Methods, application, and risk of 'adaptive' health technology assessment

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Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy

University of London

Submitted September 2024, Revised April 2025

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This thesis was partially funded by the Bill and Melinda Gates Foundation, OPP1202541

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I, Cassandra Nemzoff, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background: In striving for universal health coverage, many countries use evidence-based priority setting methods to allocate finite resources. To achieve allocative efficiency, cost-effectiveness analysis (CEA) is often central to these assessments. Current guidance and references cases for CEA aims to be rigorous, but achieving full rigor in practice can be challenging. 'Adaptive' health technology assessment (aHTA) methods have been proposed as a complement, that aim to systematically examine which elements of assessment methods should be simplified given time, data, and capacity constraints. While aHTA is used by various priority setting institutions and practitioners, no standardized approach exists. There is a need to clearly characterize and test aHTA methods to improve their standardization and enhance their replicability.

Methods: This thesis has three analytical sections, with the aim of designing and testing a standardized aHTA approach for CEA. The first defines and characterizes pre-existing aHTA methods. The second presents a novel approach to apply aHTA in a 'real-world' case study which assesses 49 cancers and develops potential cancer HBPs in Rwanda. The third conceptualizes and applies a method for evaluating the risk of conducting aHTA based on quantitative and qualitative uncertainties.

Results: This thesis presents a standardized aHTA approach for assessing the cost-effectiveness that captures all current worldwide approaches. Applying aHTA methods to the assessment of cancer in Rwanda helped to efficiently prioritize 49 cancers in a package focused on early-stage, curative care, within the data, time and capacity constraints. The innovative method designed for evaluating risk of conducting aHTA was tested in Rwanda and validated that the aHTA methods used in the cancer assessment were aligned with the available data and risk preferences of decision makers.

Conclusion: In the absence of perfect data, aHTA may provide a feasible and useful tool for supporting evidence-based priority setting.

Word count (max 300): 295

Acknowledgements

There are many individuals who I was lucky enough to have supported the development of this thesis. First and foremost, to my first supervisor, Anna Vassall, who not only taught me how to think like a real health economist, but about leadership in situations with multiple stakeholders; (British) communication in different and difficult situations; and navigating this field as a woman. Extra thanks for always having confidence in my capacities and providing me so many new opportunities. And to my second supervisor, Sedona Sweeney, for providing and discussing bucketloads of constructive feedback with a fresh perspective.

To my advisors - Rob Baltussen for often providing logic to some of my chaos and helping to organize various pieces of this thesis; to Lorna Guiness for sometimes reflecting that she was being 'pedantic' which improved the clarity of my writing and my thoughts; and to Francis Ruiz for helping to inspire this work by reiterating that our first pilot needed to be 'pragmatic'. Thanks also to my upgrading examiners, Andrew Briggs and Fiammetta Bozzani for valuable feedback that helped to shape the future of my PhD work.

To colleagues and friends who have supported this PhD and collaborated with me from start to finish: Nuri who was an early cheerleader of this thesis, helping refine my proposal to make it PhD-worthy and later reminding me constantly that 'you got this'; Hiral who guided me through my first peer-review and first criticism of aHTA; and Y-Ling who gave various tips on starting and surviving a PhD. To Andres for powering through many stressful meetings hunched in a corner somewhere running new data together and engaging in meaningful conversations about how we can do our work better, and to Sergio for numerous voice memos and practical advice on how to finish my thesis. To Sean, a medieval music professor who convinced me that any academic can be a writing buddy, and the best PhD is the one which is finished.

To all my colleagues in Rwanda who have helped so much to guide this work and ensure that it was policy relevant and fit in the broader context of institutionalizing priority setting in Rwanda. Special thanks to Stella for being the shepherd of the Rwandan assessment team, responding to messages at all hours, and always seeking to make sure our work was relevant to the Rwandan context; to Regis, Alexis, and Cindy for guiding and driving the priority setting agenda in Rwanda; to Inga for picking up various pieces of work always with a smile, and translating Kinyarwanda live during trainings; to James for always seeing the big picture of our work in context; and to the research assistants for their hard work and responsiveness to my teaching.

To my family for always being so supportive of this PhD. To my mom, dad, Jessie and Kim for always asking how it is going and when they can celebrate the finish line with me, and especially to Kim for boosting my confidence telling me I'm 'a world-renowned expert' in my field. And finally, to my husband Toon, who encouraged every step of this PhD, read drafts, imparted cancer knowledge, and made space and time for me so I could tackle writing this thesis. Thank you all.

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List of Abbreviations and Acronyms

aHTA	Adaptive health technology assessment
AKI	Acute kidney injury
ARCH	Appraisal of risk chart
BMJ	British medical journal
CBHI	Community-based health insurance
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CKD	Chronic kidney disease
DALY	Disability-adjusted life years
DCP	Disease control priorities
DLBCL	Diffuse large B-cell lymphoma
ESRD	End-stage renal disease
EUNetHTA	European network on health technology assessment
EVPI	Expected value of perfect information
GBD	Global burden of disease
GDP	Gross domestic product
HBP	Health benefits package
HBPD	Health benefits package design
HD	Hemodialysis
HiP	Health interventions prioritization
HL	Hodgkins' lymphoma
H & N	Head and neck
HPV	Human papillomavirus
HTA	Health technology assessment
ICD	International classification of disease
ICER	Incremental cost-effectiveness ratio
ICHI	International classification of health interventions
iDSI	International decision support initiative
INAHTA	International network of agencies for HTA
K	Thousand
LMIC	Low- and middle-income countries
M	Million
MI	Ministerial instruction
MoH	Ministry of Health
NICE	National Institute for Health and Care Excellence
NHL	Non-Hodgkins' lymphoma
NSCLC	Non-small cell lung cancer

PD	Peritoneal dialysis
PICO	Population intervention comparator outcome
PSA	Probabilistic sensitivity analysis
PPP	Purchasing power parity
QALY	Quality-adjusted life year
RMH	Rwanda Military Hospital
RSSB	Rwanda Social Security Board
RWF	Rwandan francs
SCLC	Small-cell lung cancer
SEE	Structured expert elicitation
UHC	Universal health coverage
US$	United States dollar
USD	United States dollars
VOI	Value of information
WHO	World Health Organization
WHO-CHOICE	World Health Organization CHOosing Interventions that are Cost-Effective
YLD	Years of life lost due to disability
YLL	Years of life lost

Chapter 1: Introduction

Every health system uses a mix of implicit or explicit approaches to allocate funding(1). Implicit rationing neither defines nor prioritizes the health services being covered. Services are rationed through long waiting lists, diluted quality of care, co-payments, and denial of care at the point of service(2,3). Explicit choices evaluate certain decisions to determine who gets access to which services at what price(4,5).

1.1 Economic evaluation and priority setting

"Those who plan, provide, receive, or pay for health services face an incessant barrage of questions… the answers to these questions are most strongly influenced by our estimates of the relative merit or value of the alternative courses of action they pose."

Methods for the Economic Evaluation of Health Care Programmes, Drummond et al 2015(6)

The fourth edition of Methods for the Economic Evaluation of Health Care Programmes makes the case for why economic evaluation is needed to explicitly answer the 'barrage' of questions faced by policy makers. Drummond et al formally define economic evaluation as "the comparative analysis of alternative courses of action in terms of both their costs and consequences"(6). Cost refers to the cost of providing a health service to the health system or to society. Consequences refer to the impact of an intervention on health, for example, mortality, morbidity, or other disease-specific measures(7).

Economic evaluations can be used to improve the allocative efficiency of a health system, where resources are distributed in a way that maximizes the social welfare of the community(8). Efficiency in general refers to the relationship between inputs and outputs. In health economics terms, efficiency translates these input and outputs to costs and health gains, with the aim of either maximizing health within a given budget or minimizing costs for a set amount of health gains(9). This is also referred to as

'allocative efficiency', where health outcomes are maximized using the optimal mix of health interventions with a given budget(10).

The process for addressing the incessant barrage of questions raised by Drummond et al is priority setting. Priority setting guides the assessment and appraisal of interventions to inform efficient resource allocation(11–13). Different practitioners have defined priority setting in different ways, but broadly the process requires topic selection and scoping; assessment; appraisal; and monitoring and evaluation(14–17). Topic selection and scoping require defining the research agenda, including the interventions to be assessed and the type of evidence that needs to be collected to evaluate them(14,17). Assessment evaluates the health interventions against agreed criteria, such as cost and cost-effectiveness(14,17). Appraisal convenes key stakeholders to review the evidence and makes a formal recommendation based on the evidence(17,18). Monitoring and evaluation require implementing the recommendation and tracking its progress against pre-defined indicators over time(14,15).

Many countries aim to institutionalize priority setting as part of achieving universal health coverage (UHC)(19,20). This is challenging for some countries where barriers to institutionalizing priority setting include limited data, limited technical skills, explicit decision rules, its technocratic nature, and perceptions that it puts a 'price on life'(21).

This thesis seeks to help overcome some of the barriers in the assessment step, by developing approaches that explicitly recognize and consider contextual constraints, and within them, economic evaluations used to evaluate cost-effectiveness as a central component of the priority setting process.

Principles of economic evaluation

Economic evaluation can be done either by modelling cost-effectiveness based on a single clinical trial or using decision analytic models that synthesize secondary evidence from various sources(22). Several categories of economic evaluation exist, including cost-minimization analysis (CMA), cost-benefit analysis

(CBA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA). If the health effects of two interventions are considered equal, CMA considers only the difference in cost between them. CBA standardizes costs and health effects in monetary value to enable the comparison of interventions to program budgets. CEA compares the costs of alternative health interventions with a single measure of effect for those health interventions. Health effects in CEAs vary widely. If the assessment is based on a clinical trial, the outcomes are likely to be those documented in the trial (e.g. life years gained, cost per case detected, cost per avoided infection, etc.). Finally, CUA is a type of CEA which uses a standard, generic measure of health effect, such as the disability-adjusted life year (DALY) or the quality-adjusted life year (QALY), both of which account for mortality, morbidity, and disability from a given condition in a standardized way(6). CUA is important for policy makers who compare interventions across health programs, as it enables them to assess the benefit forgone of investing in other interventions using a common outcome measure. The benefit forgone is commonly referred to as 'opportunity cost'(6). Existing guidance for and reporting of CUAs often refers to the assessment of costs and consequences as CEA, which for consistency I will also do throughout this thesis.

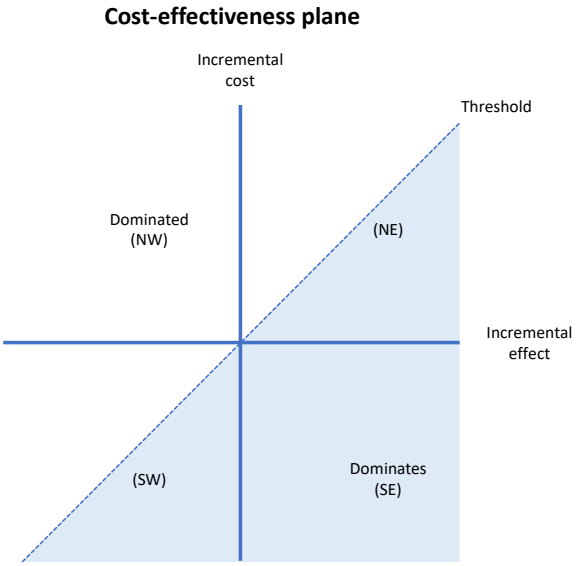
The result of an economic evaluation is typically expressed as an incremental cost-effectiveness ratio (ICER), or the additional cost per unit of health of a new intervention(7). The ICER is calculated using the following formula, where the intervention is the new intervention under consideration and the comparator is the status quo:

$$\frac{cost\ intervention - cost\ comparator}{effect\ intervention - effect\ comparator}$$

Graphically, the ICER can be plotted on a 'cost-effectiveness plane' which charts the incremental costs (the numerator) on the y-axis and incremental effects (the denominator) on the x-axis (Figure 1). The cost-effectiveness plane can help to determine whether the new intervention is cost-effective. Two decisions are obvious – if the new intervention is more expensive and less effective than its comparator

(northwest quadrant), it is considered not cost-effective, or 'dominated'. If the new intervention is more effective and less expensive than its comparator, it is considered cost-effective, or 'dominates' the status quo (southeast quadrant)(7).

Figure 1: Illustrative cost-effectiveness plane



Acronyms: NW = northwest; NE = northeast; SE = southeast; SW =southwest

However, if the new intervention is either more effective and more expensive (northeast quadrant), or less effective and less expensive (southwest quadrant), a cost-effectiveness threshold can help to determine whether the intervention is cost-effective. The threshold, represented by the dotted diagonal line in Figure 1, is an estimate of the maximum a health system is willing to pay for one additional unit of health gain. In other words, the slope of the line is the maximum acceptable ICER. If the ICER for a given intervention falls into the shaded area below the threshold, it will be considered cost-effective. If there are more than two mutually exclusive options, all interventions which are dominated would be eliminated. Then the ICER for each pair of the next most effective option would be calculated, eventually identifying the intervention with the lowest ICER as most cost-effective(7).

Uncertainty and risk in economic evaluation

The uncertainty of both the ICER and threshold contribute to the overall likelihood that the decision made is the right one, also known as decision uncertainty(23). For example, if the costs or effects used to calculate the ICER are uncertain, or the threshold is uncertain, there is a probability that a wrong decision is made about whether the intervention is cost-effective.

Using a decision model to estimate cost-effectiveness of an intervention is inherently uncertain because it draws evidence from various sources(24). The literature characterizes uncertainty into four types. Stochastic uncertainty is that stemming from random variation in outcomes among identical patients; parameter uncertainty refers to the precision of individual parameters in a model; heterogeneity is the difference between patients; and structural uncertainty focuses on the assumptions used to build the model itself(23,25). A critical component of any economic evaluation is to evaluate the effect of this uncertainty on the model results. This is often done using sensitivity analyses. Two common types of sensitivity analysis are deterministic sensitivity analysis, which assigns a range to one or more parameters to observe their effect on the outcome, and probabilistic sensitivity analysis which assigns distributions to uncertain parameters and repeatedly randomly samples from these distributions to determine the likelihood of cost-effectiveness(23,26).

The threshold is likewise uncertain. Indeed, estimating the threshold may be one of the most controversial topics in health economics, as confusion remains about how a threshold should be estimated and what evidence base is sufficient to do so(27,28). Generally, health system willingness to pay thresholds can be estimated from the 'demand side', as an aspiration of what health expenditure *should* be, or the 'supply side', reflecting the health effects of *current* health expenditure(22,28,29). Some countries, such as the UK, Spain, Australia, and Thailand have empirically derived their own, locally relevant threshold(30–34). However, these are few robust estimates of local thresholds, so global

estimates are sometimes applied in their absence(35,36). A commonly used demand-side threshold of 1-3 times gross domestic product (GDP) per capita (pc) is sourced from the 2001 World Health Organization (WHO) Macroeconomic Commission on Health(37,38). This estimate has been criticized for having a limited theoretical basis; not reflecting local affordability or budgets; and not facilitating an assessment of trade-offs between interventions(39,40). Nevertheless, it has been widely used as generic threshold guidance, particularly in economic evaluations from low-and middle-income countries (LMICs)(35,41). More recently, country-specific estimates of supply-side thresholds have been derived by Woods et al, Ochalek et al, and Pichon et al, which fall well below the WHO 1-3 GDP per capita estimate(28,29,36). For countries without local thresholds, the availability of these estimates leaves analysts to review and debate the merits of the optimal threshold to use for their context.

Moreover, thresholds can vary(6). They could depend on the nature of the intervention. For example, seminal work on thresholds by Claxton et al found that a cost-reducing intervention would have a lower threshold than average, whereas a cost-increasing intervention would have a higher threshold(32). This could be explained by non-marginal effects, where increases in expenditure increase health at a diminishing rate. It could also be the case for an intervention which is both less costly and less effective, if there is a disparity between what decision makers are willing to pay ("WTP") for health gains versus what they are willing to accept ("WTA") if there is a health loss(42–44). Alternatively, they could depend on the purchaser, where the threshold is different for a private or public purchase(45).

Selecting a threshold with this uncertainty can also impact the probability of making the wrong decision. A threshold which is too high can result in investment in interventions which are not cost-effective and crowd out more cost-effective interventions, and one which is too low can result in interventions that could save lives not being covered(46).

The uncertainty of the ICER and the threshold combined with the probability of making the wrong decision influence the risk of making the wrong decision (if the evidence is the sole source of risk)(47). Obtaining additional information reduces uncertainty to inform decision-making but comes at the cost of conducting additional research. A common framework to assess the value of obtaining more information is 'value of information' (VOI) analysis. VOI quantitatively assesses the 'cost' of uncertainty which is estimated by combining the probability of a wrong decision (uncertainty) and the consequence of the wrong decision (value of the investment or its alternative)(48), which can guide decisions makers on whether and how much to invest in additional research. However, VOI only captures parameter uncertainty. By excluding other types of uncertainty, VOI may not capture the full uncertainty and by extension, the full risk, of making the wrong decision. Another option is assessing risk using a combination of quantitative and qualitative methods. For example, a framework developed in the Netherlands evaluates potential net benefits (based on CEA) alongside potential risk of an intervention. To evaluate risk, it first identifies three key uncertainties to evaluate uncertainty, including structural uncertainty, relative effectiveness, and generalizability of utility values. It then combines these with estimated budget and health impact to estimate risk(49).

1.2 Development of empirical methods for economic evaluation

"Two realities provide a compelling context to health policy decisions in a world preparing for the twenty-first century: The availability of health-related interventions now in the marketplace exceeds by a considerable margin our societal ability to afford them; and the current decision rules are inadequate to guide choices towards those interventions that are likely to yield the most benefit for the population."

Gold et. al. 1996, Cost-Effectiveness in Health and Medicine (50)

The United States Public Health Service convened the 1996 Panel on Cost Effectiveness for experts to review the state of the art of CEA, with the aim of reaching consensus about how to standardize methods and identify areas for future methodological developments(50). A primary result of the panel's work was a 'reference case' – a set of general principles to be applied in economic evaluation. The reference case had eight categories of guidance on: the broad nature of CEA and the reference case; defining the inputs to the numerator (costs) and denominator (length of life and health related quality of life) of the ICER; measuring costs; measuring consequences, with a recommendation to use the QALY; estimating effectiveness, with a preference for the least biased sources of estimates such as randomized control trials; time preference and discounting; uncertainty using sensitivity analysis; and guidelines on reporting(51). The panel's work set the foundation for future development of standardized national and global methodological guidance for economic evaluation.

Developing empirical national and global methods for health technology assessment

National guidance for economic evaluation has been established in the context of national priority setting bodies, often referred to as health technology assessment (HTA) agencies. HTA is formally defined as *"a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system"*(52). As evidenced by the definition's mention of 'efficiency', a central aim of HTA agencies is to use economic evaluation to prioritize national health services. HTA agencies have been established since the 1970s, and now more than 70 countries have an HTA agency or committee, each with their own national methods(53,54). For example, the United Kingdom's National Institute for Health and Care Excellence (NICE) first released methodological

guidance in 2004, and most recently updated it in 2023(55,56). The current version contains an entire chapter dedicated to economic evaluation methods(56).

Several sources of global guidance for the conduct of CEA have been established as well. For example, the international Decision Support Initiative (iDSI) reference case was developed to support coherent, consistent, transparent development of economic evaluations for LMICs. It drew on the US Panel for Cost-Effectiveness, previous guidance from the WHO and NICE, and expertise from methodologists (55,57). Similar to the Panel on Cost-Effectiveness, it set out eleven key principles of economic evaluation, each with a methodological specification and suggested reporting standard(58). These included guidance on transparency; comparators; perspective; measurement of outcomes; measurement of costs; time horizon; heterogeneity; uncertainty; budget impact; and equity implications(58). The conduct of economic evaluations is also supported by checklists for standard reporting, the most common of which is the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist(59).

Developing empirical methods for health benefits packages

Around the same time as the original Panel on Cost-Effectiveness, the World Development Report of 1993 called for countries to deliver an essential health benefits package (HBP). An HBP defines an explicit list of services provided in a country, clarifies who they are provided for, and articulates how the services are paid for(60). It recommended that HBPs be prioritized based on cost-effectiveness as a means of reducing the global burden of disease, being the healthy life lost from disease(61). In doing so, it estimated that low-income countries could reduce their burden of disease by 32% by spending just $12 per capita on a minimum essential HBP(61).

Rather than assessing one intervention at a time using an ‘incremental’ approach with a threshold, the World Development Report made the case for ‘sectoral’ assessments(62). A sectoral approach evaluates

a group of interventions at once, ranking them in league tables according to cost-effectiveness to determine which interventions fit within a given budget(63–66). The allocative inefficiencies resolved in incremental and sectoral approaches are different. Incremental approaches assume that there is allocative efficiency within the current health system and assesses interventions only at the margin, with the potential of trading one currently provided service with a more cost-effective one. Sectoral approaches can affect larger allocative efficiency gains by re-allocating many or all interventions within a given budget, irrespective of current coverage(63,65,67). A popular framework for presenting how this can be done is a hypothetical bookshelf. Similar to a league table but more detailed, the bookshelf orders the height of books by cost-effectiveness on the y-axis and the width of books by total cost on the x-axis, illustrating how many of the most cost-effective interventions can be included within a given budget. The bookshelf assumes that each intervention is mutually exclusive and has a 'do nothing' comparator to enable this ranking, with each book accounting only for the total cost and effect of that intervention. Theoretically, the point at which the budget is exhausted should be equivalent to the threshold, demonstrating that the threshold and the budget are inextricably linked(68).

The advent of sectoral priority setting presented a substantial challenge for the application of economic evaluation methods, primarily developed for incremental analyses. Applying the principles of standard national or global reference cases to economic evaluations of many interventions at once can be data-demanding and time-consuming raising feasibility concerns(69,70). To reduce the extensive analytical burden placed on countries, various efforts have been made to collate and synthesize existing evidence of cost-effectiveness for many interventions in one place.

