**Modelling of oesophageal cancer within the Thanzi La Onse Model**

**Background: The Thanzi La Onse Model**

As part of the Thanzi La Onse program a model is being developed which aims to capture the health experiences of the population of Malawi and the consequent interactions with the health care system. The intent is that this model will help to inform future delivery of health care in Malawi. The model is an individual based model – which means we explcitly simulate the individual life and health experiences of a representative proportion of population of Malawi. The simulation initiates on 1 Jan 2010 and we attempt to simulate the attributes of the population at that point. We can run the model forward to any specified future time point. Each potential intervention and its associated diseases are being modelled. This is being divided into separate disease/intervention modules. This document describes the module on depression and use of antidepressants.

**Background: General approach to decisions on modelling causal influences and effects of interventions**

This module was designed in the context of an overall approach to modelling causal effects in general and causal effects of interventions in particular. The overal intent is to adopt as simple a structure as can be conceived, whilst still capturing the essential elements of a disease and the interventions used to prevent or treatment. We include a causal link between a “variable” (by which we mean a characteristic or property of an individual, whether that be demographic, social or biologic), and risk of disease or another variable if there is strong evidence from an overall body of studies that such a causal link exists and is at least moderately strong. In informing such decisions we place particular value on RCTs or studies with a quasi-experimental design such as analyses based on an instrumental variable There is no expectation that such studies will be from Malawi or even from Africa. If there are such local studies and in the unlikely event that they provide strong evidence to suggest that the causal link is substantively different in Malawi then the intent is that this is taken into account and the Malawi-specific link included.

In the special case of a potential causal variable which relates to whether an individual has experienced or is experiencing an intervention the intent is to only include interventions if there is substantial RCT evidence of their beneficial effect, based on trials with objectively ascertained clinical endpoints with low risk of serious bias. Whilst DCP-3 (and to some extent the Malawi EHP) provides an initial list of such interventions and the evidence to support them, where possible our intent has been to form our own opinion on intervention efficacy based on the source trials.

Unless there is evidence to the contrary, the intent is to summarize and incorporate intervention effects into the model as relative risks or rates rather than absolute differences due to the fact that such measures are less likely to differ substantively by context. Interactions between characterstics (on the multiplicative scale) are only to be be incorporated if there is strong evidence. Again, we have not intended to rely on data from Malawi or Africa for such evidence but if local evidence exists which strongly suggests a different effect than elsewhere then the intent is that this modified effect is incorporated in the model.

**Background: Demographic and social characteristics modelled**

Based on data on the distribution of the population in Malawi according to geographic location we assign individuals a geographic location, which maps onto whether they are classified as living in a rural or urban area. Informed largely by data from the Malawi DHS, variables are also created indicating the person’s wealth level (based on 5 quintiles), whether the person has access to improved sanitation, clean drinking water, hand washing facilities, and whether they experience indoor air pollution (wood burning stove). We assign individuals a current education status (none, primary, secondary) which is updated 3 monthly from age 5 to 20. From age 15 on there is a possibility of being assigned as being overweight, as using tobacco, drinking excess alcohol, and having low exercise. Marital status (never, currently, widowed/divorced). The status with regard to such variables for individuals can change over time. The influences between these variables are described in detail in a separate document.

**Approach to modelling oesophageal cancer and use of potentially curative interventions: rationale for model structure and choice of parameter values**

**Variables modelled**

The model updates information on each individual with regard to oesophageal cancer status every 3 months. The model structure is described in Figure 1. Variables that we create for each individual in relation to oesophageal cancer (Table 1) are as follows: **stage of oesophageal dysplasia/cancer** (variable name: “ca\_oesophagus”, categories: 'none', 'low grade dysplasia', 'high grade dysplasia', ‘stage 1’, ‘stage 2’, ‘stage 3’, ‘stage 4’ categorical), **whether a diagnosis of oesophageal dysplasia/cancer has been made** (variable name: ca\_oesophagus\_diagnosed, categories: yes/no), **whether attempted curative treatment has been received in the current 3 month period** (variable name: ca\_oesophagus\_curative\_treatment categories: no, yes (person has low grade dysplasia), yes (person has high grade dysplasia), yes (person has stage 1), yes (person has stage 2 oes cancer), yes (person has stage 3 oes cancer), date of receiving attempted curative treatment (variable name: ca\_date\_treatment\_oesophageal\_cancer), **whether death from oesophageal cancer has occurred in the current 3 month period** (variable name: ca\_oesophageal\_cancer\_death).

