to design a study to evaluate therapeutic drug monitoring in infectious diseases?** *Clin Microbiol Infect* 2020, **26**(8):1008-1016.
- 41 507
42 508
43 509 28. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ: **The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting.** *BMJ* 2015, **350**:h391.
- 44 510
45 511
46 512 29. Senkoro M, Mfinanga S, Egwaga S, Mtandu R, Kamara DV, Basra D, Fundikira L, Kahwa A, Shirima R, Range N *et al*: **Prevalence of pulmonary tuberculosis in adult population of Tanzania: a national survey, 2012.** *Int J Tuberc Lung Dis* 2016, **20**(8):1014-1021.
- 47 513
48 514
49 515 30. MoH: **Tanzania NCD Prevention and Control Program. Guidance on provision of NCD and mental health services in the context of COVID-19 outbreak in Tanzania.** 2020.
- 50 516
51 517
52 518 31. WHO: **How to investigate drug use in health facilities: Selected drug use indicators.** In: *Action Programme on Essential Drugs.* vol. WHO/DAP/93.1; 1993.

- 1
2 517 32. Riza AL, Pearson F, Ugarte-Gil C, Alisjahbana B, van de Vijver S, Panduru NM, Hill PC,
3 518 Ruslami R, Moore D, Aarnoutse R *et al*: **Clinical management of concurrent diabetes and**
4 519 **tuberculosis and the implications for patient services.** *The Lancet Diabetes &*
5 520 *Endocrinology* 2014, **2**(9):740-753.
- 6 521 33. Capiou S, Veenhof H, Koster RA, Bergqvist Y, Boettcher M, Halmingh O, Keevil BG, Koch
8 522 BCP, Linden R, Pistos C *et al*: **Official International Association for Therapeutic Drug**
9 523 **Monitoring and Clinical Toxicology Guideline.** *Therapeutic Drug Monitoring* 2019,
10 524 **41**(4):409-430.
- 11 525 34. van der Burgt EP, Sturkenboom MG, Bolhuis MS, Akkerman OW, Kosterink JG, de Lange
12 526 WC, Cobelens FG, van der Werf TS, Alffenaar JW: **End TB with precision treatment!** *Eur*
14 527 *Respir J* 2016, **47**(2):680-682.
- 15 528 35. Zuur MA, Akkerman OW, Davies Forsman L, Hu Y, Zheng R, Bruchfeld J, Tiberi S, Migliori
16 529 GB, Alffenaar JC: **Fixed-dose combination and therapeutic drug monitoring in**
17 530 **tuberculosis: friend or foe?** *Eur Respir J* 2016, **48**(4):1230-1233.
- 19 531 36. Alffenaar JC, Gumbo T, Dooley KE, Peloquin CA, McIlleron H, Zagorski A, Cirillo DM, Heysell
20 532 SK, Silva DR, Migliori GB: **Integrating Pharmacokinetics and Pharmacodynamics in**
21 533 **Operational Research to End Tuberculosis.** *Clin Infect Dis* 2020, **70**(8):1774-1780.