The 1993 report drew heavily on Disease Control Priorities 1 (DCP-1), the first international attempt at systematically assessing the cost-effectiveness of a group of interventions which could substantially reduce the global burden of disease. The Global Burden of Disease (GBD) study was reported in DALYs, a new standard outcome measure at the time, combining mortality (years of life lost, YLL) with morbidity

(years of life lived with disability, YLD). This was estimated using a combination of death records, community surveys, and a short list of six 'disability weights' used to group diseases by severity, complemented by expert opinion to fill gaps(61). To estimate cost-effectiveness, the report combined the GBD estimates with direct health systems costs which were drawn from developing countries 'as far as possible'. This methodology supported the overarching message, that implementing the 20 most cost-effective interventions could eliminate more than 40% of the total disease burden. However, it only lightly highlighted the importance of CEAs being context specific in demographics, burden of disease, costs, and many other factors, the data for which was not routinely collected or easily available from local health facilities or systems(61). Early national HBP prioritization efforts drew on the DCP-1 methods, estimating costs by collecting local primary data with simple and restrictive assumptions and using effectiveness estimates from DCP-1, but heavily supplemented with expert opinion due to data scarcity(71,72).

Additionally, the WHO released the 2003 Guide to Cost-Effectiveness Analysis which established the methods for 'generalized CEA'(73). This approach evaluated all currently funded and potentially new interventions together, to enable the identification of allocative inefficiencies in the current system alongside opportunities to invest in new interventions(65). This method was applied to "WHO CHOosing Interventions that are Cost-Effective" (WHO-CHOICE), a suite of user-friendly models designed to assess the cost-effectiveness of 20 diseases and 500 interventions. WHO-CHOICE uses the GBD estimates as well, combined with WHO-collated costs as inputs. WHO-CHOICE has been used to model several iterations of regional estimates of ICERs or can be updated using local data to estimate local ICERs(74–76).

In recent decades, these approaches have evolved considerably, and new sources of evidence collation and synthesis emerged. The GBD now uses more sophisticated population survey techniques and statistical models with data from 187 countries to estimate the burden of 291 diseases and injuries, 1160

sequelae of these causes, and 67 risk factors(77–79). DCP is now in its 3rd edition ("DCP-3") with nine substantial volumes of information about interventions which are considered cost-effective for HBPs in LMICs. DCP-3 includes a systematic review of cost-effectiveness literature reviewed by a team of over 500 experts(80,81). Additionally, the Tufts CEA Registry was developed as an online database that contains over 12,000 CEAs with pre-extracted information on costs, effects, cost-effectiveness and other key study characteristics, enabling rapid review of the global cost-effectiveness literature(82). More recently, meta-regression analyses have been used to predict ICERs for several diseases and interventions for which there are many studies in the published literature(83–85). Meta-regressions use regression analysis to quantify the association between ICERs from existing studies and covariates that are location-specific (e.g. GDP pc) and intervention-specific variables (e.g. cost and efficacy) to predict ICERs for other countries(85).

Additionally, available data has been directly linked to several analytical tools to support HBP prioritization. For example, the health interventions prioritization (HiP) tool is an open-source, online tool that uses optimization modelling for prioritizing HBPs and is pre-populated with data from DCP-3 and GBD(86). The FairChoices tool is also an online optimization tool which is now the main analytical tool for the forthcoming DCP-4, using its data(87).

These analyses of global cost-effectiveness data and tools to support their use in prioritization have contributed to many new applications of CEA to inform country-specific HBPs. For example, DCP-3 was recently used in the prioritization of Pakistan's and Liberia's health benefits packages(88,89). The HiP tool was used to inform the prioritization of HBPs in Armenia, Cote d'Ivoire, and Zimbabwe(90). The WHO-CHOICE models were used for a 2012 report on the cost-effectiveness of 11 interventions for breast cancer control in Ghana. The model was populated with local demographic, epidemiological and economic data where possible, and supplemented by recently revised GBD estimates and other international data to simulate an optimal package of breast cancer interventions(91). This analysis not

only reported on the cost-effectiveness of each intervention assessed, but it also presented the population distributions of stages, and cost-effectiveness for treatment at each stage of breast cancer, which is a valuable resource for other countries conducting similar analyses(91).

Gaps and challenges in health benefits package design

Despite decades of development, there remain substantial challenges in using the available evidence base for cost-effectiveness to inform HBP design. First, there are usability limitations. DCP has been critiqued for its lack of disaggregated information on costs and effects, lack of quantified uncertainty, and lack of systematic contextualization of evidence, making it difficult to use for analysts and decision makers(92). Similarly, WHO-CHOICE models have sometimes not been used due to concerns about understanding the underlying assumptions of the models, and by extension, whether it is feasible to determine the quality of the estimates derived from these assumptions(93). Second, the different tools and analyses do not cover all disease areas and interventions. WHO-CHOICE is limited to 20 disease areas which are WHO priorities, making it difficult for policy makers to compare interventions across programs for which WHO-CHOICE models do not exist(94). Likewise, DCP is limited to a set of 218 interventions which are considered cost-effective for LMICs, and meta-regression analyses have only been completed for 6 disease areas(83–85,95). Moreover, the topics contained within the tools may not be aligned with policy makers' demand.

During the production of these thesis, I published a comment in the Lancet Global Health on this issue in response to a new meta-regression analysis that was published and framed as an additional way forward to apply global cost-effectiveness evidence to country settings for four disease areas(96). In it, I explain that while meta-regressions are an interesting method for predicting ICERs for many countries, the method is severely constrained by the availability of multiple CEAs on a specific intervention. This limits meta-regressions to the few interventions for which there is robust cost-effectiveness data from multiple

jurisdictions and does not contribute at all to understudied topics which might be of higher priority to policy makers(97). The full text of the comment is included as Appendix 1: Aligning meta-regressions to policy makers' needs.

Additionally, cost-effectiveness is not the only criterion used to prioritize HBPs. Some argue it is an overemphasized criterion, and current approaches to priority setting are unified in acknowledging that cost-effectiveness alone is insufficient for countries seeking to make optimal decisions that are locally relevant(98). As a result, additional prioritization criteria have been added to priority setting processes for HBPs(99–104).

These include the burden of disease which reflects the health loss from a given condition, and the GBD study is a commonly used resources for this information(77). Equity and priority for the worse off are often considered. Several methods existing to evaluate equity for HBPs, including equity impact analysis and equity trade-off analysis(105). Financial risk protection evaluates whether an intervention puts households at risk of financial hardship. This can be evaluated through two measures of financial hardship: catastrophic health expenditure, where medical costs exceed a pre-determined proportion of household expenditure, or impoverishment, when medical expenses push a household further into poverty. Alternatively, financial risk protection can be integrated into an extended CEA, which is a type of equity impact analysis(106–108). Budget impact is calculated to determine the financial impact of the HBP on national budgets(109). Feasibility is assessed to determine whether an intervention can be delivered in the current health system. Social and economic impact reflects how an intervention affects societal consequences such as stigma, as well as economic consequences such as poverty. Finally, political acceptability determines whether an intervention is acceptable to decision makers(110).

The addition of these criteria increases both the data and methodological demands of evidence generation for priority setting. One analysis of lessons learned from Kazakhstan indicated that there is a

need to ensure that the scale and burden of analysis is kept to 'manageable proportions'(111). Another analysis from Kenya highlighted that its HBP assessment of ten criteria was challenged by a lack of primary data and short timelines, two of many issues that ultimately contributed to the failed implementation of the HBP(112).

Assessing multiple criteria can also increase the complexity of the decision-making process that happens during appraisal. To address this complexity, methods of multi-decision criteria analysis (MCDA) have been developed over time(113–117). MCDA takes a transparent, structured approach to deliberating on multiple criteria at once to improve the quality of decision making(116,118). There are three types of MCDA – qualitative MCDA, where a committee deliberates on the performance of interventions under considerations against explicit criteria; quantitative MCDA which builds on qualitative MCDA by scoring the performance of each intervention on each criterion and weighting them by importance for deliberation; and MCDA with decision rules, where a committee is guided by a simplified set of rules in their deliberation, often with fewer priority criteria. While all forms of MCDA appraise evidence using explicit criteria and offer consistency in process across multiple appraisals, there are several limitations. Qualitative MCDA demands that committee members independently make trade-offs between the criteria and can fall victim to more vocal committee members dominating decisions. Quantitative MCDA can be overly prescriptive, as employing a fully quantitative approach does not allow for context-specific deliberations and can also be cognitively challenging depending on how the assessment of multiple criteria are presented. MCDA with decision rules can demand more extensive deliberation of fewer criteria(114). Regardless of the approach taken, it is possible that assessing so many criteria at once can be cognitively overloading, as evidence suggest that humans are not able to effectively process more than five criteria at once(119).

1.3 Rapid methods to support economic evaluation

"There are tens of thousands of health care technologies and many more appearing each year. Only a fraction of existing technologies has been fully evaluated to date, and the resources – even worldwide – to undertake further evaluations fall far short of those needed to cover all technologies. Priorities for HTA must therefore be set and are being set – whether explicitly or implicitly – by all those involved in HTA. The aim in setting priorities should be to identify those assessments that offer the greatest benefit in relation to their costs, and thus, to maximize the benefit derived from investment in HTA".

Henshall, et al, 1997 (120)

While economic evaluation was designed to evaluate the opportunity cost of investing in different health interventions, even in its early widespread application it became apparent that it was a cost to the health system itself. Indeed, Henshall et al raised the point that there is an opportunity cost of conducting these assessments to begin with(120). A 2013 survey indicated that the time to complete the HTA process was up to a year(121). However, conducting full economic evaluations which respond to policy maker demand are likely to be affected by time, data, and capacity constraints(121–123). To overcome this barrier, methods have been developed to aid in expediting the conduct of economic evaluation.

Two important bodies of literature have supported the development of these methods: rapid review and transferability. Rapid review was first mentioned in the literature in 1997(124). Based on a recent systematic review, it is defined as *"…a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting a variety of methods to produce evidence in a resource-efficient manner"*(125). To date, there remains heterogeneity in rapid review methods, though recent guidance has been developed to support those conducting rapid

reviews(126,127). For example, the Cochrane Rapid Review Methods outline how the scope of standard systematic reviews can be narrowed, or specific components of reviews can be restricted or omitted to provide synthesized evidence faster(128). While this terminology refers to expediting systematic reviews and not necessarily economic evaluations, the same term 'rapid review' has been used to refer to rapid HTA assessments by the International Network of Agencies for HTA(INAHTA)(121). Indeed, the INAHTA database contains 908 HTA reports called 'rapid reviews'. This reflects HTA agencies' established rapid review methods, such as the Canadian Rapid Response Service(129,130). Likewise, rapid reviews have been used to inform the evaluations of cost-effectiveness in HBPs. For example, Ethiopia used a rapid review of the published literature to inform its HBP prioritization(131).

The second is transferability, which is the *"extent to which the results of a study from another jurisdiction can be adapted locally"*(122). A 2011 systematic review found seven existing tools for evaluating transferability: Heyland's generalizability criteria; Spath's transferability indicators; Welte's transferability decision chart; Boulenger's transferability information checklist; Drummond's application algorithm; Turner's transferability checklist (as part of the European Network for Health Technology Assessment, EUNetHTA); and Antonanza's transferability index(122,132–138). The tools are all different and include varying factors focused on transferability and quality of existing studies, including for example: differences in scope of the research question; clinical practice; health systems; individual parameters including costs, effects, and resource utilization; and other model features such as time and perspective. Some tools provide a short checklist of transferability and quality factors; others list more than 20 transferability factors to consider; and still others provide decision flow charts with different transferability factors to determine whether a study is transferable(122). A common feature of these tools is to assess critical factors which affect transferability, which can include study quality, transparency, level of reporting, and relevance of the intervention and comparator(122). Countries in Latin America have a long history of transferring HTA reports from other jurisdictions(139). Likewise, HBP

exercises have incorporated transferability checklists when reviewing cost-effectiveness evidence, as in the case of Pakistan(93).

Both rapid reviews and transferability frameworks have informed the development of rapid methods for economic evaluation which are heterogenous in their application. For example, Canada's Rapid Response service is housed in the Canadian HTA agency and has four separate methods of rapid reviews which vary from a summary of abstracts completed in one week to a rapid systematic review completed in nine months(140–142). Ireland's National Centre for Pharmacoeconomic receives dossiers from the pharmaceutical industry, conducts its own rapid review and appraisal of the information in the dossier, and determines whether a full HTA is needed(143). Argentina uses its own methodology to rapidly review the likely cost-effectiveness of interventions included in its HBP using local and global evidence on cost-effectiveness(144). Ethiopia assessed cost-effectiveness for its HBP by combining a review of existing cost-effectiveness literature, modelling ICERs using WHO-CHOICE, and filling gaps with expert opinion(145). These are a few of many examples of adapted economic evaluation methods to inform the assessment of cost-effectiveness. Indeed, the resources discussed in the previous section, including DCP, WHO-CHOICE, and Tufts can generally be viewed as sources of evidence to support rapid economic evaluations.

Collectively, I refer to these as 'adaptive health technology assessment'(aHTA) methods, which are the focus of this thesis. In Chapter 3, I have proposed a draft definition of aHTA as, "*a structured approach to selecting and conducting the optimal HTA analysis. It produces efficient HTA results by adjusting for analytical time, data, capacity, and source of conduct, leveraging information from other settings where possible"*(146). An important component of this definition is about time, data, and capacity, and the trade-offs between them. For example, a rapid review can be completed in only a week, whereas a full economic evaluation can take a year(121,147). Given time constraints, analysts using aHTA must consider which data are available, and whether any of the previously mentioned collated sources such as DCP and

the Tufts registry are relevant and can be used(80,82). Additionally, it is important to consider what type of analysis can be completed with the available technical capacity and skillset of the team conducting analysis. This may be especially pertinent in nascent priority setting systems, where there may be limited technical capacity to conduct economic evaluations or systematic reviews of existing evidence(148).

I first introduced the term “aHTA” in a BMJ Global Health commentary, where I coined the term, and made the case that LMICs were constrained by time, data, and capacity and could benefit from priority setting methods which adapted to these constraints(149). I outlined differences between the steps of a standard HTA process and an aHTA process, including topic selection, assessment, appraisal, and implementation(15,16,149). This commentary set the foundation for the establishment of aHTA as a discipline with the aim of defining, testing, and understanding clear aHTA methods which are replicable. The full commentary can be found in Appendix 2: Adaptive health technology assessment to facilitate priority setting in low- and middle-income countries.

Following the commentary, I proposed the first definition of aHTA (at the beginning of this section) through a systematic review of existing aHTA methods from global HTA agencies. The systematic review was the first to characterize aHTA methods under this definition, and includes five methods: de facto HTA, rapid review, manufacturer-led submissions, transfers, and rapid CEAs. Indeed, the methods of rapid review and transfers largely draw on the literature described in the previous paragraphs(146). Further elaboration of these methods and how they were derived is presented in Chapter 3.

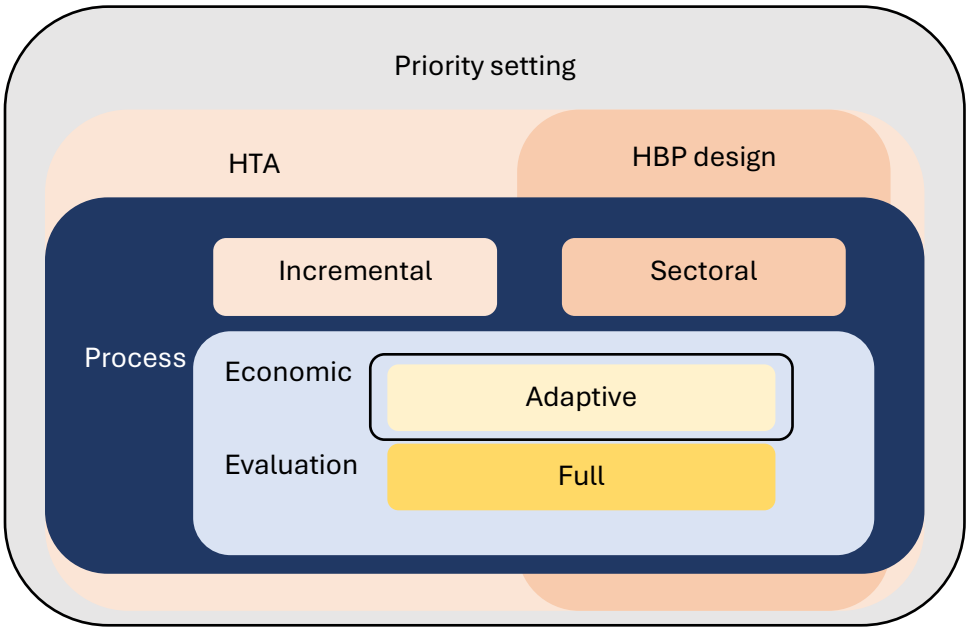
There are two important distinctions between the commentary and the review. First, the commentary focused on adaptations to the steps of the full HTA process (topic selection, assessment, appraisal, implementation), whereas the review focused only on adaptations to the conduct of economic evaluations for assessment, as a central and well-documented component of the HTA process. Second, the commentary focused on the need to develop aHTA methods specifically for LMICs, whereas the

review sought aHTA methods from any country in the world. This is because it is not only LMICs which are time, data, and capacity constrained. As the quote at the beginning of this section suggests, no country would be able to conduct an economic evaluation for all interventions in question and thus aHTA methods should probably not be designed exclusively for LMICs.

Finally, an important note on terminology. Health economics and its practice can sometimes be affected by conflation of terminology. For example, economic evaluation is sometimes used synonymously with CEA, and HTA is often conflated with economic evaluation and priority setting. Figure 2 provides a stylized characterization of key terminology in the field to summarize the terms in this introduction and clarify the focus of this thesis. The term 'priority setting' broadly refers to processes designed to maximize population health within a given budget(11). Both 'HTA' and 'HBP design' are multi-step priority setting processes(14–16). HTA processes are usually 'incremental', assessing one intervention at once, whereas HBP design processes are typically 'sectoral', assessing multiple interventions at once(65,150). Though, HTA and HBP design practice have converged in some countries where HTA agencies or HTA-like processes are used to set priorities to inform coverage under national HBPs(4,99). HTA can thus also be used to inform a sectoral approach. Within the assessment step of the priority setting process, methods can be either 'adaptive', as defined above, or 'full'. The latter has been defined by INATHA as an approach which always describes the technology and its use; evaluates safety and effectiveness; conducts systematic literature review; calculates cost-effectiveness using economic modelling; estimates budget impact; critically appraises the quality of the evidence; and optionally includes organizational, ethical, social, and legal issues(151,152). A central criterion of assessment in any priority setting process is cost-effectiveness(153). Economic evaluations for cost-effectiveness can also be 'full' by following the gold-standard of CEA as outlined in various references cases and methodological guidance, or 'adaptive', by leveraging economic evidence from elsewhere to adapt for time, data, and capacity constraints. My work is squarely focused on adaptive *methods* of assessing *cost-effectiveness,*

which can be applied to either incremental or sectoral processes. For brevity, throughout this thesis, I will refer to these methods as 'aHTA methods', acknowledging that there could be adaptations to the assessment of other criteria, or to the entire priority setting process, but which are not a focus of this thesis.

Figure 2: Relationship of terms



1.4 Methodological gaps and challenges

The previous sections have provided an overview of economic evaluation and priority setting; how empirical methods have been developed and updated over time; and why and how aHTA methods for economic evaluation have been developed. This final section describes some remaining gaps in this application of a structured approach to aHTA.

First, there is currently no consistent terminology for aHTA methods and thus no structured methods or reference case for aHTA. While a recent WHO survey indicates that 50 out of 127 responding countries have some type of rapid assessment method(54), there is no standard nomenclature for aHTA. The key

features of existing heterogeneous methods have never been reviewed and synthesized. This makes it difficult to understand what aHTA is and what the implications are of decisions made based on aHTA that could affect thousands or millions of patients(154).

Second, and relatedly, there is a need for better information on how to select between aHTA methods. While this introduction details various methods and principles which can be followed in the conduct of economic evaluation, not knowing what aHTA methods are by extension makes it difficult to know how an analyst would select between them. Central to this decision should be the trade-off between aHTA features of time, data, and capacity.

Third, existing resources that support the conduct of aHTA are siloed and developed for the institutions that they serve. HTA agencies with established aHTA methods have designed heterogeneous methods which are context specific. Sources of evidence that could support aHTA in HBPs have been funded by donors (e.g. DCP, funded by the Gates Foundation); high-income country institutions (Tufts, funded by the Gates Foundation); or global health bodies (WHO-CHOICE, funded by the WHO). While these are valuable resources, it is possible that this evidence base may not be aligned with the priorities of policy makers across contexts.

Finally, because aHTA methods are even more uncertain than standard HTA methods, they pose a risk of making the wrong decision that has not yet been fully identified and explored(155,156). VOI analysis can be used to support the quantification of the risk of making the wrong decisions based on limited data, but there are challenges when applying VOI to sector-wide HBP assessments. A modified approach to VOI was tested on Malawi's HBP design process based on secondary sensitivity analyses but was not able to capture all interventions(157). Moreover, applying VOI in this context still focuses on parameter uncertainty, which may not fully capture the uncertainty of transferring data from other jurisdictions(158). It remains unclear how best to implement VOI in circumstances with substantial data

scarcity, especially when parameter uncertainty cannot be fully characterized from the available CEA. There is currently no relevant framework to assess the risk of making the wrong decision from applying the different approaches to aHTA, considering different types of uncertainty, for use in HBP design.

1.5 Research aim and questions

The aim of this thesis was to establish a conceptual foundation and body of evidence to inform aHTA methodological development. The thesis applies this foundation in a 'real world setting' in Rwanda, as a case study to illustrate and explore a structured approach to aHTA in nascent priority setting systems. The setting and case study are further elaborated below, in section 1.7.

The research presented in this thesis links together to answer three questions:

1. How are existing priority setting institutions and practitioners adapting their economic evaluation methods, and how can these methods be characterized?
2. Can a structured aHTA approach be applied in a nascent priority setting system, constrained by time, data, and capacity?
3. How can the risk of using different aHTA methods be assessed?

1.6 Thesis structure

This thesis takes a 'research paper style' approach, in accordance with the Research Degree student handbook (2023-2024)(159). It contains six results chapters (Chapter 2-7). Each of the chapters is written for submission in a peer-reviewed journal and is accompanied by a prologue and epilogue.

Research question 1 is answered in three parts. First, an example of adapting standard economic evaluation methods is illustrated through a rapid CEA of dialysis in Rwanda in Chapter 2. Second, a systematic literature review of existing aHTA methods from global HTA agencies documents how priority

setting institutions use aHTA methods. This is used to develop the first characterization of existing aHTA methods and outline their triggers, strengths, and weaknesses in Chapter 3. Finally, a scoping review of the HBP literature and survey of HBP practitioners document how aHTA methods are used to assess cost-effectiveness in HBPs. This review is used to identify areas of overlap with HTA agencies' aHTA methods and summarize the available aHTA methods for cost-effectiveness assessment in HBP design in Chapter 4.