**Incidence of low grade oesophageal dysplasia**

Table 2 describes the parameters and their values. Jointly, the chosen parameter values produce the model outputs shown in Table 3.

Informed by incidence rates of oesophageal cancer from Malawi cancer registry (Chasimpha et al, 2017), incidence of low grade oesophageal dysplasia is assumed to occur in people from age 20 years onwards and to depend on age, sex, and tobacco intake. The rate per 3 months in men aged exactly 20 without excess alcohol or tobacco use is assumed to be 0.00001. Informed by Chasimpha et al 2017, Banda et al 2001, Moses et al 2017, the rate ratio for females is taken as 1.3-fold. The rate ratio per year older after age 20 is is assumed to be 1.1, consistent with the 100 fold increase in rate between age 20 and 70 observed in Chasimphia et al, 2017. Informed by Mlombe et al 2017, the rate ratio for tabacco smoking is 2.0. We include a parameter for an effect of excess alcohol intake but use a rate ratio of 1.0 as Mlombe et al 2017 suggests this is not an independent risk factor.

**Progression between dysplasia / cancer stages**

Informed by Kastelein et al we assume a probabilty per 3 months of high grade oesophageal dysplasia, amongst people with low grade dysplasia of 0.03. Likewise, informed by Kastelein et al 2014 and Verbeek et al 2012 (albeit this is mainly adenocarcinoma when Malawi has preponderance of squamous cell carcinoma, but prognosis is not greatly different), the probabilty per 3 months of stage 1 oesophageal cancer amongst people with high grade dysplasia is 0.01.

Progression through stages of oesophageal cancer are informed by survival according to stage at diagnosis. The 5 year survival in United States (with treatment availability): 45% stage 1/2, 24% stage 3, 5% stage 4) <https://www.cancer.org/cancer/esophagus-cancer/detection-diagnosis-staging/survival-rates.html>. The 5 year survival without surgery < 5% Kauppila et al 2018 (Sweden). The probabilty per 3 months of stage 2 oesophageal cancer amongst people with stage 1 oesophageal cancer is taken as 0.05, as is the probability of pregression from stage 2 to 3, and from stage 3 to 4.

**Diagnosis of oesophageal dysplasia / cancer**

We assume a probability per 3 months of diagnosis in a person with stage 1 oesophageal cancer of 0.1, with a rate ratio for diagnosis of 0.1 for low or high grade dysplasia, reflecting the lower chance of detection at this stage. Likewise the rate of diagnosis is assumed to increase with stage, 3 fold for stage 2, 4 fold for stage 3 and 5 fold for stage 4. We aim for these rates to eventually be informed by data on stage of oesophageal cancer at diagnosis from the cancer registry, although in the initial report from the registry for very few cancer cases was their a cancer stage at diagnosis recorded (Msyamboza et al, 2012).

**Treatment for oesophageal dysplasia / cancer**

At all stages of dysplasia/cancer except stage 4 cancer we consider potential medical treatment aimed at cure amongst people who are diagnosed (which we refer to as curative treatment, recognising that it is often not successful in achieving a cure). Depending on stage this might include surgery, radiotherapy, chemotherapy. We recognise that availability if treatment is currently extremely limited in Malawi. The probability per 3 months of receiving curative treatment aimed at cure if have low grade dysplasia, given diagnosis is 0.01 per 3 months, with rate ratios for receiving treatment for high grade dysplasia and for all three earlier stages of oesophageal cancer being currently set to 1. There were reported in 2015 to be five Malawian oncologists and haematologists involved in full-time cancer care in the whole country (Masamba et al, 2015).