- 22 534 37. Prada-Medina CA, Fukutani KF, Pavan Kumar N, Gil-Santana L, Babu S, Lichtenstein F, West
23 535 K, Sivakumar S, Menon PA, Viswanathan V *et al*: **Systems Immunology of Diabetes-**
25 536 **Tuberculosis Comorbidity Reveals Signatures of Disease Complications.** *Sci Rep* 2017,
26 537 **7**(1):1999.
- 27 538 38. Kumar NP, Moideen K, Sivakumar S, Menon PA, Viswanathan V, Kornfeld H, Babu S:
28 539 **Tuberculosis-diabetes co-morbidity is characterized by heightened systemic levels of**
30 540 **circulating angiogenic factors.** *J Infect* 2017, **74**(1):10-21.
- 31 541 39. Martin DL, Hoff JL, Gard RA, Gregosky RJ, Jones HW, Kirkwood CA, Morris DG, Shinsato TE,
32 542 Willott-Moore CL: **Data collection, processing, validation, and verification.** *Health Phys*
33 543 2008, **95**(1):36-46.
- 34 544 40. Hammarberg K, Kirkman M, de Lacey S: **Qualitative research methods: when to use them**
36 545 **and how to judge them.** *Hum Reprod* 2016, **31**(3):498-501.
- 37 546 41. Mave V, Nimkar S, Prasad H, Kadam D, Meshram S, Lokhande R, Gupte N, Jain D, Gupta A,
38 547 Golub JE: **Tuberculosis screening among persons with diabetes mellitus in Pune, India.**
39 548 *BMC Infect Dis* 2017, **17**(1):388.
- 41 549 42. Byashalira K, Mbelele P, Semvua H, Chilongola J, Semvua S, Liyoyo A, Mmbaga B, Mfinanga
42 550 S, Moore C, Heysell S *et al*: **Clinical outcomes of new algorithm for diagnosis and**
43 551 **treatment of Tuberculosis sepsis in HIV patients.** *International Journal of*
44 552 *Mycobacteriology* 2019, **8**(4).
- 45 553 43. MoH: **THE UNITED REPUBLIC OF TANZANIA:Ministry of Health, Community Development,**
47 554 **Gender, Elderly and Children:National Guidelines for Collaborative Care and Control of**
48 555 **Tuberculosis and Diabetes.** 2016.
- 49 556 44. van Crevel R, Koesoemadinata R, Hill PC, Harries AD: **Clinical management of combined**
50 557 **tuberculosis and diabetes.** *Int J Tuberc Lung Dis* 2018, **22**(12):1404-1410.
- 51 558 45. WHO: **Collaborative Framework for Care and Control of Tuberculosis and Diabetes** In.
53 559 Edited by Stop TB Department and Department of Chronic Diseases and Health Promotion
54 560 WHO, Geneva, Switzerland and The International Union Against Tuberculosis and Lung
55 561 Diseases Paris France; 2011.
- 56 562
57 562
58
59 563
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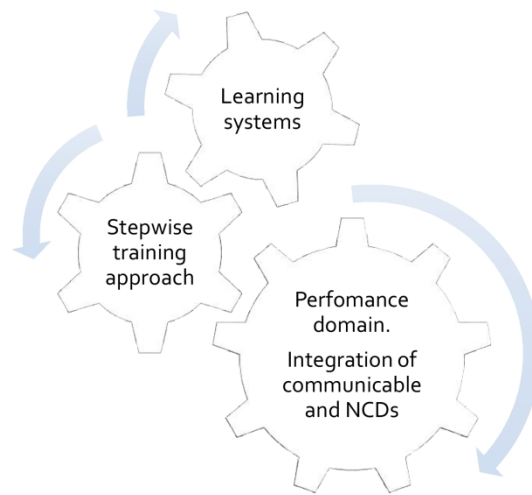
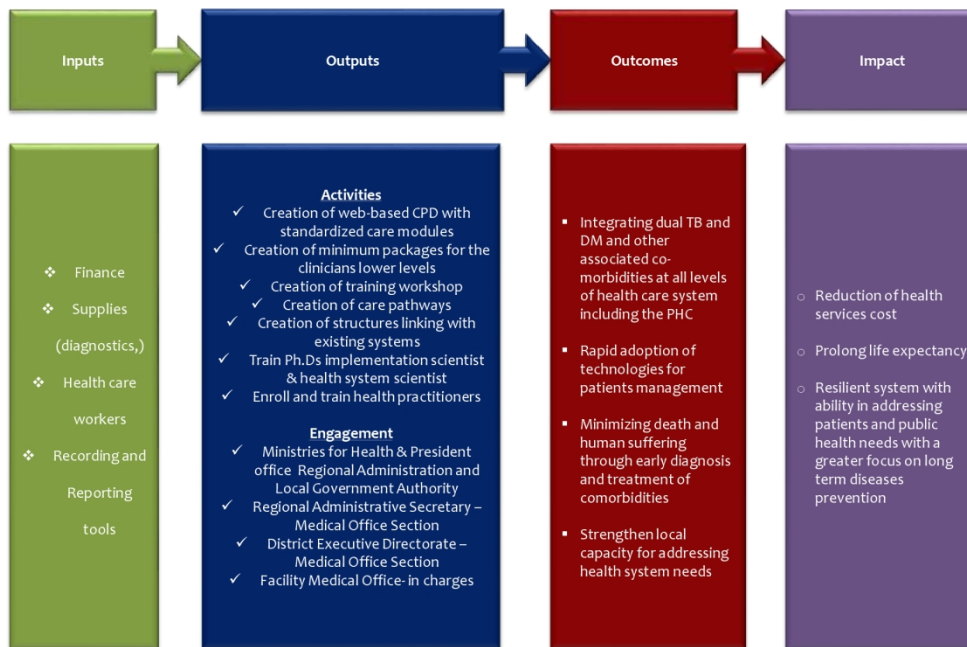