Research question 2 is answered through two case studies. In Chapter 5, a combination of rapid review and a novel approach to expert elicitation is used to evaluate the cost-effectiveness of 49 cancers in Rwanda. In Chapter 6, this evidence is used alongside costs and coverage rates to model potential cancer package investment scenarios. In the epilogues following both papers and my discussion I reflect on this application to consider how aHTA methods for HBPs could be revised based on this experience.

To answer research question 3, I extended the framework developed in Chapter 4 by conceptualizing and testing an approach for assessing the risk of aHTA in Chapter 7. This chapter identifies potential quantitative and qualitative uncertainties that can be considered in using aHTA and applies this retrospectively to the case study in Rwanda.

Chapter 8 provides a discussion and conclusion of the thesis. It summarizes the contribution of my thesis to laying the foundation for aHTA methods and future research directions.

1.7 Rwanda – the case study

I sought to apply this thesis to a 'real-world' setting with the aim of developing context-driven methods. My underlying approach was to both develop methods that could be locally used and accepted, and as far as possible, to co-develop and apply these methods in context. Indeed, part of the motivation for this thesis was my own experience working in Rwanda for two years prior to starting this PhD. In a country

that sought to introduce priority setting methods, I noticed some of the gaps and challenges highlighted in this introduction, particularly related to adapting methods for data-scarce environments. In each prologue and epilogue, I not only reflect on the development of aHTA methods, but also where relevant, the contribution of this work to Rwanda's broader priority setting ambitions. More broadly, it is envisioned that one benefit of this thesis will be to facilitate the uptake of evidence-based priority setting in Rwanda and other countries where priority setting is still nascent.

Policy makers in Rwanda have been working for the past five years to institutionalize priority setting to help make coverage decisions for its Community-Based Health Insurance (CBHI) scheme. Rwanda is a small East African country with a population of 10.5 million people(160), and has made strides towards UHC since 2000. Under-5 mortality has dropped from 196 per 1,000 live births to 45 per 1,000; maternal mortality rates dropped from 1071 per 100,000 live births to 203 per 100,000, childhood vaccination rates rose from 76% to 96%; and antenatal care by a skilled provider rose from 92% to 98%(161). Life expectancy at birth in 2022 was 69.6 years(160).

Per capita annual expenditure on health in Rwanda is $58(162). More than 90% of the population receive healthcare through its CBHI system(163). The scheme provides comprehensive medical benefits and drug coverage. It is financed through a combination of member contributions, general taxation, cross-subsidization from other insurances, earmarked taxes, co-payments, and donor funding(164). Members pay enrollment fees according to income level, which are waived for the poorest citizens(165). Co-payments are 200 Rwandan francs (RWF) at health post level, and 10% of the total hospital bills at the district and national levels(165).

Like many health insurance schemes, the CBHI scheme is constantly balancing requests for new services with a finite resource envelope. For over a decade, CBHI has faced chronic deficits. From 2011-2012 and 2015-2016 CBHI expenditure doubled. By 2018-2019, the deficit grew to 14.3 billion RWF, and by 2021 it

was projected to rise to 20 billion RWF(166,167). A key strategic focus area of the most recent Health Sector Strategic Plan (2018-2024) is strengthening the long-term financial sustainability of the CBHI scheme(167). Evidence-based priority setting was identified as one pathway to achieving this goal.

Rwanda is an appropriate country to embed in this thesis for several reasons. First, the CBHI scheme is well-established, which provides a clear implementation mechanism for explicit priority setting. Second, there is significant political support and enthusiasm for using evidence-based priority setting to improve the financial sustainability of the scheme. Third, like many countries, there is demand for priority setting to be done quickly, and thus, for the use of aHTA methods.

This thesis includes three case studies from Rwanda: a cost-effectiveness analysis on dialysis for acute kidney injury; a cost-effectiveness assessment of 49 cancer interventions; and a set of modelled potential cancer coverage packages for the CBHI scheme. The first case study served as the motivation for developing aHTA methods, and the subsequent two case studies apply aHTA methods to the broader HBP design process in Rwanda.

Dialysis as a pilot cost-effectiveness analysis

The first case study (Chapter 2) reports the results of the first priority setting pilot in Rwanda on dialysis. Dialysis is a fiercely debated topic, particularly among LMICs where demand for dialysis is high and there is pressure to cover this expensive treatment as part of UHC packages(168,169). Indeed, several LMICs have already conducted CEAs on dialysis(170–172).

Dialysis was selected as the topic for a CEA pilot in 2019 in Rwanda due to its existing coverage by the CBHI scheme; its high cost to the scheme; the availability of a recent local costing study on dialysis; and a global movement to reduce untreated acute kidney injury (AKI) in low-income countries(173). Policy makers sought to complete a CEA quickly to make a defendable decision about dialysis coverage, and subsequently other priority topics. Given the substantial time constraints, the context was ripe for the

use of aHTA methods. The case study highlights the overall challenge in aHTA methods, that there was a lack of clarity on the methodological options for aHTA and how they could be adapted to the available time and data.

Prioritizing cancer services for the health benefits package

The second case study, in Chapter 5, reports the cost-effectiveness results of a broader HBP prioritization process in Rwanda. In 2021, the Government of Rwanda moved beyond a priority setting pilot and established a formal priority setting mechanism. The Ministry of Health (MoH) issued a Ministerial Instruction (MI) with guidance on determining the methodology to define the CBHI HBP. The MI articulated the establishment of a new national HBP prioritization committee, and nine criteria for assessment including cost, cost-effectiveness, budget impact, financial risk protection, burden of disease, individual effectiveness, feasibility, vulnerable groups and life-threatening conditions(174). Several in-country scoping workshops explored potential topics for prioritization, centered on local priorities. Possible topics were mostly drawn from an unpublished list of potential new services that CBHI was under pressure to cover.

Cancer was selected as a priority topic for this analysis for three reasons. First, there is a rising burden of disease: 75% of global cancer deaths are predicted to take place in LMICs by 2030(175). Second, CBHI currently provides limited coverage of cancer services; much of the country's cancer care is covered through a national cancer center sponsored by a non-government organization, Partners in Health(176). Finally, policy makers were concerned about financial risk protection, as cancer services are high cost and could result in catastrophic expenditure for patients and their families.

The choice to evaluate cancer highlighted the disconnect between the available evidence and the priorities of policy makers. The DCP chapter on cancer only presents economic evidence for six cancers: breast, cervical, colorectal, liver, oral, and several types of pediatric cancers(177). Through systematic

review, DCP found 16 CEA articles on cervical cancer, and only 15 articles for the remaining five cancers combined(177). The latest WHO-CHOICE models estimate cost-effectiveness for only breast, cervical, and colorectal cancers(76). The Tufts Registry contains over 2,000 CEAs on cancer, though more than 80% of them are conducted in North America, Europe, and Central Asia(178). To complement these resources, the National Comprehensive Cancer Network (NCCN) has a set of evidence-based resource-stratified and harmonized guidelines, designed to be adapted to different resource levels and geographies(179). While the guidelines are partially stratified based on providing the most health gain for the lowest cost, cost-effectiveness evidence in the form of cost-effectiveness ratios (CERs) is not reported in these guidelines. Calls have been made to improve cancer research across LMICs, for example through more clinical trials in LMICs, better data and registries, strengthened research capacity, and generally more research including more CEAs, but the evidence base remains limited for these contexts(180). Yet, Rwandan policy makers sought to prioritize the 67 cancers (eventually 'grouped' to 49 cancers based on common clinical pathways) listed in their own National Cancer Guidelines(181). Adapted methods were needed for generating economic evidence within the existing time and data constraints.

Modelling potentially cost-effective cancer packages

The third case study, in Chapter 6, reports a set of potential cancer packages in Rwanda, leveraging the cost-effectiveness evidence alongside costs and coverage rates estimated as part of the broader HBP assessment. While there are pre-existing tools for modelling HBPs as mentioned above, the methods behind these tools are difficult to unpack because they have been developed by different groups of modelers who often support their use(90,94,182). Instead, this case study shows that it is possible to model scenarios in a more simplistic way but still illustrating the trade-offs of potential packages of services.

1.8 Funding

This PhD was completed under the 'international Decision Support Initiative' (iDSI) grant, which was a $15 million, five-year grant from the Bill and Melinda Gates Foundation to support the institutionalization of priority setting in LMICs (grant number OPP1202541). Tuition was self-funded. Rwanda was one of the focal countries in the grant, and I was the Center for Global Development's lead in this work. Several other development partners supported this work as well, including iDSI partners London School of Hygiene and Tropical Medicine and the Clinton Health Access Initiative; the World Health Organization; Palladium; and Management Sciences for Health.

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Chapter 2: Rapid cost-effectiveness analysis: hemodialysis versus peritoneal dialysis for patients with acute kidney injury in Rwanda

2.1 Prologue

This paper is included as the motivating paper for my PhD and as an example of aHTA, but prior to developing my aHTA methods. The analysis was Rwanda's first pilot for integrating evidence-based decision making into coverage decisions for its CBHI scheme. Policy makers selected dialysis as the topic because it was a political priority and a recently completed costing analysis from Rwanda was available.

I was asked to complete a CEA of dialysis within six weeks, in time for the annual national leadership retreat where key ministries report on their progress. As such, I had no time for any primary data collection and had to use secondary data throughout. While a recent local costing study was available, it focused on the cost of hemodialysis, the standard of care, and not peritoneal dialysis, the potential intervention. Additionally, only costs borne by the CBHI scheme rather than the whole health system were included. This demanded a pragmatic approach to collating secondary data quickly, and thus an aHTA method which adapted for the time and data available.

I co-designed the cost-effectiveness model and scope for this chapter with Francis Ruiz and Nuri Ahmed. Additionally, I prepared ethics in both Rwanda and UK; reviewed available local evidence and conducted a literature review for the secondary data to parameterize the model; led consultations with local nephrologists for expert opinion to fill data gaps; conducted budget impact analysis; wrote the

manuscript; and published it in Cost-Effectiveness and Resource Allocation. The full author contributions for this paper are included in the research cover sheet.

2.2 Cover sheet

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2100817	**Title**	Mrs
First Name(s)	Cassandra		
Surname/Family Name	Nemzoff		
Thesis Title	Methods, application, and risk of 'adaptive' health technology assessment		
Primary Supervisor	Anna Vassall		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Cost-Effectiveness and Resource Allocation		
When was the work published?	April 2024		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	For this paper, I co-designed the markov model and scenarios analyses with Francis Ruiz and Nuri Ahmed; collected and synthesized all data for parameterizing the model; conducted budget impact analysis; interpreted cost-effectiveness and budget impact findings; wrote the first draft of the manuscript; and revised the manuscript with feedback from co-authors and peer reviewers. Co-authors helped to conceptualize the work, collect data, conduct analysis, and revise the manuscript.

SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	1 September 2024

2.3 Paper

Rapid cost-effectiveness analysis: hemodialysis versus peritoneal dialysis for patients with acute kidney injury in Rwanda

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Abstract

Background: To ensure the long-term sustainability of its Community-Based Health Insurance scheme, the Government of Rwanda is working on using Health Technology Assessment (HTA) to prioritize its resources for health. The objectives of the study were to rapidly assess 1) the cost-effectiveness and 2) the budget impact of providing peritoneal (PD) versus hemodialysis (HD) for patients with acute kidney injury (AKI) in the tertiary care setting in Rwanda.

Methods: A rapid cost-effectiveness analysis for patients with AKI was conducted to support prioritization. An 'adaptive' HTA approach was undertaken by adjusting the international Decision Support Initiative reference case for time and data constraints. Available local and international data were used to analyze the cost-effectiveness and budget impact of PD compared with HD in the tertiary hospital setting.

Results: The analysis found that HD was slightly more effective and slightly more expensive in the payer perspective for most patients with AKI (aged 15-49). HD appeared to be cost-effective when only comparing these two dialysis strategies with an incremental cost-effectiveness ratio of 378,174 Rwandan francs (RWF) or 367 United States dollars (US$), at a threshold of 0.5 x gross domestic product per capita (RWF 444,074 or US$431). Sensitivity analysis found that reducing the cost of HD kits would make HD even more cost-effective. Uncertainty regarding PD costs remains.

Budget impact analysis demonstrated that reducing the cost of the biggest cost driver, HD kits, could produce significantly more savings in five years than switching to PD. Thus, price negotiations could significantly improve the efficiency of HD provision.

Conclusion: Dialysis is costly and covered by insurance in many countries for the financial protection of patients. This analysis enabled policymakers to make evidence-based decisions to improve the efficiency of dialysis provision.

Introduction

Background

Rwanda's community-based health insurance (CBHI) scheme covers more than 80% of the population, most of whom are in the informal sector(1). The scheme has three main funding sources: member contributions, government subsidies, and donors, and operates mostly on a fee-for-service basis(2). Members are entitled to a comprehensive benefits package covering drugs and medical services, and their contributions vary based on income level(3). Co-payments are 200 Rwandan francs (RWF) at the health post level, and 10% of the total bill at higher levels of care(3). As part of the scheme's success in covering most of the population, the government continues to face growing demand for a wide range of healthcare services, which it must balance with an estimated $58 per capita expenditure on health(4).

To strengthen the financial sustainability of the CBHI scheme, health technology assessment (HTA) is being introduced to support explicit, evidence-informed priority setting(5). As a first step, a rapid cost-effectiveness analysis on dialysis for acute kidney injury (AKI) was undertaken(6).

Dialysis is a common topic of interest for low- and middle-income countries (LMICs) facing a growing burden of non-communicable diseases due to its high costs(7). Across LMICs, only 2-5% of patients needing treatment receive it; for many, it is unaffordable(8). At the time of analysis, six weeks of dialysis was covered by CBHI in Rwanda with a 10% co-pay, averaging 218,000 RWF out of pocket per patient(9). For scale, this represents 25% of GDP per capita(10).

Some LMICs have conducted cost-effectiveness analyses on dialysis to inform their coverage decisions(11,12). However, these have been disproportionately focused on dialysis for patients with end-stage renal disease (ESRD)(13–16). ESRD is the last stage of chronic kidney disease (CKD), which permanently impairs kidney function and renders patients 'dialysis dependent' to survive.

Dialysis is also used to treat AKI, which, unlike ESRD, temporarily impairs kidney function. AKI is reversible if diagnosed and treated early. Depending on the severity of a kidney injury, patients may only need dialysis for a limited period to allow for at least partial, and sometimes full recovery of kidney function.

LMICs bear a disproportionate amount of the globally estimated burden of AKI(17), and in these countries, it is commonly a disease of the young, often caused by a single, curable condition(17–20). In Rwanda, these single conditions that cause AKI most commonly include malaria; pneumonia; sepsis; pregnancy-related conditions such as eclampsia and hypertension; intoxication caused by treatment from traditional healers; and diabetes(21). The median age for AKI patients in Rwanda is 38 years old, and the mortality rate is 34%(21). However, barriers to optimal management of AKI in Rwanda remain. These include knowledge gaps among healthcare providers, sub-optimal diagnostic capacity, particularly in sub-tertiary hospitals, and limited treatment options(22).

The main treatment options for AKI in Rwanda are hemodialysis (HD) and peritoneal dialysis (PD). Evidence suggests little difference when comparing HD and PD in terms of their clinical outcomes or the risk of complications – though the evidence base remains moderate to poor(23).

Currently, all dialysis provision in Rwanda is exclusively delivered in the hospital setting. Most of this provision is HD, with a small proportion being PD. While in other settings, HD is often provided in hospitals and PD in smaller facilities or at home this type of PD was discontinued a few years ago in Rwanda. This was partially because of challenges in sourcing dialysate and difficulty in guaranteeing hygienic conditions for at-home PD.

Aim and Objectives

At the time of writing, Rwanda's CBHI benefits package officially covered up to six weeks of dialysis per patient with AKI. Dialysis for ESRD was not covered. However, the diagnosis of AKI versus CKD can

sometimes be challenging, especially when there is a previously undiagnosed kidney dysfunction. Due to the considerable cost of providing dialysis, this study aimed to help the Rwandan CBHI scheme decide on the optimal delivery of dialysis services.

The objectives of the study were to rapidly assess 1) the cost-effectiveness and 2) the budget impact of providing PD versus HD for patients with AKI in the tertiary care setting in Rwanda. This may be the first study of its kind comparing dialysis modalities for AKI in LMICs where both HD and PD are provided exclusively at the tertiary care level.

Methods

Our rapid cost-effectiveness analysis used an 'adaptive' HTA (aHTA) approach, which adjusts HTA methods for time, data, and capacity constraints(24). To respond to policy makers' demand, the aim was to complete the assessment in six weeks. It was thus decided to use a rapid cost-effectiveness analysis which builds basic economic models using opportunistically or rapidly sourced local data(24). The assessment used the international decision support initiative (iDSI) reference case for economic evaluation as a guide(6,25). Table 1 summarizes the application of the eleven iDSI reference case principles. Highlighted rows indicate principles that were adapted for time and data constraints.

Table 1: Methodological Approach Using the iDSI Reference Case

Principle	The analysis should …	Dialysis approach
Transparency	Be clearly communicated.	A 'learn-by-doing' approach was undertaken to ensure stakeholder engagement, learning, and translation of results.
Comparators	Reflect decision problem. 'No comparator' optional.	The comparator was HD, to reflect the decision problem and local standard of care. 'No comparator' was excluded as it was not considered a reasonable policy option.
Evidence	Consider all available evidence.	Dialysis was partially selected due to already available local cost data, and a recent systematic review on clinical effectiveness. Additional data needs were supplemented by rapid review and personal communication with co-authors.
Health outcomes	Be appropriate to decision problem, capture positive and negative effects on length and quality of life, and be generalizable across disease states.	Quality-adjusted life years (QALYs) were selected given availability of evidence from other jurisdictions.

Costs	Reflect all differences in intervention and comparator costs.	Costs reflect best available evidence on HD and PD, though limitations with PD data affect the certainty of results. No estimation of changes due to (diseconomies) of scale were made.
Time horizon	Be sufficient to capture all costs and effects.	A lifetime horizon was used.
Non-health effects and costs outside the health budget	Be identified if relevant to the research question.	The analysis' focus was limited to the payer perspective, due to lack of locally available data to inform the optional societal perspective.
Heterogeneity	Explore sub-populations.	Two age groups were explored – 15-49 and over 50 to reflect the young age of most patients undergoing dialysis in Rwanda.
Uncertainty	Be appropriately characterized.	Deterministic and probabilistic sensitivity analysis were undertaken.
Constraints	Evaluation budget impact including infrastructural/ resource constraints.	Budget impact analysis was undertaken. Infrastructural constraints were likely underestimated for PD due to limited data.
Equity considerations	Consider equity implications.	Equity implications were considered only qualitatively.

Population and subgroups

The population for this analysis were dialysis-eligible patients with AKI in a tertiary care facility in Rwanda. Two age groups were considered: patients aged 15-49 and patients aged 50 and above.

Comparators

The intervention was tertiary care delivered PD, compared with tertiary care delivered HD. In the base case, the model assumed that patients receive the maximum allotted care covered by CBHI. This included three sessions per week for six weeks of HD or six weeks of continuous ambulatory PD for hospitalized patients.

Model structure and assumptions

A *de novo* Markov model was used to reflect the costs and effects of the initial acute condition of AKI combined with the long-term health effects that can follow the condition. The cycle length was one year (Appendix 1). The model was informed by the published literature and validated through consultation with local and international nephrology specialists. Patients enter the model at the tertiary care facility, starting on hospital HD or hospital PD. Over time, patients may stay with the same modality or switch

modalities. They may develop complications or not, and subsequently fully recover rendering them dialysis independent or partially recover with no further treatment. They may then die from AKI progressing to CKD, from co-morbidities, or from natural causes.

Modelling perspective and scenarios

A payer perspective was used. The payer perspective included all direct medical costs to Rwanda Social Security Board (RSSB) plus salaries, overhead, and depreciation of the HD machines paid by the Ministry of Health. A 'decreased provision' scenario was also explored, which assumed the actual number of sessions patients receive on average was five instead of the full eighteen sessions(9).

Evidence for model parameters

Given an initially short timeline, a pragmatic approach was taken to select data to inform the model. Available local data was supplemented by a rapid literature search and sources known to the authors (Appendix 2). Where needed, gaps were addressed based on personal communication involving Rwandan nephrologists and international experts.

Cost and resource use

Costs and resource use data were sourced primarily from a 2018 RSSB Utilization and Expenditure Review on Dialysis made available by RSSB(9). These were supplemented by published data from other jurisdictions and assumptions made by co-authors on this study. The total cost for HD, PD, and palliative care are expressed as per patient unit costs and reflect the cost of providing HD and PD at the tertiary care level (Table 2). Direct medical costs (including catheters, drugs, lab tests, kits, dialysate, other consumables, and palliative care) were sourced from an average across four facilities for HD and one facility for PD. Direct non-medical costs (costs of healthcare professionals, overheads, and depreciation) were estimated by combining local reports, peer-reviewed literature, and personal communication and allocated per patient based on patient volumes. Only one facility provides a minimal amount of PD, and

thus there remain uncertainties regarding the PD unit costs. All costs were incurred during the six weeks of treatment; no additional costs of complications were included. For further details of costs included, see Appendix 3.

Costs in the model are expressed in RWF and are inflated to 2022 prices using the Consumer Price Index(26). They are converted to current US dollars using the latest available exchange rate of 1 United States dollar (US$):1030 RWF(27).

Effectiveness

Clinical effectiveness parameters were drawn from several sources. Population mortality rates were sourced from the World Health Organization's Global Health Observatory Data repository(28). Mortality rates for AKI patients undergoing dialysis were from a local observational study(21). Transition probabilities were from an Indonesian study that compared HD and PD for patients with ESRD(14), and on assumptions made by co-authors of this study.

Quality-adjusted life years (QALYs) were the primary health outcome in this study. Utility values for dialysis patients with AKI were sourced from two studies from Argentina and Canada, which used the EuroQoL EQ-5D-3L(29,30). Utility values for dialysis independence was sourced from Garay et al(30).

Discounting

Costs and outcomes were discounted at a standard 3% per annum after the first year following the iDSI Reference Case, though most costs are incurred in the first year(25). The impact of varying the discount rate between 0% to 5% was explored in a sensitivity analysis(31).