**Effect of treatment**

The rate ratio for high grade dysplasia for people with low grade dysplasia if had curative treatment at low grade dysplasia stage is assumed to be 0.1 informed indirectly by evidence from Kauppila et al 2018. Likewise the rate ratio for stage 1 oesophageal cancer for people with high grade dysplasia if had curative treatment at high grade dysplasia stage is 0.1. Similarly for the effect of curative treatment on progression from stage 1 to stage 2 and from stage 2 to stage 3. For progression from stage 3 to stage 4 the rate ratio is taken as 0.4. All these are indirectly informed by Kauppila et al 2018.

**Rate of death from oesophageal cancer**

Probability per 3 months of death from oesophageal cancer amongst people with stage 4 oesophageal cancer is assumed to be 0.4 per 3 months.

**Disability weights**

Salomon et al give disability weights for cancer as follows: diagnosis and primary therapy 0·294, metastatic 0·484, terminal phase: with medication 0·508, terminal phase: without medication 0·519.

We have gone with utilities as follows: low/high grade dysplasia 0.01, stage 1 cancer 0.20, stage 2 cancer 0.30, stage 3 cancer 0.40, stage 4 cancer 0.51.

**Main Limitations**

The main limitations are the relative lack of data to directly inform many of the parameter values. Underlying progression of the condition is assumed to follow a similar course as in studies in other parts of the world. For incidence of low grade dysplasia (as the first stage in the path of progression to oesophageal cancer) and rates of diagnosis and availability it is necessary to consider data from Malawi itself given that these are likely to depend on the setting. As it becomes possible to perform more analyses in collaboration with the cancer registry we expect to be able to further inform our parameter values.

**Figure 1. Diagrams illustrating model structure and parameters.**

**(a) oesophageal cancer status**

**(b) Oesophageal cancer diagnosis status**

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**(c) Curative treatment for oesophageal dysplasia/cancer**

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**(d) Palliative care**

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| **Table 1. Description of variables created relating to oesophageal cancer**  |
| **Variable** | **Description** | **Notes**  |
| ca\_oesophagus | oesophageal dysplasia/cancer stage: 'none', 'low grade dysplasia' 'high grade dysplasia' "stage 1", "stage 2", "stage 3", "stage 4" categorical) |  |
| ca\_oesophagus\_curative\_treatment\_requested | (Attempted) Curative treatment requested of health care system in this 3 month period. yes/no | This variable denotes whether treatment was indicated and requested of the health care system |
| ca\_oesophagus\_curative\_treatment | (Attempted) Curative treatment received in this 3 month period (categorical): no, yes (person has low grade dysplasia), yes (person has high grade dysplasia), yes (person has stage 1), yes (person has stage 2 oes cancer), yes (person has stage 3 oes cancer)  | This variable denotes whether treatment was given. |
| ca\_oesophagus\_diagnosed | oesophageal dysplasia/cancer diagnosed (yes/no) |  |
| ca\_oesophageal\_cancer\_death | death from oesophageal cancer |  |
| ca\_date\_treatment\_oesophageal\_cancer | date of receiving attempted curative treatment |  |