Figure 1: The ADEPT model includes three essential domains. The performance domain is identified as integration of communicable and non-communicable diseases. For effective delivery of adaptive service, the performance domain requires support by the second and third domains called a stepwise training approach and learning systems. The stepwise training approach will ensure the frontline health care providers acquire knowledge and skills necessary for integrating communicable and NCDs. The learning system domain should be continuously operating by including processes like implementation research and clinical audits which serves as a system lens to continuously inform the operation of the performance domain. Information flow including clinical guidelines and new practices will go through the stepwise training approach. The three functioning domains create an adaptive service delivery model for the health system.

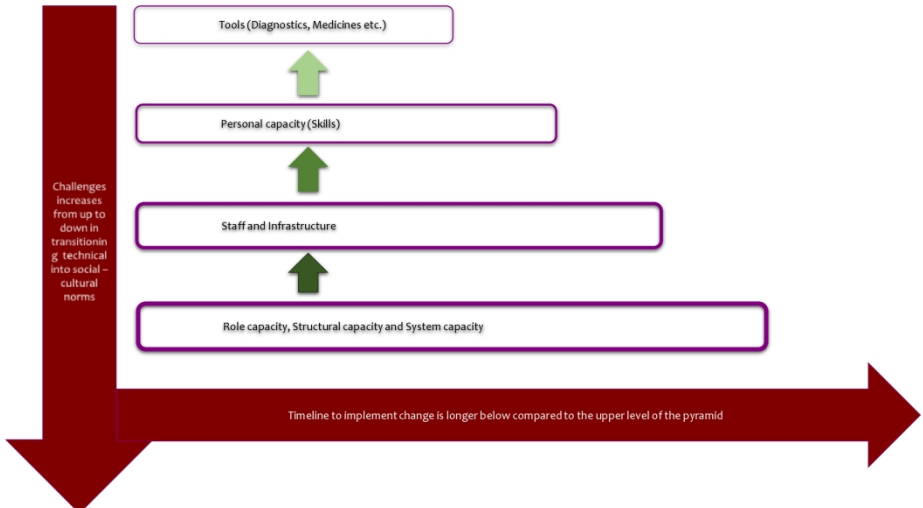
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Logic framework model for measuring outcomes and impact

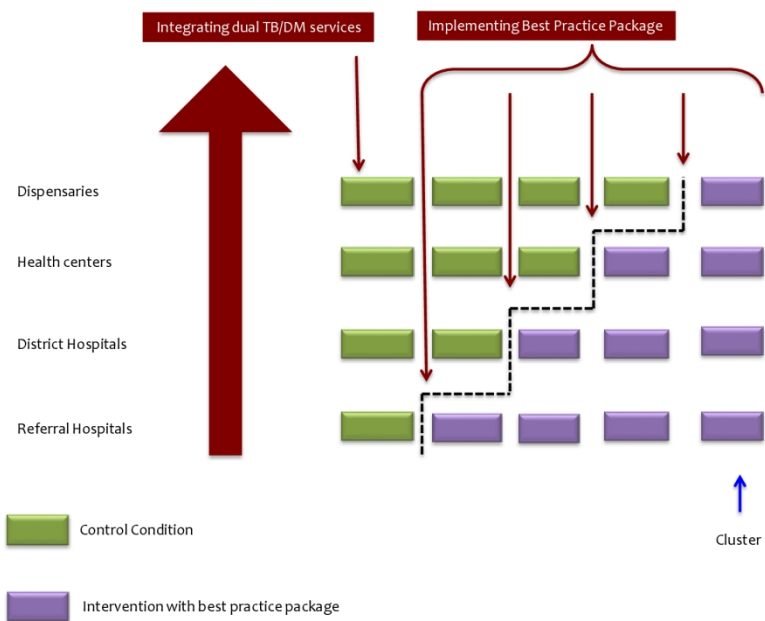
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Hierarchy of needs for strengthening the health system as described by Potter & Brough³⁴

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Introduction of integration of TB/DM services thereafter stepwise introduction of packages comprises of susceptibility, therapeutic drug monitoring, HbA1c for optimal TB/DM case management at all levels of health facilities

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