Table 2: Input parameters

Parameters	Base Case	Sensitivity Analysis	Distribution	Sources	Source Number
Disease Burden					
Prevalence	2.8%			Igiraneza et al. 2018	(19)
In-hospital annual mortality from not recovering from PD or HD	34%			Igiraneza et al. 2018	(19)
Annual mortality for AKI hospital survivors on dialysis from other comorbidities	8.2%	7.2% - 9.2%	Normal	Klarenbach et al. 2009	(27)
Annual in-hospital mortality from PD or HD complication plus other comorbidities	63%	45% - 65%	Normal	Klarenbach et al. 2009	(27)
Unit costs per patient (RWF, inflated, 2022)					
Total costs					
Payer perspective (full 18 sessions)					
Costs of PD treatment	3,187,259	+/- 30%	Gamma	RSSB 2018	(7)
Cost of HD treatment	3,656,194	+/- 30%	Gamma	RSSB 2018	(7)
Payer perspective (5 sessions)					
Costs of PD treatment	1,687,615	+/- 30%	Gamma	RSSB 2018	(7)
Cost of HD treatment	1,890,082	+/- 30%	Gamma	RSSB 2018	(7)
Direct medical costs					
Bundled cost of catheter, drugs, labs, etc. PD	955,589	+/- 30%	Gamma		
Bundled cost of catheter, drugs, labs, etc. HD	613,262	+/- 30%	Gamma		
Palliative care (same for PD and HD)	690,296	+/- 30%	Gamma	Afiatin et al. 2017	(11)
Kit costs HD	1,984,847	+/- 30%	Gamma		
Dialysate costs PD	1,474,494	+/- 30%	Gamma		
Direct non-medical costs					
Staff costs PD	530,024	+/- 30%	Gamma	HLMA 2019, Author's calc	(30)
Overheads PD	227,153	+/- 30%	Gamma	Aboagye et al. 2010, Author's calc	(31)
Staff costs HD	716,146	+/- 30%	Gamma	HLMA 2016, RSSB 2018	(7,30)
Overheads HD	306,920	+/- 30%	Gamma	Aboagye et al. 2010, Author's calc	(31)
Annualized machine depreciation HD	35,019	+/- 30%	Gamma	Authors' assumption	
**Operating costs = staff + overhead*					
Transition probabilities					
Transition probability HD complication to hospital PD	1%	0.5% - 5%	Beta	Authors' assumption	
Transition probability PD complication to hospital HD	1%	0.5% - 5%	Beta	Authors' assumption	
Transition probability hospital HD to HD complication	4%	2% - 6%	Gamma	Afiatin et al. 2017	(11)
Transition probability hospital PD to PD complication	25%	20% - 50%	Gamma	Afiatin et al. 2017	(11)
Transition probability of HD complication to partial recovery	0.2%	0.1% - 0.5%	Beta	Authors' assumption	
Transition probability of PD complication to partial recovery	0.2%	0.1% - 0.5%	Beta	Authors' assumption	
Transition probability HD complication to recovered	71%	46% - 82%	Beta	Klarenbach et al. 2009	(27)
Transition probability PD complication to recovered	71%	46% - 82%	Beta	Klarenbach et al. 2009	(27)
Transition probability HD complication plus other complications	0.2%	0.1% - 0.5%	Beta	Authors' assumption	
Transition probability PD complication plus other complications	0.2%	0.1% - 0.5%	Beta	Authors' assumption	
Transition probability hospital HD to not recovery	34%	50% - 80%	Beta	Igiraneza et al. 2018	(19)
Transition probability hospital PD to not recovery	34%	40% - 75%	Beta	Igiraneza et al. 2018	(19)
Utility					
Utility of dialysis independent	0.81	0.65 -0. 90	Normal	Garay et al. 2019	(28)
Utility for PD without complication	0.62	0.52 – 0.72	Beta	Klarenbach et al. 2009	(27)
Utility for HD without complication	0.62	0.52 – 0.72	Beta	Klarenbach et al. 2009	(27)
Utility for PD with complication	0.31	0.13 – 0.49	Beta	Afiatin et al. 2017	(11)
Utility for HD with complication	0.37	0.15 – 0.59	Beta	Afiatin et al. 2017	(11)
Discounting					
Discounting rate for cost	3%	0% - 5%		iDSI Reference Case	(23)
Discounting rate for utility	3%	0% - 5%		iDSI Reference Case	(23)

HLMA: Health Labour Market Survey 2016; RLFS: Rwanda Labour Force Survey 2016

Thresholds

The base case analysis uses a cost-effectiveness threshold of 0.5 x GDP per capita (RWF 444,074 or US$431). This is broadly in line with recently estimated values for Rwanda based on cross-country studies of US$325 to US$426 (2022), or 39% - 51% of GDP per capita(32–34).

Budget impact analysis

The budget impact analysis rapidly assessed the five-year (2020-2024) costs associated with providing dialysis services in four scenarios. In the baseline scenario, 'HD preferred,' a stable distribution of HD (91%) to PD (9%) was maintained (i.e., status quo). Alternative scenarios included scenario 1 - 5% annual shift to PD provision over 5 years; scenario 2 - 10% annual shift to PD provision over 5 years; and scenario 3 – HD provision maintained at 91% but with reduced costs for HD kits.

Analyses

The cost-effectiveness analysis was completed in TreeAge software (version 2023 R1.2), and the budget impact analysis in Microsoft Excel. Uncertainty was analyzed using one-way sensitivity analysis and probabilistic sensitivity analysis (PSA), with distributions set according to standard practice for different parameter types.

Results

Base-case results

Overall, the intervention (PD) was less expensive and less effective relative to the comparator (HD). Table 3 presents the incremental costs and QALYs for the intervention (PD) and status quo (HD), stratified by age. The total estimated per patient cost for PD was RWF 1,824,886 (US$1,771) compared with a total estimated cost of HD of RWF 2,059,354 (US$1,999). The expected net QALYs lost in delivering PD compared with HD were -0.62 for patients aged 15-49 and -0.27 for those over 50, the latter due to the

older cohort's increased mortality rate. The difference in QALYs is mostly attributable to health-related quality of life.

At a threshold of 0.5 x GDP per capita (RWF 444,074 or US$431), the analysis suggests that HD provision, as the standard of care, was cost-effective compared with PD provision for patients aged 15-49, with an ICER below the threshold at RWF 378,174 (US$367). Notably, the interpretation of the ICER (Table 3) is reversed, because incremental costs and effects are both negative(35). In other words, the ICER falls below the threshold, and thus the comparator (HD) is considered cost-effective.

For patients above 50, the analysis suggests that PD was the preferred option compared with HD with an ICER of RWF 868,399 (US$843). The same reverse interpretation of the ICER also applies to this scenario; as the ICER is above the threshold, PD is the preferred option.

Table 3: Incremental cost-effectiveness analysis

		Cost in RWF (2022)	Inc cost in RWF (2022)	Cost in US$ (2022)	Inc cost in US$ (2022)	Effect QALY	Inc effect	ICER in RWF (2022)	ICER in US$ (2022)
Payer Perspective (Age 15-49 years)	Intervention (PD)	1,824,886		1,771		10.01			
	Status quo (HD)	2,059,354	-234,468	1,999	-228	10.63	-0.62	378,174	367
Payer Perspective (Age >= 50 years)	Intervention (PD)	1,824,886		1,771		5.13			
	Status quo (HD)	2,059,354	-234,468	1,999	-228	5.4	-0.27	868,399	843

One-way sensitivity analysis

One-way deterministic sensitivity analysis was applied to individual parameters that affected the ICER most. Varying the costs of HD kits, HD commodities, HD salaries, and HD overhead by +/-30% increased the ICER when the cost of each parameter increased and decreased the ICER when the cost of each parameter decreased. When varying the cost of PD dialysate, PD commodities, PD salaries, and PD

overhead by +/-30%, increasing the costs of the parameters decreased the ICER, and decreasing the costs increased the ICER. In other words, this suggests that there may be opportunities to reduce HD-related costs and enhance the favorability of the ICER; but the same is not true for PD. See Appendix 4 for a tornado diagram.

Scenario analysis

In the reduced provision scenario, HD appeared to be cost-effective compared with PD. Again, for both age groups, the ICER falls below the threshold (Table 4).

Table 4: Scenario Analysis

		Cost in RWF (2022)	Inc cost in RWF (2022)	Cost in US$ (2022)	Inc cost in US$ (2022)	Effect QALY	Inc effect	ICER in RWF (2022)	ICER in US$ (2022)
Scenario analysis: 5 sessions (Age 15-49 years)	Intervention (PD)	1, 075,065		1,043		10.01			
	Status quo (HD)	1,176,297	-101,232	1,142	-98	10.63	-0.62	163,278	158
Scenario analysis: 5 sessions (Age >= 50 years)	Intervention (PD)	1,075,065		1,043		5.13			
	Status quo (HD)	1,176,297	-101,232	1,142	-98	5.4	-0.27	374,934	364

Probabilistic sensitivity analysis

PSA was used to estimate the joint impact of uncertainty in all input parameters. Gamma distributions were applied to costs and beta distributions to health utilities (Table 2). By randomly sampling from each parameter distribution, 10,000 Monte Carlo simulations of incremental costs and incremental effects were obtained. The results of the PSA are presented in two figures. An incremental cost-effectiveness scatterplot (Figure 1) and a cost-effectiveness acceptability curve (CEAC) (Figure 2), which both summarize the impact of uncertainty in relation to the threshold(36). At the threshold of 0.5 x GDP (RWF 444,074 or US$431) and above, HD provision has a 56% probability of being cost-effective relative to PD.

Figure 1: Incremental Cost-Effectiveness Scatterplot

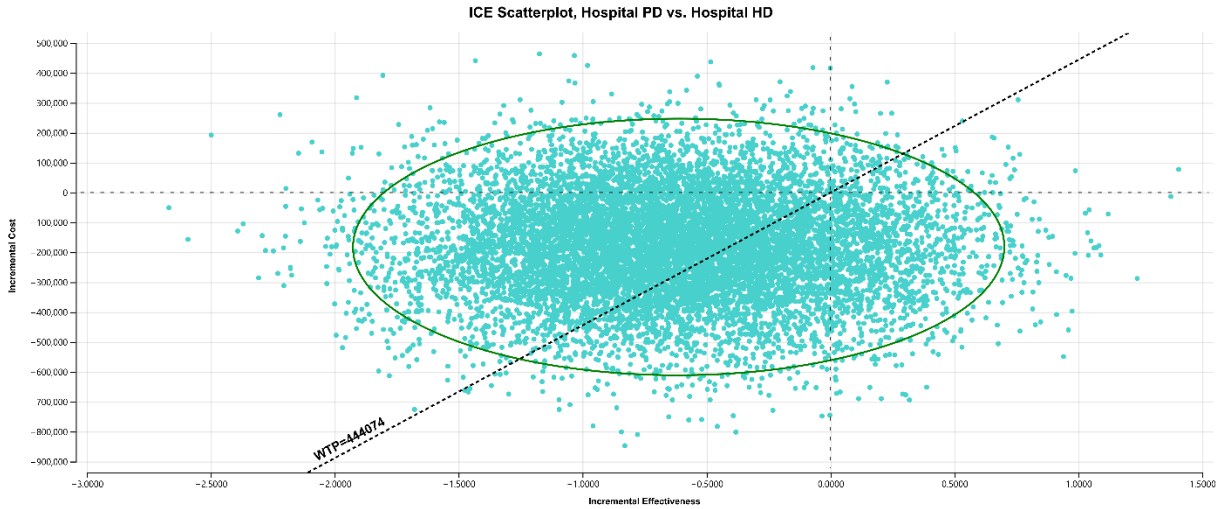
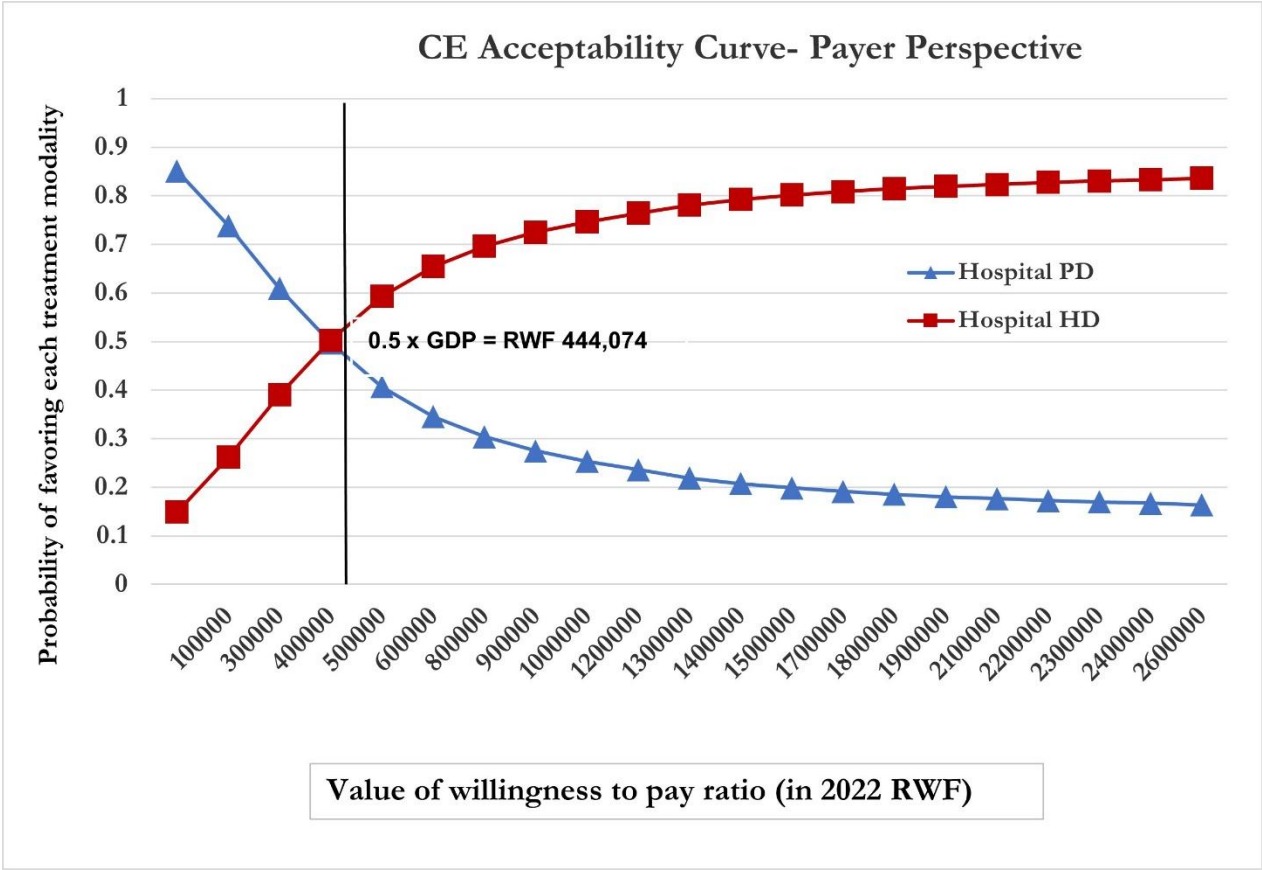


Figure 2: Cost-effectiveness acceptability curve



Budget impact analysis

Table 5 presents the four scenarios of the budget impact analysis. Compared to an 'HD preferred' baseline scenario, shifting to PD coverage would generate some savings. Maintaining an HD-preferred strategy and decreasing the cost of HD kits could achieve significantly more savings because HD kits represent more than half of the overall baseline cost of dialysis (Table 5).

Table 5: Budget Impact Results by Scenario

	Baseline HD preferred	Scenario 1 5% Δ to PD	Scenario 2 10% Δ to PD	Scenario 3 HD + efficiency
5-year cumulative costs				
RWF	2,071,800,000	2,036,700,000	2,001,100,000	1,616,900,000
US$	2,000,000	2,000,000	1,900,000	1,600,000
Cost difference versus baseline scenario				
RWF		(35,100,000)	(70,700,000)	(454,900,000)
US$		-	(100,000)	(400,000)
Average cost per patient				
RWF	3,011,337	2,960,320	2,908,576	2,350,145
US$	2,907	2,907	2,762	2,326

Discussion

At a threshold of 0.5 x GDP per capita, the analysis suggests that HD is cost-effective compared with PD for most AKI patients receiving dialysis in Rwanda, i.e., those aged 15-49 years. The budget impact analysis suggests that shifting to PD would cost less than maintaining the status quo over five years. However, it also suggests that maintaining the HD status quo *and* decreasing the cost of the HD kit, which is a major cost driver in providing HD, would save even more than shifting to PD. A reduction in the cost of the kit could also reduce the overall co-pay for the patient.

One-way sensitivity analysis suggests that decreasing the cost of HD commodities and kits decreases the ICER. This may be achievable, as one hospital, Rwanda Military Hospital (RMH), procures HD kits directly

from a local supplier and pays about half the price of those procured for other hospitals providing dialysis(9). If all hospitals were to get the RMH price for kits, the ICER would decrease to below the threshold for all ages, and HD would be more cost-effective relative to PD. Indeed, this information has led to ongoing price negotiations for the kits for all facilities.

This study contributes to a sparse literature on dialysis for AKI. A recent systematic review published after the time of analysis identified only seven other studies on dialysis for patients with AKI. It presented mixed results, where earlier studies preferred HD and recent studies found PD to be cost-effective; it also indicates a recent increase in industry-sponsored studies(37). Our study is thus a valuable, independent contributor to this sparse literature.

From a cost-effectiveness perspective, this analysis should be seen only as a starting point for discussion rather than a policy recommendation. Indeed, results of the PSA illustrate that HD is slightly more cost-effective at the threshold compared with PD, but there is still uncertainty. Moreover, policymakers raise several issues that the analysis cannot address. These include the cost or requirements for changing or expanding services; the cost-effectiveness of service delivery at lower levels of care; and the impact of removing patient co-pays. It also does not reflect any patient preferences related to dialysis modality, although this is becoming an increasingly important consideration among dialysis practitioners.

Additionally, since the time of analysis, dialysis policies have changed in Rwanda. More coverage of dialysis is now available, as is kidney transplantation. Our analysis reflects the coverage at the time of analysis, and further analyses could be conducted to reflect current available health services.

Limitations

Our rapid cost-effectiveness analysis has several important limitations.

The study team's approach to data collection was largely pragmatic, given time constraints. No attempts were made to synthesize the evidence for input parameters quantitatively or to systematically quality

assure the data using available checklists. Data for the model came from several sources focused on patients with AKI where possible and supplemented by studies on CKD, author assumptions, and personal communication. Utility values, survival data, and transition probabilities are from various international sources. Importantly, the age of patients in papers from which utility values were sourced ranged from 45-to 65, while the average Rwandan dialysis patient is 38, and thus, utilities were overestimated. Local costing data were valuable in contextualizing the study. However, they were more focused on HD due to limited provision of PD, and they excluded the cost of infrastructure, overhead, and staff time for both HD or PD(9). Other local reports, co-author assumptions and personal communication were used to fill data gaps, including staff time and equipment costs. Overhead was estimated as a percentage of operating costs (overhead + staff). Uncertainty remains about the costs and resources needed for PD because the local secondary data used reflected sparse provision of PD in hospitals. If time had allowed, the study would have benefited from more detailed costing on PD.

While the aim was to complete the analysis within six weeks, ultimately the assessment took about three to four months to complete.

Generalizability

A few factors may limit this study's generalizability. First, these results reflect an analysis of PD and HD delivered in a tertiary care setting due to current practice and data availability. If the intervention had been PD delivered at lower-level facilities or at home, as is often the case in other countries, the analysis may have found PD to be much more cost-effective(13). Second, these results are based on a time and data-constrained analysis that pragmatically sourced local and international data. This increased the chance of uncertainty and bias. Our findings may have limited generalizability to other contexts and should not be interpreted without caution alongside other studies on dialysis in LMICs. Other studies often focus on ESRD patients who can either get HD in hospital or PD in lower-level facilities or at home,

and often conclude that a PD-first policy is preferable(13–16). If policymakers in Rwanda were considering coverage options for patients with ESRD or lower-level provision of PD, a separate cost-effectiveness analysis and budget impact analysis would need to be undertaken to understand the implications of the new policy choice.

Reflections on 'adaptive' HTA

This cost-effectiveness analysis undertook an aHTA approach by deviating from what may be regarded as the 'gold standard' of HTA. This was done to reflect the local policymaker context, the availability of data, and general practicality constraints. The iDSI reference case served as a crucial principles-based framework to explore the suitability of the present analysis. Strategic choices were made on how to deliver evidence given the constraints, in a way that was still fit for policy makers' purposes. This was done in two ways.

First, policymakers sought to conduct a rapid HTA to have 'proof of concept' for using HTA in decision-making. To conduct the analysis quickly, a topic was selected for which there were locally available cost data and supplemented by a pragmatic approach to collecting additional data as described in the limitations above. The implication of these choices naturally has impacts on the generalizability and potential bias of the analysis.

Second, the choice to exclude a 'no comparator' arm was made to reflect the local context. Dialysis is a hotly debated topic everywhere due to its high cost, and for ESRD, its limited effectiveness. From a purely economic perspective, some have argued that dialysis is an inefficient use of resources better spent elsewhere(38). However, dialysis is a good illustration that priority-setting choices are not limited to cost-effectiveness. Dialysis is provided in many countries, including LMICs, on the grounds of financial risk protection and it being a moral imperative for universal health coverage(39). The reality is that many LMICs have a shifting burden of disease, with existing coverage for dialysis services in LMICs being

described as inadequate(40). There is a real need to provide evidence to inform open debates about the optimal solution to providing dialysis.

Thus, the 'adaptive' choices in methodology made by the co-authors for this paper reflect a conscious effort to address policymaker needs in a deliberate departure from ‘gold standard’ HTA approaches. The pilot successfully raised awareness about HTA among key stakeholders, provided evidence for price negotiations, and identified key data needs that should be considered part of a strategy to support HTA development in the country(41,42).

Conclusion

Our *de novo* model suggests that HD may be cost-effective from the payer perspective compared with PD, and significant cost savings may be achieved by reducing the costs of HD commodities. While the relative robustness of this economic evaluation was constrained by adopting an aHTA approach, it was nonetheless a useful policy tool for Rwandan policymakers as it helped build the foundation for evidence-based priority setting in the future.