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| **Table 2. Description of parameters and proposed values**  |
| **Parameter** | **Proposed value** | **Description** | **Notes**  |
| r\_low\_grade\_dysplasia\_none | 0.0000005 | probability per 3 months of incident low grade oesophageal dysplasia, amongst people with no oesophageal dysplasia (men, age20, no excess alcohol, no tobacco)  | in conjunction with rate ratios below, informed by incidence rates of oesophageal cancer from Malawi cancer registry (Chasimpha et al, 2017) |
| rr\_low\_grade\_dysplasia\_none\_female | 1.3 | rate ratio for low grade oesophageal dysplasia for women  | Chasimpha et al 2017, Banda et al 2001, Moses et al 2017 |
| rr\_low\_grade\_dysplasia\_none\_per\_year\_older | 1.1 | rate ratio for low grade oesophageal dysplasia per year older from age 20 | rate increases 100 fold between age 20 and 70 (Chasimphia et al, 2017) |
| rr\_low\_grade\_dysplasia\_none\_tobacco | 2 | rate ratio for low grade oesophageal dysplasia for tobacco smokers | Mlombe et al 2017  |
| rr\_low\_grade\_dysplasia\_none\_ex\_alc | 1 | rate ratio for low grade oesophageal dysplasia for no excess alcohol | Mlombe et al 2017 suggests not an independent risk factor |
| rr\_high\_grade\_dysplasia\_low | 0.03 | probability per 3 months of high grade oesophageal dysplasia, amongst people with low grade dysplasia  | Kastelein et al 2014 |
| rr\_high\_grade\_dysp\_undergone\_curative\_treatment | 0.1 | rate ratio for high grade dysplasia for people with low grade dysplasia if had curative treatment at low grade dysplasia stage | indirect evidence from Kauppila et al 2018 |
| r\_stage1\_high\_grade\_dyspl | 0.01 | probability per 3 months of stage 1 oesophageal cancer amongst people with high grade dysplasia  | Kastelein et al 2014; Verbeek et al 2012 (mainly adenocarcinoma when malawi has preponderance of SCC, but prognosis is not greatly different)  |
| rr\_high\_grade\_dysp\_undergone\_curative\_treatment | 0.1 | rate ratio for stage 1 oes cancer for people with high grade dysplasia if had curative treatment at high grade dysplasia stage | indirect evidence from Kauppila et al 2018 |
| r\_stage2\_stage1 | 0.05 | probability per 3 months of stage 2 oesophageal cancer amongst people with stage 1 oesophageal cancer  | see \* below |
| rr\_stage1\_undergone\_curative\_treatment | 0.1 | rate ratio for stage 2 oes cancer for people with stage 1 oesophageal cancer if had curative treatment at stage 1  | some evidence from Kauppila et al 2018 |
| r\_stage3\_stage2 | 0.05 | probability per 3 months of stage 3 oesophageal cancer amongst people with stage 2 oesophageal cancer  | see \* below |
| rr\_stage2\_undergone\_curative\_treatment | 0.1 | rate ratio for stage 3 oes cancer for people with stage 2 oesophageal cancer if had curative treatment at stage 2  | some evidence from Kauppila et al 2018 |
| r\_stage4\_stage3 | 0.05 | probability per 3 months of stage 4 oesophageal cancer amongst people with stage 3 oesophageal cancer  | see \* below |
| rr\_stage3\_undergone\_curative\_treatment | 0.3 | rate ratio for stage 4 oes cancer for people with stage 3 oesophageal cancer if had curative treatment at stage 3  | some evidence from Kauppila et al 2018 |
| r\_death\_oesoph | 0.4 | probability per 3 months of death from oesophageal cancer amongst people with stage 4 oesophageal cancer  | see \* below |
| r\_curative\_treatment\_low\_grade\_dysp | 0.01 | probability per 3 months of receiving medical treatment aimed at cure if have low grade dysplasia, given diagnosis (surgery, radiotherapy, chemotherapy)  | currently availability of treatments limited, however this is increasing see \*\* below  |
| rr\_curative\_treatment\_high\_grade\_dysp | 1 | rate ratio for receiving treatment aimed at cure if have high grade dysplasia | currently availability of treatments very limited  |
| rr\_curative\_treatment\_stage1 | 1 | rate ratio for receiving treatment aimed at cure if have stage 1 oesophageal cancer | currently availability of treatments very limited  |
| rr\_curative\_treatment\_stage2 | 1 | rate ratio for receiving treatment aimed at cure if have stage 2 oesophageal cancer | currently availability of treatments very limited  |
| rr\_curative\_treatment\_stage3 | 1 | rate ratio for receiving treatment aimed at cure if have stage 3 oesophageal cancer | currently availability of treatments very limited  |
| r\_diagnosis\_stage1 | 0.01 | probability per 3 months of diagnosis in a person with stage 1 oesophageal cancer | low probability of diagnosis before symptoms appear - probability likely to increase with grade of cancer - looking for data on stage of oesophageal cancer at diagnosis from cancer registry |
| rr\_diagnosis\_low\_grade\_dysp | 0.01 | rate ratio for diagnosis if have low grade oesophageal dysplasia  | as above |
| rr\_diagnosis\_high\_grade\_dysp | 0.01 | rate ratio for diagnosis if have high grade oesophageal dysplasia | as above |
| rr\_diagnosis\_stage2 | 2 | rate ratio for diagnosis if have stage2 oesophageal cancer | as above |
| rr\_diagnosis\_stage3 | 50 | rate ratio for diagnosis if have stage3 oesophageal cancer | as above |
| rr\_diagnosis\_stage4 | 100 | rate ratio for diagnosis if have stage4 oesophageal cancer | as above |