Acknowledgments

The authors are grateful to all the stakeholders involved in this study, including RSSB, the MoH, and the School of Public Health, for their engagement at each step in the HTA process. In particular, the authors would like to thank nephrologists Dr. Joseph Ntarindwa, Dr. Kabahizi Jules, and Dr. Rugamba Gilbert; Dr. Regis Hitimana from the University of Rwanda School of Public Health; the entire team at the Clinton Health Access Initiative including Diana Kizza, Maelle Barbancon, and Natasha Salant; and Pete Baker from the Center for Global Development. Additionally, the team would like to thank Dr. Nick Pritchard, the director of nephrology at Addenbrooke’s Hospital in Cambridge, UK, for providing expert opinion into the care pathway and available research on dialysis used to inform the model.

2.4 Epilogue

Delivering this analysis led me to reflect on how many 'unwritten rules' and practices there are in health economics when providing analyses in a rapid time frame. I made a series of pragmatic decisions about how to fill data gaps, but I had no clear references to rely upon to guide me. Rather, these choices are often learnt skills in the health economics discipline, guided by those with experience, but this may not be available. This led me to reflect on the dearth of tools available for national policy makers and analysts to design and conduct their own rapid analyses, particularly in contexts where data and capacity may be constrained.

This analysis is one of the first CEAs done in Rwanda. It illustrates how to potentially approach one aHTA method, rapid CEA, and what some key challenges are. It also presents new and unique evidence on the cost-effectiveness of dialysis for acute kidney injury in an LMIC setting. The intervention (peritoneal dialysis) and comparator (hemodialysis) were both delivered at the tertiary care level because that is where the costing was done. It excluded any option for delivery of peritoneal dialysis at lower levels of care, which is often done in other countries, and cheaper to deliver. The indication was acute kidney injury because that was what was currently covered by CBHI; this excluded chronic kidney disease which has vastly different outcomes.

While the local costing data was available, more work was required to ensure it was fully relevant to the specific research question. Several consultations with nephrology experts locally and globally were required, as well as reviewing the literature for specific parameters, was required. Despite the original timeline of six weeks, the analysis still took about 3-4 months to complete even with a narrowed research question. This highlighted the mismatch between policy timeframes and even the simplest CEA. Additionally, while there were expectations that the analysis would build local capacity, building a CEA model and teaching one in such a constrained timeframe was impossible.

Ultimately, this assessment was successfully used as proof of concept for using evidence to inform policy. It was used in local price negotiations to reduce the price of the main cost driver for the standard of care, hemodialysis kits. While I was not part of the price negotiations, I presented the results to the Ministry of Health and RSSB leadership, where it was well received. For both myself and The Ministry this work was one of the first steps in the development of formal priority setting mechanisms in Rwanda.

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Chapter 3: Adaptive health technology assessment: a scoping review of methods

3.1 Prologue

Following my experience in Chapter 2, I became interested in systematic approaches to decide how to adjust cost-effectiveness methods when faced with time constraints. Initially, I wrote the commentary for the BMJ Global Health mentioned in the introduction to highlight this gap (Appendix 2). The commentary identified some of the better-known aHTA methods from various countries and called for standardization, particularly to support countries with nascent priority setting systems. The motivation for this paper (Chapter 3) was to build on the commentary by more thoroughly and systematically reviewing existing aHTA methods to define them and improve their replicability.

For Chapter 3, I wrote the protocol; designed the extraction; wrote and refined the search strategy with support from a librarian; led double extraction of the literature; conducted the analysis and synthesis; authored the first draft and refined it with co-author feedback; published the paper in Value in Health; and presented its results at the international Health Economics Association conference in Cape Town, 2023. Full author contributions for this paper are included in the research cover sheet.

3.2 Cover sheet

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

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Thesis Title	Methods, application, and risk of 'adaptive' health technology assessment		
Primary Supervisor	Anna Vassall		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Value in Health		
When was the work published?	October 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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Where is the work intended to be published?	
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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	For this paper, I designed the study, wrote the protocol, and designed the search strategy. I also led data extraction, conducted data analysis, wrote the first draft of the paper and revised it based on co-author and peer reviewer feedback. Co-authors supported with concept and design, data acquisition and extraction, and revision of the draft.

SECTION E

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Date	1 September 2024

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3.3 Paper

Adaptive health technology assessment: a scoping review of methods

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Abstract

Background: Health technology assessment (HTA) is an established mechanism for explicit priority setting to support universal health coverage. However, full HTA requires significant time, data, and capacity for each intervention which limits the number of decisions it can inform. Another approach systematically adapts full HTA methods by leveraging HTA evidence from other settings. We call this 'adaptive' HTA (aHTA), although in settings where time is the main constraint, it is also called 'rapid HTA'.

Methods: The objectives of this scoping review were to identify and map existing aHTA methods, and to assess their triggers, strengths, and weaknesses. This was done by searching HTA agencies' and networks' websites, and the published literature. Findings have been narratively synthesized.

Results: This review identified 20 countries and one HTA network with aHTA methods in the Americas, Europe, Africa, and South-East Asia. These methods have been characterized into five types: rapid reviews, rapid cost-effectiveness analyses, rapid manufacturer submissions, transfers, and de facto HTA. Three characteristics 'trigger' the use of aHTA instead of full HTA: urgency, certainty, and low budget impact. Sometimes, an iterative approach to selecting methods guides whether to do aHTA or full HTA. aHTA was found to be faster and more efficient, useful for decision makers, and to reduce duplication. However, there is limited standardization, transparency, and measurement of uncertainty.

Conclusion: aHTA is used in many settings. It has potential to improve the efficiency of any priority-setting system, but needs to be better formalized to improve uptake, particularly for nascent HTA systems.

Introduction

Policy makers working to achieve universal health coverage (UHC) must balance limited financial resources with increasing demand for healthcare services(1–3). One approach to this challenge is to shift from ad-hoc 'implicit' rationing of services, to 'explicit' rationing, which uses evidence to explicitly decide which services to fund(4).

A common approach to explicit priority setting is health technology assessment (HTA). HTA is *"a multi-disciplinary process that uses explicit methods to determine the value of a health technology… to inform decision-making… to promote equitable, efficient, and high-quality health system*(5)*".* Health technologies include for example drugs, procedures, or public health interventions. Many countries in Europe, Latin America, and Asia already have established HTA systems(6,7).

However, there are thousands of existing and emerging health technologies worldwide. Only a small fraction of them can be evaluated using full HTA which requires an intensive process of evaluation, systematic review, and cost-effectiveness analysis(8,9). Further, there is often a disconnect between the time full HTA takes, and the time policy makers have to make decisions(10).

Due to these constraints, countries are increasingly using various methods for 'rapid HTA'(11). While established HTA systems often adapt HTA to reduce the time needed to respond to urgent policy questions, in nascent HTA systems, capacity and data scarcity may also drive simplification compared to established practice globally(12). Indeed, it is increasingly common to avoid duplication and leverage published evidence (e.g. from HTA reports, systematic reviews, and economic evaluations) from other settings in decision making(8).

The focus of this review is 'adaptive' HTA (aHTA), which builds on rapid HTA to adapt for analytical time, data, capacity, and source of conduct. With a view towards standardizing aHTA nomenclature globally, we propose to define aHTA as: *'a structured approach to selecting and conducting the optimal HTA*

analysis. It produces efficient HTA results by adjusting for analytical time, data, capacity, and source of conduct, leveraging information from other settings where possible'. We consider an 'optimal' aHTA method as one which balances these aspects of time, data, and capacity to produce timely and appropriate evidence to inform policy decisions.

Despite increasing aHTA practice, there are no standardized norms or nomenclature for aHTA(13). A recent WHO survey which assesses the general state of practice and development of HTA in WHO member states provides some context. It found that 45 out of 97 countries had provisions for rapidly assessing and appraising evidence, but given that the survey question only requested a yes/no response, further details of these methods were unavailable(11). What constitutes 'full HTA' versus 'aHTA' remains ill-defined.

The objectives of this review were to identify and map 'aHTA' methods; summarize what 'triggers' institutions to use aHTA; and synthesize the evidence on aHTA strengths and weaknesses. Our primary target audience was practitioners in nascent HTA systems who may benefit from a structured explanation of different approaches to aHTA that allow adaptation for local constraints.

Methods

This scoping review was guided by the Joanna Briggs Institute Manual for Evidence Synthesis(14) and reported using the Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) extension for scoping reviews(15).

For clarity, we used the International Network of Agencies for Health Technology Assessment (INAHTA) definition of 'full HTA'. INAHTA defines it as always describing the technology, evaluating safety and effectiveness through a systematic literature review, calculating cost-effectiveness using economic modelling, estimating budget impact, and critically appraising the quality of the evidence(16). We used the only available aHTA definition to guide our search: *"a blanket approach to HTA methods and*

processes which are fit-for-purpose and focused on context-specific practicality constraints. Methodologically, aHTA may leverage or adapt available international data, economic evaluations, models, and/or decisions from the published literature or established HTA agencies to expedite policy decisions while adequately accounting for concerns of transferability and uncertainty(13)*"*. Generally, we anticipated that aHTA may be called 'rapid HTA' or similar in other countries.

Literature review approach

The literature search had two stages.

Using the WHO's global list of HTA agencies, members of INAHTA, and members of the HTA Network of the Americas (RedETSA), we first identified a long list of HTA agencies and networks (n=88) (Appendix 1)(17–19). We then reviewed their websites to identify any HTA guidance or institutional reports that fit our definition of aHTA. We did not impose a time limit. Publications in English and Spanish were also included, the latter due to known practice of transfers in Latin America(20). Grey literature in additional languages was reviewed using Google Translate(21). We excluded papers that apply aHTA methods, as well as rapid methods for horizon scanning.

The peer-reviewed literature search was then constructed using terms identified in the grey literature. This included any words to describe rapid (or adaptive) HTA methods. Publications from 2006 onwards were reviewed as this is when there was the first uptick in rapid HTAs being produced(22). Included papers provided additional details on aHTA methods from the grey literature; detailed aHTA methods not found in the grey literature; or aHTA strengths or weaknesses. We excluded papers on application of the method. Our focus was on national or regional HTA and thus we also excluded 'hospital-based' or 'mini' HTAs(23).

Specific inclusion and exclusion criteria can be found in Appendix 2.

Search strategy and screening

Each HTA agency's website was screened by two reviewers in September and October 2021. aHTA methods that were detailed enough to understand and apply the method were included. Conflicts regarding inclusion were resolved by consensus discussions between two reviewers.

The published literature search was run on February 17, 2022, in EMBASE, Global Health, Global Index Medicus, Medline (via Ovid), SCiELO, SCOPUS, and VHL. The final strategy was reviewed using the Peer Review of Electronic Search Strategies guideline (Appendix 3)(24). Duplicates were removed, and titles and abstracts were each screened by two reviewers for eligibility using Covidence software(25). Conflicts were resolved by consensus. The same was done for full text review. A follow-on citation search was conducted using the Web of Science Core Collection on June 30, 2022. The same screening and selection approach was used.

Data extraction and synthesis

Microsoft Excel was used to extract information from the grey literature including country; agency/department; name; year; objective/purpose; timeline; details of the approach including topic selection, methods, appraisal and implementation; producer of analysis; triggers; strengths; and weaknesses. Covidence was used to extract information from the peer-reviewed literature including new aHTA approaches; further details of approaches from the grey literature; strengths; and weaknesses. All aspects of extraction were drawn directly from the peer-reviewed or grey literature. This was done by the first author and checked by co-authors. Through extraction, we found the focus of adaptations to be on aHTA methods and narrowed our synthesis accordingly.

To categorize the methods, we first reviewed self-reported names to bucket the methods into categories. We then reviewed the methodological details and identified recurring adaptive characteristics, alongside the producer of the analysis to check for consistency. This was used to finalize the categorization. Further

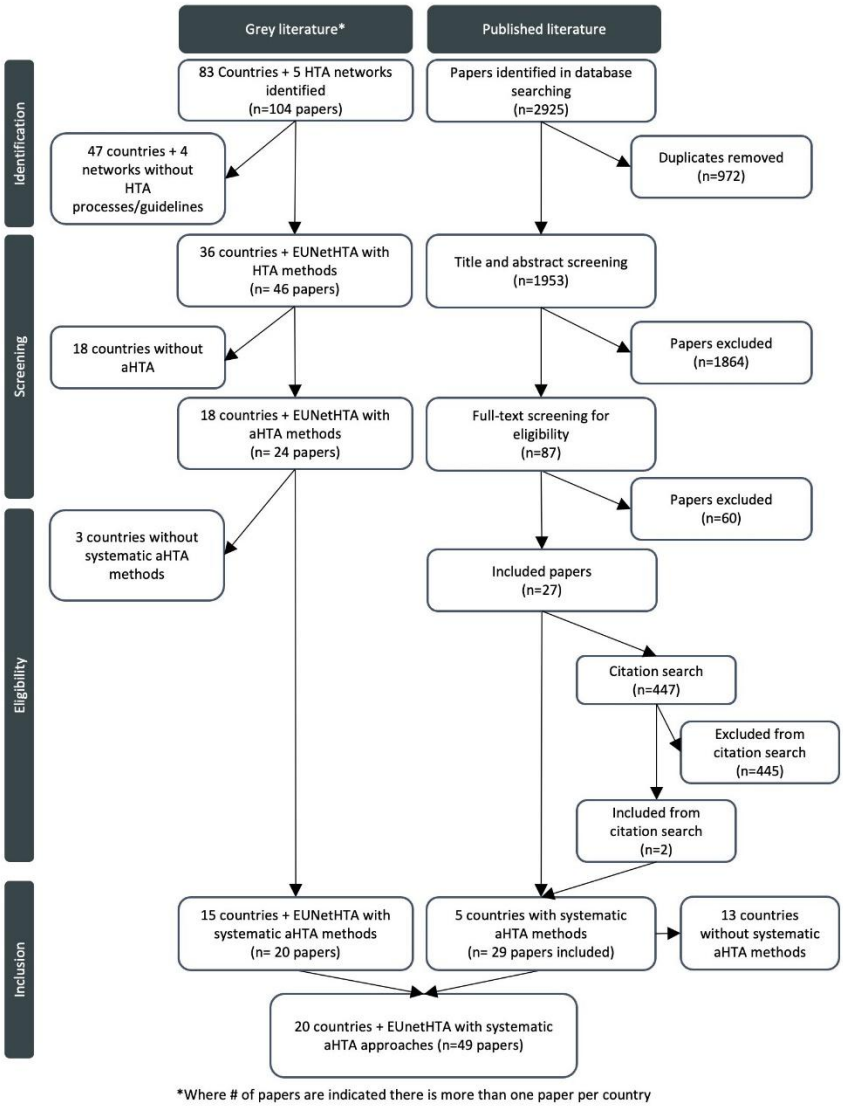
details of the method for developing the taxonomy can be found in Appendix 4 and the full extraction is available in Supplement 1.

Results

In the grey literature, we identified 83 countries with a national HTA agency and 5 HTA networks for review. Of those, 15 countries and 1 HTA network (EUNetHTA) were identified to have aHTA methods (n=16/88 HTA agencies and networks, 20 papers). Of the 15 countries, 7 are EUnetHTA members that also had national aHTA methods.

The published literature search identified 2925 studies; duplicates were removed, and 1953 papers remained. Title and abstract screening removed 1864 studies, leaving 87 for full text review. Of those, 27 studies were included. Reasons for full text exclusion included irrelevance, lack of adaptation, or focus on hospital-based HTA. The citation search identified 447 additional studies, from which 2 papers were added. The most common reason for exclusion on the citation search was saturation of information. All 29 peer-reviewed papers included evaluate the strengths or weaknesses of aHTA methods. Additionally, these papers provided details of England and Scotland's aHTA methods first identified in the grey literature and found 5 more countries with aHTA methods for inclusion.

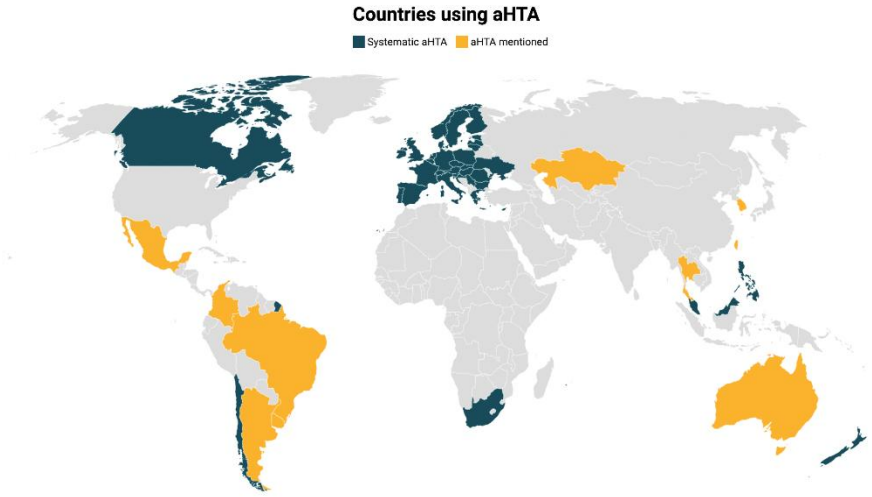
Figure 3: PRISMA Diagram



Together, a total of 35 countries and 1 network were identified to have aHTA methods, but only the 20 countries (15 from grey literature + 5 from published) and EUnetHTA members included had aHTA methods which we could report on in detail (n=21/88). These are depicted in Figure 2, with all countries with detailed aHTA methods in blue, and those without detailed methods in yellow.

A full list of the papers included is in Appendix 5.

Figure 2: Countries using aHTA



Triggers of aHTA methods

aHTA is used differently in different settings. However, we identified three recurring characteristics that trigger the use of aHTA methods, enabling analysts to balance the need for evidence with the consequence of making the wrong decision. These include urgency (n=17), certainty (n=7), and low budget impact (n=5) (Table 1). Importantly, how these triggers are defined vary across jurisdictions.

Table 1: Triggers of aHTA methods

Country/Network	Urgency	Certainty	Low budget impact
Belgium	x	x	
Bulgaria	x		
Canada	x		
Chile	x		
Croatia	x		
Denmark			x
England		x	x
EUnetHTA	x		
France	x		
Hungary	x		
Ireland	x		

Malaysia		x	
New Zealand	x	x	x
Philippines	x		
Romania	x		
Scotland		x	x
Serbia	x		
Singapore	x	x	x
Slovakia	x		
South Africa	x	x	
Spain	x		
Total	17	7	5

aHTAs supports questions that policy makers need answered urgently or efficiently. This includes questions about procurement and clinical practice in Belgium; essential medicines listings in South Africa; subsidies for medical devices and diagnostics in Singapore; and public health emergencies in the Philippines, and specifically COVID-19 in France(26–31). In some countries, such as England, Denmark, and Scotland, urgency is not used as trigger of aHTA, perhaps in lieu of using the other two triggers described below, certainty and low budget impact.

Certainty captures technologies for which the research question is simple; evidence is certain; or cost-effectiveness is likely. Single technologies or simple decision problems are common in aHTA(26,30,32–34). For example, Malaysia's 'mini-HTA' reviews single technologies for the Ministry of Health(32). For technologies that have relatively certain and robust clinical and cost data, aHTA is more likely(29,30,35–37). For example, expediting Singapore's medical technology and drug and vaccine evaluations requires certainty regarding clinical and cost parameters(29,35). Additionally, technologies which are likely to be cost-effective are subject to aHTA in England's fast-track appraisal and Ireland's rapid review (RR)(37,38).

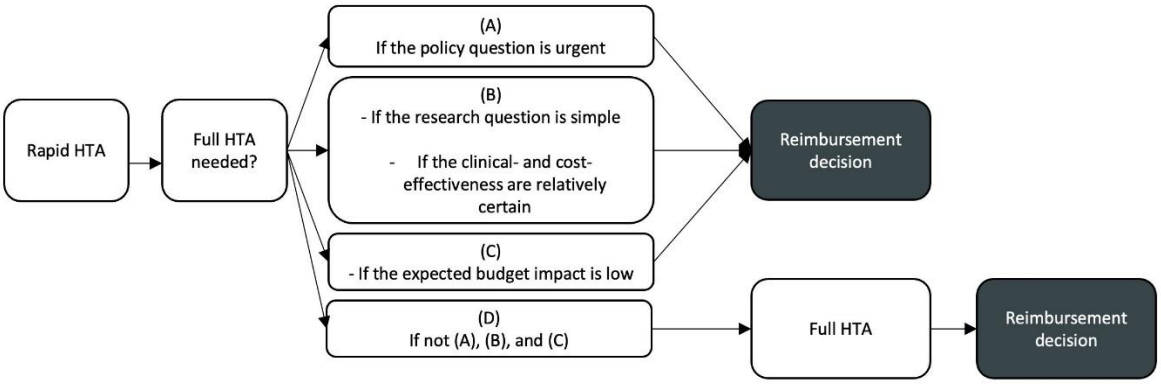
Finally, aHTA is used for technologies with an expected low budget impact, and thus with a lower consequence of decision error. This includes technologies implemented on a small scale in Denmark, or those expected to have an equivalent or lower cost than their alternative in Scotland(29,35–40).

Using a combination of these triggers, some countries apply rapid HTAs first, and HTA practitioners then decide whether full HTA is needed.

Examples include Ireland, where all medicines undergo an initial RR. Those with higher costs relative to potential comparators or with questionable comparative efficacy or value-for-money are subject to full HTA(41). New Zealand has varying levels of rapid cost effectiveness analysis (CEA). Practitioners conduct further analysis based on time required, expected budget impact, certainty of results, available information, and available resources for analysis(36). In South Africa, an initial RR is completed. Additional targeted analyses are done if there is significant uncertainty related to clinical effectiveness, cost, cost-effectiveness, or other factors(30). In the Philippines, clinically non-inferior technologies are only subject to cost-minimization analysis and budget impact analysis (BIA), whereas clinically superior technologies are routed to full CEA and BIA(42). And England's interventional procedure method refers a research question to systematic review if the evidence base is too large, the procedure may result in serious adverse events, or the procedure has more than one indication or employs more than one technique(43).

Figure 3 draws on triggers used in England, Ireland, New Zealand, Scotland, and Singapore into a single illustrative 'iterative HTA' process of how a country might sequence an aHTA and use these triggers to determine if full HTA is needed. It is possible that not all countries would use all three triggers simultaneously, and thus this iterative process should be adapted for different contexts.