\* progression rates informed by survival according to stage at diagnosis (5 year survival in United States (with treatment availability): 45% stage 1/2, 24% stage 3, 5% stage 4) https://www.cancer.org/cancer/esophagus-cancer/detection-diagnosis-staging/survival-rates.html; 5 year survival without surgery < 5% Kauppila et al 2018 (Sweden)

\*\* treatment access: Six private and public medical oncology units have been established, spanning all three regions of the country. These can administer cytotoxic chemotherapy under the supervision of either an oncologist or a haematologist and other experienced doctors. This has enabled management of most chemotherapy-sensitive tumours. Radiotherapy not available (Masamba 2015). Queen Elizabeth Central Hospital in Blantyre has a single procedure room and is a World Gastroenterology Organisation International Endoscopy Training Centre forming the centre of a hub-and-spoke endoscopy training programme for the three other central hospitals in the country. It performs around 1200 upper gastrointestinal endoscopies per annum, of which 300 are therapeutic—mainly dilatation or stenting of squamous cell carcinoma and banding of oesophageal varices. Thirty-nine per cent (620 patients) underwent bougie dilatation of their tumour for symptom relief, 11% (179 patients) had placement of a self-expanding metal stent (only sporadically available in our hospital), and one patient had alcohol injection of the tumour for debulking. Two perforations were identified after bougie dilatation and were managed conservatively. One per cent (17 patients) underwent an Ivor Lewis oesophagectomy with end-to-end anastomosis and 1% (22 patients) had palliative gastrostomy tubes inserted. Seventeen per cent (274 patients) received chemotherapy. Though palliative stenting has good efficacy in our setting (<4% complication rate and a median survival of 210 days),7 the cost is unfortunately prohibitive for the health service and for patients, and as such, bougie dilation is often undertaken. There is a paucity of evidence of long-term outcomes for this procedure though itseems effective in other settings22 and carries

a risk of malignant perforation. (Chetwood et al. 2018).

**Table 3. Model outputs and observed data from Malawi**

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|  | **Model Output** | **Observed Data** | **Notes** |
| Number of incident diagnoses of oesophageal dysplasia per year (low / high grade) | < 100 | --- | No data identified |
| Number of incident diagnoses of oesophageal cancer per year (total; stage 1, 2, 3, 4) | 1285 (300, 300, 465, 220) | 620 | Derived from Msyamboza et al 2012 \* |
| Incidence rate of diagnosed oesophageal cancer (all stages combined) / 100,000 population aged ge 20 | 15 | 25.3 | Derived from Chasimpha et al 2017. \*\* (considered to be some under-ascertainment) |
| Current total number of people who have diagnosed oesophageal cancer (total; stage 1, 2, 3, 4) (including people who have been given attempted curative treatment for stage 1 oesophageal cancer at some point in the past and have not progressed to a higher grade) | 5,250 (1150, 1600, 2300, 200) | --- | No data identified |
| Number of people given attempted curative treatment for low grade oesophageal dysplasia per year | 0 | --- | No data identified – assumed currently low. |
| Number of people given attempted curative treatment for oesophageal dysplasia per year (total; low, high grade) | < 100 | --- | No data identified – assumed currently low. |
| Number of people given attempted curative treatment for oesophageal cancer per year (total; stage 1, 2, 3, 4) | < 100 | --- | No data identified – assumed currently low. |
| Number of deaths from oesophageal cancer | 560 | --- | No data identified but 620 identified cases of oesophageal cancer per year, most reported to be identified at late stages. New death registration system should provide data in future. |

\* 18,946 new cases of cancer in 44 month period 2007 – 2010; 12.0% oesophageal, implying 620 new cases of oesophageal cancer diagnosed per year in Malawi. Registry covers 96% of relevant clinics in Malawi.

\*\* 368 cases in Blantyre 2008-2010 from population 248,728 men and 236,355 women age ge 20 = crude rate 25.3 / 100,000 population aged > 20.

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