Figure 3: Iterating aHTA

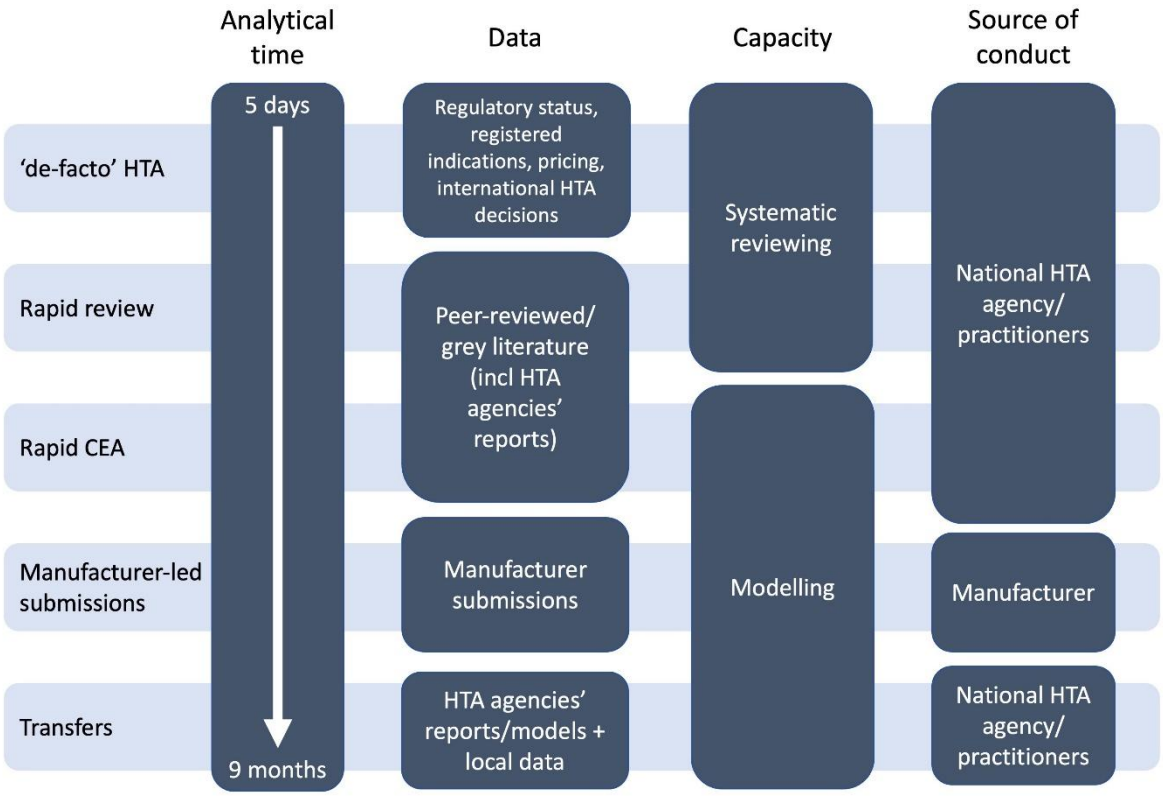


This iteration can be used to support improved efficiency in decision making. For example, a review of ten years of Ireland's RR showed that half of medicines were subject to full HTA and the other half to aHTA. If all drugs had been subject to full HTA, 15,000 more appraisal days would have been required(44).

Types of aHTA

We identified five types of aHTA methods: RR, rapid manufacturer submissions, transfers, rapid CEA, and de facto HTA. These are briefly summarized in Figure 4. This is not meant to be definitive but rather to provide a framework to illustrate broad differences between the types. More details can be found in Appendix 6 and Supplement 1.

Figure 4: Characterization of aHTA methods identified



Rapid Review

'Rapid review' (RR) reviews and synthesizes HTA results from other contexts.

RR was originally mentioned in the literature in 1997(45). It often refers to rapid methods for systematic reviews, but it is also commonly applied to HTA(16). Reviews of RRs indicate that there is vast heterogeneity in their application(33,46). Nonetheless, typical adaptations include narrowing research questions, number of databases, data abstraction and synthesis; using a single reviewer for screening; and omitting analysis of bias and quality(47).

RRs can inform multiple decisions. They provide information on medical, surgical, and dental technologies to healthcare decision makers(32,48–51). They also inform inclusion on the national formulary, essential medicines lists, and standard treatment guidelines(30,42,43).

Methods for RR were found in Belgium(26), Canada(48–50), Chile(52), Denmark(53), France(54), Malaysia(32), Philippines(42), South Africa(30), Spain(31,51), and England(43). While referred to as 'rapid', the time required ranges widely. A summary of abstracts in Canada takes five days, while an appraisal of interventional procedures in England takes nine months(43,50).

Rapid manufacturer submissions

Rapid manufacturer submissions require manufacturers to drive the HTA analysis, which is then critically appraised.

This typically requires manufacturers to submit information on clinical effectiveness, cost-effectiveness (often including a model), and expected budget impact(29,35,37,55–57). It is used to make decisions about whether to reimburse new drugs to market, or to determine whether full HTA is needed. Indeed, full HTA processes also use manufacturer submissions. However, *rapid* manufacturer submissions are a specific form of aHTA method used by agencies that rely predominately on the manufacturer's evidence. It is only triggered if the technology meets specific criteria such as certainty and low expected budget impact (e.g. less than $1-2 M per year)(29,35,38,58). Countries that employ rapid manufacturer submissions include Denmark(55), Ireland(56), Scotland(57), Singapore(29,35), and England(37).

Transfers

Transfers use a structured process or checklist to determine and guide the transfer of evidence from one jurisdiction to another.

There are many frameworks for transferring HTA evidence, all designed for slightly different purposes(59). This is different from generalizability, which adopts an existing HTA from another jurisdiction without adjustments. Studies are often evaluated for their quality, transparency, level of reporting, and local relevance(59). Then they can be transferred locally using a combination of global data on transferable parameters (e.g. relative effectiveness and utility values) and local data on less transferable parameters (e.g. baseline disease risk, unit costs, and resource use)(60).

Transfers are used to inform reimbursement or coverage decisions, and price negotiations and decisions(61). The European Network for HTA (EUnetHTA) has a detailed Adaptation Toolkit that can be adjusted for individual countries, such as Croatia(62,63).

Rapid cost-effectiveness analysis

Rapid CEA builds basic economic models using opportunistically sourced or rapidly collected local data.

In contrast to RRs, it requires building a de novo model, and in contrast to rapid manufacturer submissions, modelling is done in-house rather than being outsourced to pharmaceutical companies. Rapid CEA is used to inform inclusion on essential medicines and immunization lists(30,36). Two rapid CEA methods were found in New Zealand and South Africa(30,36).

De facto HTA

De facto HTA varies in scope. Generally, it reviews local and international regulatory status, registered indications, drug prices, and/or clinical effectiveness, costs, and cost-effectiveness from other HTA agencies.

Documentation of this approach is solely focused on medicines. It has also only been used as a rapid screening procedure for manufacturer submissions, to decide what further information is needed to inform medicines reimbursement.

Methods for de-facto HTA were identified in Romania and called by the same name(64,65). A similar approach called a 'balanced assessment system' was tested in Bulgaria, Hungary, Serbia, and Slovakia(66). These are the only methods found which have not been institutionalized by HTA agencies; as a group they have faced criticism regarding whether they adequately address transferability issues(67,68).

Strengths and weaknesses of aHTA

Strengths and weaknesses of aHTA methods were assessed in the 29 peer-reviewed papers using systematic review (n =2), literature/aHTA report review (n=15), systematic survey (n=4), or expert opinion of co-authors (n=8).

Overwhelmingly, the most cited strength of aHTA was that it was faster than full HTA – faster conduct and faster decisions means faster access to care for patients and market access for manufacturers(38,44,61,69–74). Further, aHTA is popular among decision makers because it responds to their needs. In Canada, hundreds of them are requested annually(10,66,75). RRs were viewed as having similar results to systematic reviews(34). Transfers were viewed as reducing duplication and variability across settings(31,67,73,76). Rapid manufacturer submissions potentially encourage reduced prices to avoid full HTA(38). Both transfers and rapid manufacturer submissions were considered more 'efficient' by optimizing agency resources to focus on select full HTAs(38,44,67,72).

All methods were found to be heterogenous and lack standardized guidance(34,46,55,73,77–79). Even the elements of analysis included (modifications to full HTA evaluation of safety and efficacy; cost-effectiveness; and budget impact) vary between aHTA methods and within them, between countries.

RRs are generally inconsistent in definition, methods, and application. Reporting of methods is often inadequate or not transparent(33,46,55,79,80). This makes it difficult to distinguish a good RR from a poor systematic review(47). Additionally, quality of the studies included is often not

assessed(33,69,74,81). There is no consistency in measuring or reporting uncertainty of the information in RRs, which risks making unreliable conclusions(33,82). While there is a clear trade-off between rapid advice and losing detail from a more comprehensive method, there is no quantified understanding of this trade-off. Thus, there is no guidance on the consequences of aHTA which could significantly impact health systems' budgets and patients' health(10,74,82,83).

Cited obstacles to transfers included differences in practice patterns or standard of care; lack of applicability due to differences in gross domestic product; and poorly reported studies(61). Reliance on rapid manufacturer submissions were generally found to not be as fast as expected in England(70,84), and not transparent in decision making in Ireland and Denmark(38,55).

Discussion

The use of aHTA is widespread; of the 88 HTA agencies and networks we reviewed globally, 35 reported using aHTA and of those, 21 had aHTA documentation which we could report on in detail. The majority of these exist in high-income countries (HICs) (n=15/21). Most aHTA methods improve the speed of results available to decision makers, and are triggered by urgency, certainty, and low budget impact. Some countries use an 'iterative' HTA approach to decide whether it is cost-effective to do a full HTA or whether a reasonable conclusion can be drawn in its absence. aHTA can be fast and efficient, useful for decision makers, and reduce duplication. However, it varies in methods and which technologies it applies to, has limited transparency in reporting and quality, and has limited measurement of uncertainty.

The importance of aHTA for all HTA systems

aHTA has its critics. There is a concern that aHTA could challenge the perceived 'gold standard' of HTA. Some might argue that the gold standard from an evidence perspective is full HTA with the best possible data giving the most precise and locally relevant evidence. However, as with the whole health sector, there is a limited budget for HTA, and there is an opportunity cost associated with full HTA. The triggers

identified demonstrate that there are instances where aHTA is appropriate and can supplement or replace full HTA to maximize population health more efficiently. It is critical that aHTA is used when it is appropriate; used inappropriately, it carries the risk of creating a veneer of credibility while potentially stymieing broader establishment of HTA and priority setting.

The need for aHTA is particularly acute in nascent HTA systems. Many countries seeking to achieve UHC are working to use HTA methods to prioritize entire health benefits packages (HBPs). This can affect large-scale allocative efficiency gains (e.g. Ethiopia(85)). However, doing full HTAs for tens or hundreds of interventions further exacerbates the challenge in balancing policy makers' decision timeframes and analytical rigor. HBP exercises could benefit equally from aHTA methods, but likewise, the methods lack categorization. This limits their conduct to HTA experts making pragmatic judgments about how to ensure the methods are maximally efficient.

Advancing aHTA development

Further developments of aHTA should focus on ensuring the efficiency and iteration of HTA methods, avoiding duplication, and making the best use of existing evidence.

There is a need to determine when aHTA is appropriate, and which method to use. Work could be done to build on existing iterative approaches, routing topics that meet certain triggers to aHTA or full HTA. It could articulate which technologies should be subject to which aHTA method. It could also explore additional triggers beyond those identified here. For example, we would have expected very high-cost interventions with limited clinical benefit as good aHTA candidates, though this criterion was not found in the literature. Additionally, we would have expected low technical capacity or capacity constraints in general to be other triggers, but we also did not find this in the literature. This could be summarized in a locally tailored version of Figure 3.

Additionally, better clarity on the aHTA methods articulated here is required for its replicability. For example, while we defined 'rapid CEA' as an approach that builds de novo models using pragmatically sourced data, a rapid CEA could theoretically also adapt existing models, but we did not find evidence of that in the literature reviewed. This could be done by drawing on experiences of aHTA practitioners from normative bodies including HTA agencies and networks.

Finally, more consideration should be given to where aHTA is conducted and what evidence it draws on. Common reference countries for aHTA practitioners include the United Kingdom, Australia and Canada(61), but these are not representative health systems. Newer HTA agencies may seek to source evidence from their respective geographic regions.

Limitations

This paper sought to systematically categorize aHTA methods. However, because aHTA is a new term, the definition itself is a limitation. The definition we presented in the introduction is a proposed revision to the existing definition which guided our search in the methods. It draws on the findings of this review to add the dimensions of analytical time, data, capacity, and source of conduct as the key characteristics of aHTA. These distinguish it from rapid HTA to highlight that it is about more than just time. Nonetheless, it would benefit from consultation with wide-ranging experts in the same way re-defining HTA was done(5).

To develop a taxonomy of aHTA methods, it needed to be informed by well-defined methods with enough detail for categorization. This was easier for RR, where systematic reviews have been done to define them and their characteristics(47), while there was less consistency in reporting the other types. We did not identify names a priori but have tried to reflect as best we can the names found in the literature. While our taxonomy may not be perfect, it is a first step to bucketing aHTA methods into broad categories so that they can be replicated and reported consistently.

Further, categorization relied heavily on the grey literature, which was limited to HTA agencies' websites, and to methodological guidance rather than applied papers. Agencies were not contacted, so some guidance may be outdated. We may have also missed aHTA methods if only applied papers have been published or, indeed, have not been published at all. Disproportionately, established HTA agencies in HICs had detailed guidelines, so our results are biased towards their practice. We were unable to capture the nuances of the 14 other countries mentioned to conduct aHTA including Argentina, Australia, Brazil, Colombia, Germany, Kazakhstan, South Korea, Mexico, the Netherlands, Poland, Switzerland, Taiwan, Thailand, and Uruguay(34,46,61,64,76,77,79,83). They may have aHTA methods that vary from our review.

The published literature search was focused on triggers, strengths, and weaknesses of aHTA, alongside more details on methods. The former were difficult to extract as many papers were descriptive in nature. Additionally, the search combined the concepts 'HTA' and 'rapid'. We therefore may have missed details on rapid CEA. However, because all CEA is somehow 'adaptive' and we were seeking to only capture detailed aHTA methods, we justified limiting the approach in this way. Likewise, we excluded papers on the history of HTA which could include the use of aHTA. This body of literature is substantial and would warrant its own review. The citation search identified several papers refining the methods for RRs which we excluded due to saturation of information.

Finally, we are aware of protocols and applications of aHTA-related methods which have been undertaken in various settings. These include for example, the hospital-based HTA, mini HTA, and horizon scanning methods that we excluded, as well as other more newly developed methods such as 'living HTA' 'proportionate HTA' (86,87). While the design of our review focused on national approaches documented in HTA guidance and the grey literature and thus did not detail these approaches, exploration of their features may be warranted and helpful in further developing aHTA.

Conclusion

Decisions in the health system will be made regardless, but implicit rationing will occur unless explicit methods are employed. aHTA is used widely but is poorly defined; it must be better established to support the overall efficiency of any country's priority-setting system, and particularly nascent HTA systems.

Acknowledgements

The authors would like to thank Marit Johansen, from the Norwegian Institute of Public Health (NIPH) who supported the development executed on the published literature search and strategy. Additionally, Diana Diaz-Guzman, an independent consultant assisted with review and extraction of Spanish-language literature.

3.4 Epilogue

This chapter characterizes existing aHTA methods in five categories: de facto HTA, rapid review, manufacturer led submissions, transfers, and rapid cost-effectiveness analysis. It also lists some of the common triggers for their use, including urgency of policy decisions, certainty in the evidence base, and low budget impact. Characterizing aHTA methods here is a first step towards better standardization, but there remains heterogeneity within and between the methods. Each is done in a slightly different way, likely because they are context specific. Additionally, the relatively high proportion of rapid review practice in countries compared with other aHTA methods suggests some preference for this method.

As policy conversations in Rwanda started shifting towards the HBP, these results sparked my own reflections about which of these methods might be able to be applied to multiple interventions at once as part of sectoral analyses, and how analysts should select among them. For example, I characterized Canada's Rapid Response Service as a 'rapid review', which is a well-established method in Canada for single interventions. This could easily be transferred to an assessment of multiple interventions, as the methods rely on quick reviews of secondary literature. I also included the UK's 'single technology appraisal' as a 'manufacturer-led submission' method, where the agency critically appraises manufacturers' analysis and has done so for many years. A manufacturer-led submission is less likely to be used for an assessment of multiple interventions at once. Different manufacturers would submit analyses for different interventions, and countries using them would need methods and capacity in place to critically appraise these submissions.

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Chapter 4: Leveraging global cost-effectiveness evidence: a framework for selecting methods for health benefits package design

4.1 Prologue

Chapter 4 builds on Chapter 3 by applying aHTA principles to HBP design, selecting the assessment methods for cost-effectiveness. This fills a gap, reflecting on the incremental methods featured in Chapter 3 and considering how they can be used for sectoral priority setting methods used to assess cost-effectiveness for HBPs.

The impetus for this chapter was Rwanda launching a Ministerial Instruction to prioritize multiple interventions at once as part of the CBHI's health benefit package design. This was partially informed by the Ministry of Health's reflections on the work in Chapter 2: that making one decision for one intervention was not sufficient to meet the needs of policy makers in Rwanda. The Ministry was under pressure to improve the financial sustainability of the CBHI scheme and had a long list of potential topics for prioritization. While some of them were quite narrow, like dialysis for kidney conditions, others were broad, including cancer; chronic conditions; prevention and treatment of diabetes and hypertension; and assistive technologies. These efforts in Rwanda were likely to need faster methods to evaluate multiple interventions at once.

Beyond clarifying methods, the work in this chapter was intended to facilitate the local selection of aHTA methods. Many tools have been developed by technical assistance providers and global health

organizations to support prioritization of HBPs and assess cost-effectiveness of multiple interventions. There is a risk that cost-effectiveness methods are selected in a supply-driven way, based on whichever method is embedded to a technical assistance provider's tool. In this chapter, I sought to shift the locus of assessment design driven by supply, to one focused on demand to support local decision-making. The paper aimed to provide a framework to review the global tools based on local context.

In Chapter 4, I conducted the scoping review and completed extraction; designed and executed the survey of HBP practitioners; conducted the analysis; drafted and revised the paper; presented the work at iHEA 2023; and submitted to the International Journal of Health Policy and Management (May 2024). The full author contributions for this paper are included in the research cover sheet.

4.2 Cover sheet

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2100817	**Title**	Mrs
First Name(s)	Cassandra		
Surname/Family Name	Nemzoff		
Thesis Title	Methods, application, and risk of 'adaptive' health technology assessment		
Primary Supervisor	Anna Vassall		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	International Journal of Health Policy and Management
Please list the paper's authors in the intended authorship order:	Cassandra Nemzoff, Sedona Sweeney, Rob Baltussen, Anna Vassalll
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	For this paper, I conceptualized the framework, conducted the literature review and survey, wrote the first draft of the manuscript, and revised the manuscript based on co-author feedback. All co-authors provided feedback on the draft of the framework and subsequent manuscript drafts.

SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	1 September 2024

4.3 Paper

Selecting Cost-Effectiveness Methods for Health Benefits Package Design: A Systematic Approach

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Abstract

Background: Cost-effectiveness is a common prioritization criterion in health benefits package (HBP) design. However, to assess cost-effectiveness is a time- and data-demanding process, so most HBP exercises rely wholly or partially on global evidence. Extensive investment has been made to develop analyses, models, and tools to support cost-effectiveness analyses (CEAs) for HBPs. However, little attention has been paid to how national HBP assessors should both understand and select cost-effectiveness methods and estimates between these different sources, and any locally available evidence and expertise. A structured national process to review and select assessment methods is essential for ensuring the accuracy, ownership, and transparency of HBP design. This can be supported by 'adaptive' health technology assessment (aHTA) principles, which focus on making structured methodological choices based on the time, data, and capacity available. The objective of this paper was to apply aHTA framing to CEA methods selection for HBPs, and to make recommendations on how countries may consider making these choices going forward in a systematic way.

Methods: To apply aHTA to HBP design, we first reviewed the definitions and categorization of different aHTA methods. We then conducted a scoping review of previous HBP assessments to understand how CEA methods used in HBPs fit into the aHTA framework, and a follow-up survey of authors to fill gaps in their time, data, and capacity requirements. Results of the literature review and survey were interpreted and narratively synthesized.

Results: Our synthesis of aHTA methods is rooted in evidence quality and the requirements of country-specific HBP processes and capacity. We found that previous HBP assessments used four aHTA methods: expert opinion (n=3/20), review (n=12/20), transfer (n=6/20), and new model (n=2/20). Some countries used more than one method simultaneously. The literature review and survey responses found that aHTA methods in HBP prioritization take between 1-13 months; require different data sources depending

on the methods used; and generally, require capacity in health economics, medicine, public health, and cost-effectiveness modelling. We supplement our reporting with a discussion of key considerations for methods selection.

Conclusion: Trading off time, data, and capacity needs for different cost-effectiveness assessment methods can help to support structured, local design of HBP assessments.

Background

Many countries design or refine their health benefits packages (HBPs) for either government-funded or social insurance as part of the road to universal health coverage (UHC). This is often done using health technology assessment (HTA), a process to facilitate evidence-based priority setting(1). Cost-effectiveness is typically a central criterion in this process with the aim of ensuring HBPs improve allocative efficiency(2,3). However, the conduct of a *de novo* cost-effectiveness analysis (CEA) on a single intervention can take up to a year to complete(4). In the context of HBP design, which sometimes requires sourcing cost-effectiveness ratios (CERs) for more than 100 interventions at a time, this is not feasible. Instead, 'adaptive' heath technology assessment (aHTA) methods can be applied by employing global evidence on cost-effectiveness to adapt for time, data, and capacity constraints(5).

Various databases, tools, and resources of evidence, also known as 'global public goods' (GPGs), have been developed to make accessible and, in some cases, synthesize the global evidence. These include the Tufts CEA registry, a database that synthesizes more than 12,000 CEAs; WHO-CHOosing Interventions that are Cost-Effective (WHO-CHOICE), a set of models to evaluate cost-effectiveness for 20 disease areas; Disease Control Priorities (DCP), nine volumes reporting systematic reviews on the evidence for cost-effective interventions for low- and middle-income countries (LMICs); and more recently, meta-regressions, which predict incremental cost-effectiveness ratios (ICERs) for many countries at once using regression analysis based on existing CEAs(6–11). However, there is little guidance on how to select which GPG to use or the pros and cons of each, which could be facilitated by clearly considering the trade-offs in time, data, and capacity requirements of different methods.

Centering the selection and use of CEA estimates within national assessment teams, rather than determined by the producers of specific GPGs, is not only important for sourcing the best available estimates. It is equally important for supporting the institutionalization of legitimate, transparent priority

setting processes(12). Like many global health projects(13), the current GPGs are predominately produced by development assistance agencies or non-governmental organizations. Currently efforts are being made to regionalize such resources, but it is possible that methods selection may be driven by technical partners who are producers of specific GPGs. While these tools and technical assistance may support capacity strengthening, it is important that the selection process for each CEA estimate remains centered and driven by the local decision context and actors, and not predetermined by whichever funder or group is a technical partner. We propose that this could help to ensure local ownership and facilitate the uptake of results.

The inspiration for this work was co-authors' experience working with policy makers and stakeholders involved in HBP design for the first time, who articulate which interventions they want to prioritize, but may need help to articulate how they might be able to prioritize them by outlining options clearly and articulating trade-offs between them. The objective of this paper was thus to apply aHTA framing to CEA methods selection for HBPs, and to make recommendations on how countries may consider making these choices going forward in a systematic way.

Methods

Our methods were carried out in three steps: 1) defining aHTA and its characteristics; 2) conducting a scoping review and survey of existing CEA methods for HBPs to articulate aHTA methods used in HBP design and 3) aligning the scoping review and survey to the aHTA framework.

Step 1 – Defining adaptive health technology assessment and its characteristics

Our starting point was the concept of aHTA, which is an approach to HTA that adapts for time, data, and capacity constraints and makes use of evidence from other jurisdictions where possible(5). Time refers to the analytical time for assessment; data includes all primary or secondary data inputs required for

assessment; and capacity reflects the technical and applied skills needed from an assessment team to conduct assessment.

A recent systematic review characterized the aHTA methods undertaken by global HTA agencies into a framework with five methods. These include de-facto HTA, which collates key characteristics of an intervention including registration, pricing, and international HTA decisions; rapid reviews, which review and synthesize existing literature; rapid manufacturer submissions, which review evidence produced in manufacturers' dossiers; transfers, which use existing transferability frameworks to transfer economic evaluations from one jurisdictions to the other; and rapid CEA, which conduct de novo CEA using pragmatically sourced data. Overall, aHTA can reduce the analytical time needed for analysis and has the potential to improve the efficiency of the priority setting process(5).

These aHTA methods were defined based on HTA agencies' methods which typically conduct incremental analyses that inform coverage decisions for one intervention at a time. However, HBP assessments are considered 'sectoral analyses' because they analyze and prioritize many interventions at once. Assessments for HBPs must also adjust for time, data, and capacity constraints, are increasingly adopting HTA-like procedures(14). Indeed, the aHTA systematic review mentions that there is a need to better categorize aHTA methods for HBP design(5). We therefore sought to better understand how aHTA principles and methods have been applied in HBP design.

Step 2 – Scoping Review and Survey

Scoping review

A rapid scoping review was designed to identify cost-effectiveness assessment methods used for HBPs globally. The search combined the concepts 'health benefits package', 'cost-effectiveness', and 'assessment' (Supplement 1), with the aim of mapping them to the aHTA-based framing outlined in Step 1. Our search was run in MEDLINE (via Ovid) in July 2022, and re-run in December 2023. Papers

identified through snowballing and those known to co-authors were also reviewed for inclusion. This approach achieved saturation, in that the search is replicable, and further searching would obtain no additional unique methods for assessing cost-effectiveness in HBPs(15).

Papers that reported the assessment of cost-effectiveness in the context of HBP design or prioritization from individual countries or regions were included. To eliminate outdated methods, we included any papers from 2010 to present. CEAs for a single intervention; systematic reviews or broad overviews of cost-effectiveness methods; and commentaries or papers focused exclusively on lessons learned were excluded. Extraction for each paper was completed in Microsoft Excel by the first author and was split into three parts: methods; time and capacity; and data.

Methods extraction included the name of the method, a summary of how cost-effectiveness was assessed, and how many interventions were assessed. For methods that required transferring CEA estimates from other countries, criteria used to determine transferability were documented. We used the Welte knock-out criteria as a guide, which include geographic relevance, relevance of the intervention and comparator, and quality(16). For methods that required re-parameterizing CERs (e.g. with unit cost, resource use, effect size, burden of disease), any adjustments made to CERs to account for bias from this approach were documented.

Time to complete the assessment was documented for each method as described in the paper. Capacities needed were captured using the international Decision Support Initiative (iDSI) HTA capacity assessment questionnaire as a guide(17). This included listing any university-level skills reported (health economics/econometrics, economics, clinical/medical, pharmacy, epidemiology, public health) or applied skills (cost-effectiveness analysis, budget impact analysis, clinical evidence synthesis, policy analysis, HBPs, ethics and values in policy decision making, evidence to policy translation) reported. Finally, data included a list of global or national sources of cost-effectiveness studies or parameters used.

Survey of HBP practitioners

Approaches to estimating CEAs, particularly their data, time, and capacity requirements were not fully described in the literature. A survey of first authors of the HBP papers from the scoping review was conducted to complement the literature.

The survey was split into the same three sections as the data extraction. The methods section sought further detail on the methods used, e.g. the number of interventions assessed; whether the scope of analysis was a full or partial HBP; and why the method was selected. It also filled gaps on which of the Welte transferability criteria were used, whether any additional transferability criteria were used, and whether any adjustments were made if analysts recalculated CERs to reduce bias.

Surveys further requested more detail on how many people conducted the assessment and how much analytical time was needed. The iDSI capacity assessment questionnaire was again used for respondents to indicate all capacities of the assessment team. Questions about data provided a full list of potential data sources collated from the literature review to validate the breadth of possible data that could be used for each method.

First authors of the papers identified in the scoping review were requested to fill in the survey in Google Forms. Where clarity was needed, brief emails were sent in follow-up. Simple descriptive statistics were used to analyze the quantitative survey data, while qualitative data was narratively summarized.

Step 3 – Aligning the scoping review and survey to aHTA framework

Finally, we mapped our findings against the aHTA frame, adapting for new categories of methods where necessary. Our findings are summarized in a table of aHTA methods for cost-effectiveness in HBP design. Columns are split by method, and rows describe the methods' characteristics, time and capacity requirements, and data used.

To define the methods columns, we compared the definitions of the five aHTA methods from the systematic review to the names and summaries of methods extracted from the HBP papers. Where possible, we matched aHTA methods to HBP methods. If the HBP method did not match the five categories, we added a new category based on the most common name used in the literature. If an aHTA method was not reported in the HBP literature, we excluded it.

The first block of the table includes a summary of each method, drawn from the literature and the survey. This includes a brief explanation of the method; potential types of assessment; and whether transferability criteria or CER adjustments are used.

The next rows report time and capacity requirements, and potential data sources for each method. Time estimates are a summary from survey responses, which assume an average assessment team of three full-time equivalent staff. Capacity requirements are listed using the pre-specified skills categories. Data sources from the HBP literature were validated with the survey and listed in the table.

Results

We included 20 papers from the peer-reviewed literature (Table 1), from which we identified four methods for CEA in HBPs: expert opinion, review, model adaptation, and new model. Some of the 20 papers reported using more than one method concurrently. Additionally, we received 13 completed surveys from authors of the peer-reviewed literature, covering 16/20 papers; some respondents co-authored multiple papers from the same country.

Table 1: Papers included

Paper title	Country	Type	# of interventions	Interventions per method	Team size	Time
The Use of Evidence-Informed Deliberative Processes for Health Insurance Benefit Package Revision in Iran (2022)	Iran	Partial HBP	9	Review: 7 New model: 2	13	3-6 months
Revision of Malawi's HBP - a critical analysis of policy formulation and implementation (2024)	Malawi	Full HBP	305	Review: 141 Expert opinion - 164	10	1-3 months
Using allocative efficiency analysis to inform HBP design for progressing towards UHC - proof of concept in countries seeking decision support (2021)	Armenia	Full HBP	135	Review: 135	4	1-3 months
Using allocative efficiency analysis to inform HBP design for progressing towards UHC - proof of concept in countries seeking decision support (2021) Report on developing the Liberia Universal Health Coverage Essential Package of Health Services (2021) Lessons from the development process of the Afghanistan integrated package of essential health services (2023)	Armenia, Cote d'Ivoire, Zimbabwe	Full HBP	100-245	Review: 74 Expert opinion: 171	2	<1 month
Assessing global evidence on cost-effectiveness to inform Pakistan's Health Benefits Package (2024)	Pakistan	Full HBP	170	Review: 170	5	3-6 months
Contextualization of cost-effectiveness evidence from literature for 382 health interventions for the Ethiopian essential health services package revision (2021) Generalised cost-effectiveness analysis of 159 health interventions for the Ethiopian essential health service package (2021) Revision of the Ethiopian Essential Health Service Package: An Explication of the Process and Methods Used (2020) (Survey responses n= 2)*	Ethiopia	Full HBP	1018	Review: 382 Model adaptation: 159 Expert opinion: 477	3	3-6 months
Kazakhstan - The use of evidence-informed deliberative processes for health benefits package design in Kazakhstan (2022)	Kazakhstan	Partial HBP	25	Review: all	5	1-3 months
Supporting the development of a health benefits package in Malawi (2018)	Malawi	Full HBP	67	Review: all	2	<1 month
Evidence-Informed Update of Argentina's Health Benefit Package: Application of a Rapid Review Methodology (2022)	Argentina	Full HBP	164	Review: all	5	9 months -1 year
Cost-Effectiveness of Interventions to Improve Maternal, Newborn and Child Health Outcomes: A WHO-CHOICE Analysis for Eastern Sub-Saharan Africa and South-East Asia (2021)	Eastern SSA + SE Asia	Partial HBP	37	Model adaptation: all	2	> 1 year
Priority Setting for Health Service Coverage Decisions Supported by Public Spending: Experience from the Philippines (2018) Reflections on the use of the World Health Organization (WHO) OneHealth Tool: Implications for health planning in low- and middle-income countries (LMICs) (2018)	Philippines	Full HBP	48	Model adaptation: all	20	<1 month
Supporting the revision of the health benefits package in Uganda a constrained optimization model (2023)	Uganda	Full HBP	120	Review: all	3	1-3 months

**Ethiopia reports 3 separate papers: the first uses the literature to do a rapid review of cost-effectiveness of 382 interventions; the second adapts WHO-CHOICE models for 159 interventions; and the third explains the HBP prioritization process as a whole, including these two CEA methods as well as the use of expert opinion to fill gaps.*

The narrative synthesis of our detailed findings is summarized in Figure 1 and elaborated below. It includes an overview of the four resulting methods; time and capacity required for each; data requirements; and example countries. The full data extraction from the literature and all survey responses are included in Supplement 1.

Table 2: Methods for cost-effectiveness in health benefits package design

	Expert opinion	Review	Model adaptation	New model
Methods	Elicit expert opinion on CERs	Review and select published/estimated/ synthesized CERs using pre-specified transferability criteria*	Estimate CERs inputting context-specific data to existing models (e.g. WHO-CHOICE) and employing specific methods for reducing bias*	Conduct de novo cost-effectiveness modelling for each intervention
Scope	Assessment of full HBP, partial HBP, or few interventions**			Assessment of few interventions
Time***	1 – 3 months	1-10 months	1 – 8 months	7-13 months
Capacity	HBP design; clinical/ medical expertise; public health expertise	HBP design and evidence synthesis	HBP design and health economics/econometrics, including cost-effectiveness modelling and budget impact analysis	
Data	Expert opinion	Peer-reviewed literature (MEDLINE, EMBASE, PubMed); meta-analyses; Tufts CEA registry; DCP; WHO-CHOICE regional estimates; other countries' HBPs	Local, regional, global, and default unit costs, resource use, coverage, burden of disease, effectiveness	Local unit costs; local resource use; local coverage rates; local, regional, and global effectiveness evidence
Countries using these methods	Armenia, Cote d'Ivoire, Ethiopia, Liberia, Zimbabwe	Argentina, Armenia, Cote d'Ivoire, Ethiopia, Ghana, Iran, Kazakhstan, Liberia, Malawi, Pakistan, Philippines, Uganda, Zanzibar, Zimbabwe	Ethiopia, Philippines, Sub-Saharan Africa/Southeast Asia	Iran, Thailand

**Specific transferability criteria and methods for reducing bias are elaborated in the text*

***Assessment of full and partial HBP could include a broad set of interventions across conditions, sometimes up to 500. Assessment of few interventions typically includes one or a few interventions within a condition. For detail on the typology, see Baltussen et al. 2023(18)*

****The time for each method assumes an average team of three full-time equivalents for comparability; it also reflects the number of interventions assessed, where many more interventions are assessed using the methods to the left of the frame, and fewer to the right*

Acronyms: CER = cost-effectiveness ratio; HBP = health benefits package; DCP = disease control priorities; WHO-CHOICE = World Health Organization CHOosing Interventions that are Cost-Effective; CEA = cost-effectiveness analysis

Methods and Scope

We identified three methods that roughly aligned to aHTA categories: review (n=12/20), model adaptation (called 'transfers' in aHTA terms) (n=6/20), and new model (called 'rapid cost-effectiveness analysis' in aHTA terms) (n=2/20). One additional method was unique to HBPs: expert opinion (n=3/20).

We excluded two aHTA methods: 'de-facto' HTA and manufacturer-led submissions, as we did not find any evidence of these in the HBP literature.

'Expert opinion' elicits experts' opinion on the best estimate of CERs. This can be done in multiple ways. A simple approach is to set all missing CERs equal to the threshold. This was done by analysts using DCP, because the interventions included in DCP's essential HBP are considered a priority based on cost-effectiveness evidence, and thus this was deemed a reasonable assumption. Alternatively, a standard process of structured expert elicitation can be undertaken.

The 'review' method reviews and selects published, estimated, or synthesized CERs. Sources for each are further described under *Data* below. It then uses pre-specified transferability criteria to select the best CERs for the country under study. Survey responses confirmed common use of the Welte knock-out criteria in HBP design (geographic relevance, relevance of the intervention and comparator, quality), as well as preference to newer studies and similarity of health systems in some cases.

'Model adaptation' estimates CERs by inputting context-specific data to pre-existing CERs or models. To adjust CERs, analysts have re-calculated CERs using local costs; reduced all CERs by 30% to adjust for service delivery conditions; or adjusted CERs through validating pre-populated disease burden, spending, and impact. To model new CERs, context-specific data is input to existing models (e.g. WHO-CHOICE).

'New model' builds a *de novo* cost-effectiveness model or analysis, with the specific method depending on the type of intervention. This was done in both Iran and Thailand, where rapid CEAs were completed on a limited set of topics.

Importantly, the aHTA methods are not mutually exclusive. For example, gaps from review have been filled with expert opinion; review has been conducted alongside new model for a small set of select interventions; or review and model adaptation have been conducted together with gaps filled by expert

opinion. Additionally, different combinations of expert opinion, review, and model adaptation have been used for a full HBP or partial HBP, whereas new models have been built for very few interventions.

Time

The four methods vary substantially in analytical time. Many interventions have been assessed using expert opinion in one to three months, whereas one or two interventions have been assessed using new model in seven to thirteen months.

Capacity

Survey respondents indicated that irrespective of method, the most common university-level skills in assessment teams included health economics or econometrics, medicine, and public health. The most common applied skills included cost-effectiveness modelling, budget impact analysis, and health benefits packages. Our interpretation of capacities which are specific to each method are reflected in Figure 1.

Data

Data availability was the most important aspect of selecting methods according to survey respondents, in comparison to relevance and quality of data obtained; time; and capacity. It is a required input for the review, model adaptation, and new model methods. Sources of data for each are summarized below.

Review

Several databases, types of synthesized evidence, and meta-analyses are available for review. Databases offer the most comprehensive resource for CERs, whereas synthesized evidence and meta-analyses are focused on a smaller subset of interventions.

Databases used for HBPs include the Tufts CEA registry and peer-reviewed literature databases. The Tufts CEA registry offers a database of more than 12,000 CEAs. It includes studies that exclusively use quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) as measures of effectiveness, rather

than disease- or study-specific measures, to ensure comparability across interventions(6). Pre-extracted CERs and other key aspects from the CEA studies are available for download from Tufts. MEDLINE, EMBASE, and PubMed are the peer-reviewed databases most used in HBP design, and also offer non-DALY or QALY studies.

We found the most common resource for synthesized cost-effectiveness estimates for HBPs is DCP. DCP provides CERs for 218 interventions considered 'essential' for LMICs. Estimates reflect systematic reviews of global cost-effectiveness evidence, validated by hundreds of experts(19). WHO-CHOICE also offers synthesized evidence in the form of regional cost-effectiveness estimates. Values are produced for 20 disease areas and 500 interventions, using their suite of user-friendly models(20–22). While these estimates are reported in the literature as regional analyses, they are also incorporated into countries' HBP assessments. Finally, there may be existing systematic reviews of cost-effectiveness for specific disease areas that could facilitate the review of cost-effectiveness.

A new promising source of cost-effectiveness values are meta-analyses. They gather existing cost-effectiveness evidence on well-studied interventions and use statistical models to predict country-specific CERs. However, due to the demand for multiple studies to inform meta-regressions these analyses are currently only available for HPV vaccination, rotavirus, HIV, tuberculosis, malaria, and syphilis interventions(23–25).

Model adaptation/new model

For model adaptation, data sources include local, regional, or global estimates of costs, resource-use, burden of disease, and/or effectiveness. Local intervention costs can be used to re-calculate CERs. User-friendly models for this method were limited to the WHO-CHOICE modules. To model health benefits and disease burden, WHO-CHOICE offers the following modules: the tuberculosis impact model and estimates (TIME) for tuberculosis; the lives saved tool (LiST) for reproductive, maternal, neonatal, and

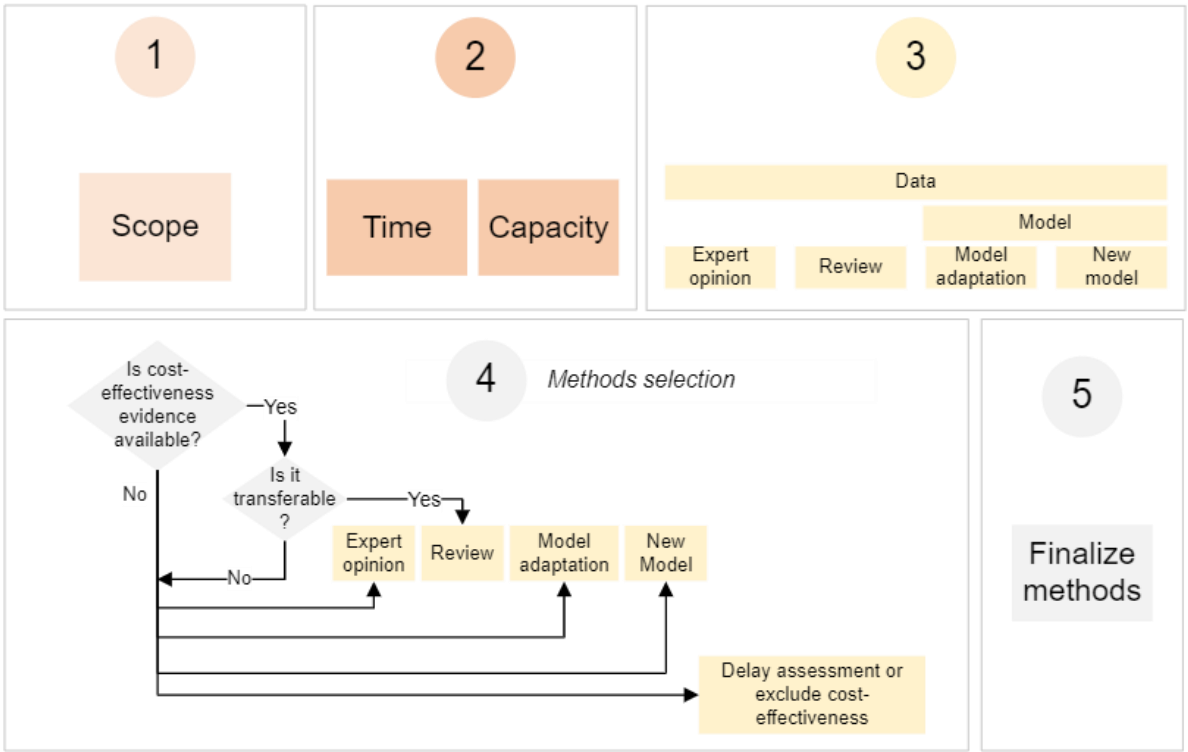
child health, nutrition, and water and sanitation; 'FamPlan' for family planning; 'OpenMalaria' for malaria; AIDS impact module (AIM) for HIV/AIDS; and the non-communicable disease (NCD) impact module. Additionally, 'DemProj' models population growth and other demographics; the 'OneHealth' tool is pre-populated with default costing estimates; and the WHO generalized CEA tool can be used to estimate new CERs.

For new models, local epidemiological models can be identified to pair with de novo cost-effectiveness models.

Discussion

Based on our findings, we have outlined several considerations that national assessment teams may wish to think about when designing HBP assessments (Figure 1).

Figure 1: Considerations for assessment design



1: Define the Scope

Whether the scope of assessment is a full HBP or partial HBP should be agreed by the assessment team(2). The number of interventions and descriptions of each should be listed. Then, it is important that analysts consider whether the interventions are aligned with the nomenclature and scope of available data sources for later mapping. For example, if the assessment will use DCP or WHO-CHOICE, analysts can review whether the alignment of interventions with these resources is possible. If not, other structures can be considered for alignment such as standard coding systems like the International Classification of Disease (ICD) and the accompanying International Classification of Health Interventions (ICHI) or the WHO UHC-Compendium(26,27). Interventions for HBPs are defined in many ways which is inherently a difficult part of HBP design, and thus mapping to existing lists and data is a critical first consideration. In many contexts, it is equally important that this alignment be integrated with the overall health system. In this way, alignment with the ICD may be preferred for connecting with billing systems which is common practice, whereas alignment to the WHO UHC-Compendium may not be equally useful because it was not designed for this purpose. The only exception is where the scope is instead an incremental analysis of a single intervention, which would not require alignment with existing data but rather would be defined using a standard scoping framework such as population, intervention, comparator, outcome (PICO)(28).

2: Time and Capacity

The amount of time available for cost-effectiveness assessment should also be considered with either the government or social insurer, as part of broader time expectations for the assessment of all criteria and subsequent appraisal. We find that the times reported from our survey appear to be quite short and may only reflect the actual CEA assessment time. It is important to consider the time for the full prioritization process including the analysis of all criteria, any changes in approach, or any potential political delays.

The capacity of the team will also be linked to the type of method which is feasible. While survey responses were consistent about technical and applied skills needed across methods, we posit that there are important variations. All methods arguably require an understanding of HBP design. For expert opinion, additional skills may be more focused on clinical, medical, or public health expertise. For review, analysis mostly requires evidence synthesis skills, such as systematic reviewing. And for model adaptation or new models, further health economics expertise is required including cost-effectiveness modelling and budget impact analysis.

The available capacity of any additional contributors to the assessment can also be considered and documented. For example, in expert opinion, there is a need for local experts willing to participate in elicitation. In model adaptation and new model, a local modeler may need to be recruited to the assessment team depending on the disease area in scope.

3: Define data and models by method

Available data and models for assessment vary considerably depending on the types of interventions being assessed. It may require some initial work to identify all stakeholders who are actors in the service area(s) to ensure a comprehensive review of data availability.

The review of data availability may comprise three components. First, an initial review of possible global data sources for review and model adaptation can be undertaken. Potential sources are listed in Figure 1, though additional sources may be available depending on the scope of analysis. Importantly, analysts may wish to consider whether global sources contain incremental cost-effectiveness ratios (ICERs) or average cost-effectiveness ratios (ACERs). In our reporting, we have intentionally referred to ‘CERs’ generally, as using ICERs or ACERs is a hotly debated topic(29). While ACERs are considered preferred for HBP design because they assume that HBP design will address the allocative efficiency of a full health

system, the global literature contains a mix of ACERs and ICERs, the implications of which should be considered by the assessment team.

Second is a review of available national data. This could include identifying available cost-effectiveness studies or data on cost-effectiveness parameters (e.g. unit costs, resource use, burden of disease, health effects) for the topic under consideration. These could be used for the model adaptation method to either recalculate CERs or to input to WHO-CHOICE modules.

Finally, it is worth exploring whether any available global or local models are available. This could include whether WHO-CHOICE modes are available for the disease being studied, and whether any national epidemiological models or cost-effectiveness models on the topics under study are available. If new model is selected as an assessment method, further identification of national and global data will be required to parameterize the model. For example, availability of data for the cost-effectiveness parameters should be reviewed, as well as methods for filling data gaps.

Beyond availability, it is also important to consider the accessibility of the global data sources, including Tufts, DCP, WHO-CHOICE, and meta-regressions. Tufts is an online database which is comprehensive and provides extracted details of more than 12,000 CEAs. While it is accessible to LMIC researchers free of charge, for other researchers there is an access fee. DCP is reported in nine free volumes online, and downloadable data on ICERs is available for the set of interventions included. However, the source of these ICERs is not well specified which limits their adaptation. WHO-CHOICE has published regional estimates in the literature, but their models for adaptation are not accessible online and require close collaboration and training with WHO colleagues. The results of meta-regressions are published in several peer-reviewed papers, though as mentioned, they are only available for a few specific diseases. Additionally, the ICD nomenclature may prove useful to countries which also use ICD for their billing

systems, whereas the UHC-Compendium is not linked to any such function and thus may have questionable applicability to a broader health system.

4: Methods selection

In reviewing the scope, time, data, and capacity, several considerations can be made for methods selection. In the first instance, the interaction between time and scope is important to consider. While a full HBP could be assessed using any combination of expert opinion, review, and model adaptation, it would be impossible to do the same using new model for the same number of interventions. If an assessment seeks to consider many interventions at once, this may automatically eliminate new model as a methodological choice.

Next, since the majority of HBP papers we identified used the review method (n=12/20), methods selection may begin by considering whether cost-effectiveness evidence is available and transferable to the national context. This requires conducting a rapid review of availability literature to document roughly what literature exists in the area, and whether the interventions appear to be relevant to local context. This is not a full 'review'. Rather, it is a quick check of the listed resources to understand approximately how many CERs are available on the topic, whether there are any studies from similar geographic contexts, and whether the interventions in those studies are similar to those being delivered in the study setting.

If the global data are broadly available and transferable, then the main method of choice may be review. The availability of cost-effectiveness evidence on the topics of analysis in each of the data sources is likely to narrow the list of data sources analysts use. If cost-effectiveness evidence is only available in one of the data sources (Tufts, DCP, WHO-CHOICE, meta-analysis, or systematic reviews), analysts can default to using this source. If cost-effectiveness evidence is available in multiple data sources, additional considerations should be made. For example, it may be preferred to maintain the simplicity of using only

one data source with the most cost-effectiveness evidence, which is likely to be Tufts or the peer-reviewed literature. Or analysts may prefer to focus on interventions and evidence which are considered by many experts to be cost-effective in low-and middle-income countries, in which case DCP is a better choice. Another consideration is whether any adjustments to CERs will be made, for which the Tufts downloadable data is helpful. For example, if local costs are available, analysts may wish to recalculate CERs using effects extracted from studies in Tufts, as was done in Malawi and Kazakhstan. If using ACERs, this would require an estimate of the local cost of the intervention, divided by the effect of that intervention reported in Tufts. Alternatively, if regional estimates of CERs are considered sufficient, WHO-CHOICE may be preferred. Finally, analysts could also create a hierarchy of evidence; for example, the small pool of meta-analyses may be reviewed first to prioritize predicted country-specific CERs, and then a review conducted of one of the other broader data sources.

If the data identified under review are not available or deemed not transferable, options include using one of the other three methods; delaying the assessment; or excluding a cost-effectiveness assessment for some interventions. In doing so, there are trade-offs. Expert opinion takes little time and only requires deciding an approach for eliciting expert opinion and convening experts. It is a tested approach to 'fill gaps' when CERs are missing in HBP assessments that analyze many interventions at once. Alternatively, a model adaptation is possible using the WHO-CHOICE modules, but this requires an understanding of or willingness to learn how to use these models. More information on the utility of these tools and others to support HBP design is reported in a recent framework on resource allocation tools(30). A new model requires far more time and substantial modelling expertise. If this is available locally, it may be a favorable option for building capacity and calculating nationally relevant estimates. However, it should be weighed against the available time and envisioned scope of assessment. If an assessment seeks to evaluate 100 interventions in less than a year, this option may not be feasible. A final option is to delay assessment or not assess cost-effectiveness for some interventions. The latter is

an alternative to filling gaps using expert opinion and has been done in some HBP assessments that used review but did not find CERs for all interventions assessed.

Additional consideration should be given to whether local decision makers will be willing to make a recommendation based on the evidence presented. They may be comfortable making recommendations based on expert opinion for the topic(s) in scope, or may prefer to wait until more detailed, nationally relevant data and analysis are available.

After exploring these considerations, a national assessment team should be equipped to compose draft assessment methods. If more than one option is available, it may be useful to summarize each option in terms of the time, data, and capacity needs.

5: Finalize Methods

Finally, agreeing the methods through consensus by a group of key stakeholders may be valuable in setting expectations for the future HBP assessment. This could include the local HBP committee, government stakeholders, clinical experts, and the assessment team. Any adjustments to the scope, time, and capacity required can be discussed and deliberated. Interventions may be assigned to different methods depending on data availability, and others may be postponed for future assessments. Depending on the perceived quality of the evidence to be used, the group could also consider how this will be reflected when the evidence is presented for appraisal.

Importantly, these are all only considerations regarding the selection of methods for HBP design, which may not fully reflect shifting dynamics in country or the prioritization process as a whole (31). Completing an HBP assessment can be facilitated by strong leadership from a government institution and/or leading agency, but also requires careful balancing of government ownership and development partner involvement, as well as building capacity of local teams to prioritize HBPs independently in the future. Thus, these considerations are likely to shift in any given context.

Summary

Our work is the first attempt to classify aHTA methods for CEA in for HBPs. It articulates four methods used in HBPs for obtaining CEA values – expert opinion, review, model adaptation, and new model – and the scope; time and capacity; and data for each.

The primary audience of this work is HBP practitioners, including academics and policy makers, in any country in need of practical guidance for selecting assessment methods. It is not meant to be definitive. Rather, it should be tested as an aid to review existing methods for cost-effectiveness assessment in HBPs in a structured way. In doing so, it could help to ensure national ownership and enable transparent methodological choices to be presented to appraisal committees. Using such an approach is also an opportunity for practitioners to reflect and provide feedback to producers of CEAs on how to design their work in a way that supports HBP design, as well as report the strengths and weaknesses of different approaches.

Through experience, the table and guidance presented here should be adapted and expanded. For example, our present work only considers transferability of existing data or adjustments made to CERs. It does not dig into deeper issues of bias, uncertainty, transparency, or risk of the different estimates from key sources. Further development of the framework could consider these issues to establish an approach for estimating the risk of making the wrong decision by using different aHTA methods, which can better inform methods selection.

It is possible that we missed some CEA methods due to focusing on what *has been* done for HBPs, but not what *could be* done. The rapid nature of our scoping review restricted us to papers labelled as HBP assessments, but we may have found additional methods if we had broadened our scope to other priority setting exercises. However, as we wanted to ensure we reflected on methods choice in the context of existing HBP resources, we consider our scoping approach to be fit-for-purpose. Moreover,

because our reporting is based on what has been done previously been done in HBPs, using the aHTA framing has not yet been fully tested in a live a policy context. Further refinement of our findings and considerations would benefit from countries that have tested our approach.

Conclusion

Reviews of HBPs have been ongoing since the 1993 World Bank report(32). While 30 years have passed, the development of resources to support CEA for HBPs has been disproportionately driven by technical partners. It is time to shift away from focusing on these resources to a nationally owned process for selecting context-appropriate methods, and it is our hope that this paper is a first step to supporting this approach.

4.4 Epilogue

The work presented in this paper reflects the HBP methods for cost-effectiveness reported in the literature alongside experience of surveyed HBP practitioners from approximately 15 countries. The scoping review in the paper found several reports of the full prioritization process and results of the assessment of many criteria in HBPs. However, few papers presented the full details on the evidence review and choices made around secondary data, or the time, data, and capacity requirements for different methodological approaches. Surveying practitioners was an effective step in filling the gaps in these details.

Most interestingly, surveys also helped to validate more unwritten rules for HBP design. For example, many HBP design processes collect local cost data, and pull secondary sources of cost-effectiveness assessments. I also uncovered a specific issue with the estimate of local effects that emerged. To estimate population wide costs and effects, many sectoral analyses do not explicitly model costs and effects separately. Costs are estimated, and analysts use ICERs to then estimate the impact of incurring those costs. There is therefore no 'transfer' or examination of the population impact to different populations (although if sub-group CERs within studies are available these may be applied). There is considerable structural uncertainty and potential substantial bias in this approach, as it does not reflect local clinical practice, or reflect population characteristics. If there is uncertainty on the transfer of cost data, that will also then increase the uncertainty in the impact estimate. Nevertheless, this is commonly done, as the feasibility of either re-modelling or conducting systematic reviews on multiple interventions' impact is hugely time-consuming task. Likewise, if CERs are missing but needed for optimizing HBPs, modelers either use 'expert opinion' or some set the CER equal to the threshold. In the latter case, setting CERs equal to the threshold effectively puts them on the decision margin which means that appraisers must debate their inclusion in the package.

The ideas presented in this chapter are not intended to be prescriptive. Rather, it provides a template for structured conversations about assessment design that can be adapted to local context. This paper is the first of its kind to suggest that methods selection be locally driven and to provide information and guidance to do so.

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Chapter 5: Cost-effectiveness of cancer interventions in Rwanda: results and lessons for health benefits package design

5.1 Prologue

Chapter 5 and Chapter 6 apply the methods identified in Chapter 4 to the assessment of cancer services in Rwanda.

To begin addressing its long list of priority topics to improve the financial sustainability of the CBHI scheme, a 2021 Ministerial Instruction set up a national HBP committee and articulated nine criteria for prioritization. Cancer was selected as a priority topic because it is a service that is in high demand reflecting the shifting burden to non-communicable diseases, and because a recent costing assessment across the health system had been done which would facilitate the costing of multiple cancers at once.

This was a unique request in the context of HBP design. The scoping review from Chapter 4 identified HBP assessment from 15 countries with varying scope, but none of them focused exclusively on cancer. Nevertheless, the methods synthesized in Chapter 4 helped to select the assessment method by reflecting on the time, data, and capacity available. The original assessment was requested to be completed in a few months. Cancer was considered a generally well-studied topic in other countries from which data could be sourced. Additionally, a small assessment team comprising two senior health economists and eight research assistants from the University of Rwanda School of Public Health were

available to support. For the cost-effectiveness assessment, a review of existing cost-effectiveness studies was agreed to be the best method, results of which are presented in this chapter.

In Chapter 5, I designed and executed the review of cost-effectiveness; designed and executed elicitation of expert opinion of cost-effectiveness; synthesized results; submitted for ethics approval in both the UK and Rwanda; and wrote the first draft of the paper. To complete the analysis, I trained four research assistants from University of Rwanda School of Public Health and Inga Mumukunde from Clinton Health Access Initiative. The chapter presented here is a draft which will eventually be co-authored with the individuals listed herein, as well as others involved in the full HBP process; full contributions are listed in the research paper cover sheet.

5.2 Cover sheet

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2100817	**Title**	Mrs
First Name(s)	Cassandra		
Surname/Family Name	Nemzoff		
Thesis Title	Methods, application, and risk of 'adaptive' health technology assessment		
Primary Supervisor	Anna Vassall		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	BMJ Global Health
Please list the paper's authors in the intended authorship order:	Cassandra Nemzoff, Andres-Madriz Montero, Inga Mumukunde, Jean Marie Sindambiwe, Isabelle de Valois Ndishimye, Felix Nzeyimana, Valentine Uyisabye, James Humuza, Rob Baltussen, Anna Vassall, Sedona Sweeney & Stella Umuhoza (joint last)

Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	For this paper, I designed the cost-effectiveness methods, wrote the search strategy, led the systematic review of cost-effectiveness studies, designed and executed expert elicitation methods, and wrote the first draft. Co-authors participated in the systematic review of CE studies, co-facilitated expert elicitation methods, and provided feedback on the draft manuscript.

SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	1 September 2024

5.3 Paper

Cost-effectiveness of cancer interventions in Rwanda: results and lessons for health benefits package design

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Abstract

Prioritizing health benefits packages (HBP) can be done through a review of all interventions in an HBP, or sectoral reviews of disease-specific clusters. Cancer is a good candidate for a disease-specific review, given its known high cost and rising disease burden, particularly in low- and middle-income countries.

The Government of Rwanda recently assessed forty-nine cancers against nine criteria. Each cancer had a basic, core, and enhanced package of services, and one preventive intervention was assessed, totalling 148 interventions. This paper focuses on the results of one of the criteria: cost-effectiveness. The objectives were to specify which cost-effectiveness methods were selected and why; to assess the cost-effectiveness of 148 cancer interventions; and to make recommendations on how to strengthen global cost-effectiveness evidence base.

Assessment methods were selected using an adaptive health technology assessment (aHTA) approach, by considering the trade-offs between available time, data, and capacity. The assessment undertook a review of the Tufts cost-effectiveness assessment (CEA) registry and filled evidence gaps with structured expert elicitation. Analysts summarized lessons learned to recommend improvements to the global cost-effectiveness evidence base.

Of the 148 cost-effectiveness ratios sought, 39 were from the Tufts registry and 83 were expert elicited. Analysts recommend better reporting of CEAs to support HBP design and improved consistency in extraction from CEAs.

This is the first study to assess many cancers at once for HBP design. It presents the characteristics and limitations of the existing cost-effectiveness evidence on cancer which may be useful for other countries prioritizing cancer services.

Introduction

A common policy instrument for countries striving to achieve universal health coverage (UHC) is a health benefits package (HBP). An HBP defines which health services are paid for, by whom, and for which patients(1). To ensure HBPs are financially sustainable, there is a need to balance demand for new services with a constrained budget. This is often done through a formal, deliberative priority setting process known as health technology assessment (HTA)(2).

HBPs have been prioritized in many countries, often taking a 'sectoral' approach that assesses a broad set of services in the health system(3–5). Another option is to focus on disease-specific clusters, which reduces the analytical burden of full HBP design whilst still addressing a broader set of topics than a single intervention. Cancer is a good candidate for a disease-specific assessment, given the rising global burden of disease and known high-costs of cancer treatment(6). Resources that have been developed to aid in prioritizing cancer services include Disease Control Priorities (DCP), which dedicated one of its nine volumes on essential health services in low- and middle- income countries (LMICs) to cancer, and the National Comprehensive Care Network's (NCCN) resource-stratified guidelines which define potential cancer treatment pathways for common cancers based on available resources(7,8).

The Government of Rwanda recently led a process of prioritizing cancer services. This was part of an effort to respond to demand for coverage of key services under its community based-health insurance (CBHI) scheme, while maintaining its financial sustainability. The CBHI HBP covers more than 80% of the population(9), and is managed by the Rwanda Social Security Board (RSSB). A multi-stakeholder process of assessment and appraisal was designed to prioritize 49 cancers against nine criteria: cost-effectiveness; burden of disease; financial risk protection; cost; budget impact; feasibility; vulnerable groups; individual effectiveness; and life-threatening conditions(10). This paper focuses on results from

the cost-effectiveness assessment. Of the nine criteria, cost-effectiveness is often central in HBP assessments, because ranking interventions by their cost-effectiveness defines the optimal mix of services to maximize population health(11,12).

Despite cost-effectiveness being a key feature of HBPs since the 1990s, gaps in the methodological literature remain(13). First, HBP assessments are data-demanding which necessitates the use of 'adaptive' health technology assessment (aHTA) methods. aHTA methods deliberately adjust assessments for local time, data, and capacity constraints and leverage data from other jurisdictions where possible, rather than conducting analyses from scratch(14). However, how these methods are selected is not reported in the literature. Second, practice reports that include details about how cost-effectiveness ratios (CERs) were sourced, transferred, and presented are sparse(15). Finally, there are limited recommendations in the literature about how to improve the global cost-effectiveness evidence base to support HBPs(16).

This paper serves to support Rwanda's cancer prioritization and fill the gaps in the literature through three objectives: to specify which cost-effectiveness methods were selected and why; to assess the cost-effectiveness of cancer services and report how transferability was accounted for; and to make recommendations on how to strengthen the global cost-effectiveness evidence base.

Methods

Defining the services to be assessed

Two rounds of cancer assessments were undertaken. The first ("round one") piloted the assessment methods by assessing the top seven cancers by incidence and top three childhood cancers by incidence (n = 10) (Appendix 1). The subsequent assessment ("round two") grouped and assessed the remaining

cancers in the Rwanda National Cancer Guidelines (n=39)(17). The full list of 49 cancers assessed can be found in Appendix 2.

Each cancer was divided into three 'packages': basic, core and enhanced. These are defined using the NCCN 'resource stratification framework' definitions which uses the available evidence and global clinicians' expertise to stratify cancer services based on availability, affordability, and cost-effectiveness(18). Basic includes the basic minimal standard of care which improves disease-specific outcomes; core includes basic plus additional care that provides major outcome improvements without being cost prohibitive; and enhanced includes core plus additional care that provide lesser disease outcomes and are cost prohibitive(18). One additional 'prevention' package was added for human papillomavirus (HPV) vaccination for cervical cancer prevention. The NCCN resource stratified guidelines have been produced for 16 cancers. As part of the broader HBP process, a local expert committee was consulted to refine the packaging of services into these groups for appropriateness in Rwanda and stratified the remaining cancers which were not stratified by the NCCN.

Methods selection

Our CEA methods were driven by the available analytical time, data, and capacity for assessment. We made use of a recent overview of aHTA methods for HBP design which explicitly considers these constraints against four possible methods: expert opinion, review, model adaptation, or new model(15). The initial time envisioned for assessing all cancers was a few months. Data was available on costs and coverage for some cancers, but there was only one Rwanda CEA estimate available(19). The assessment team's capacity included two senior coordinators and eight research assistants from the University of Rwanda School of Public Health (SPH). They were supported by three health economists from the London School of Hygiene and Tropical Medicine and the Center for Global Development, members of the international Decision Support Initiative (iDSI) network.

Given the timeline, limited local data on cost-effectiveness, and small assessment team, it was agreed adapting existing models or developing new models for so many cancers was not feasible. Rather, a review of existing literature would be conducted using the Tufts CEA Registry as the primary data source for CER estimates(20). Any gaps would be filled with structured expert elicitation (SEE)(21). The Tufts registry is particularly useful for HBPs, because it offers a comprehensive database of more than 12,000 cost-effectiveness studies with pre-extracted data including CERs and quality scores. This can save significant analytical time and minimize the need to review original studies, but does exclude studies that have outcomes other than disability-adjusted life years (DALYs) averted or quality-adjusted life years (QALYs) gained.

Cost-effectiveness analysis

A search strategy was developed for the Tufts registry in each round (Appendix 3). We combined keywords related to cancer in general; keywords for the specific cancers being assessed; and drugs used for cancer treatment. Keywords were drawn from the local cancer treatment guidelines and a recent unpublished analysis of cancer drug costs in Rwanda(17,22). The searches were run on 2 October 2022 for round one and 6 June 2023 for round two.

Selection of studies from the literature

The best estimate of cost-effectiveness for each cancer was selected by assessing their bias from transferability to local context. For this, we adapted Welte's 'knock-out' criteria because of its simplicity and common use in HBP assessments(23–25). The criteria include relevance of the intervention and comparator; geographic relevance; and quality of the study. We included studies with both DALYs averted and QALYs gained, aligned with recent findings that this practice is acceptable(26). This was useful for economic evaluations of cancer interventions, which disproportionately use QALYs, even

though DALYs are more often used in LMIC settings. Studies with irrelevant interventions or comparators, or from high-income countries (HICs) were excluded.

A 3-step approach was taken to select studies: study selection; CER adjustment; and CER scoring. Two members of the assessment team reviewed each paper in step 1, with decisions resolved by consensus. Steps 2 and 3 were completed by the first author.

In step 1a, titles and abstracts were reviewed for general relevance. Following our exclusion criteria, studies from HICs were removed. Studies which were generally irrelevant were also removed, such as those not focused on cancers being assessed, or interventions not provided in Rwanda.

In step 1b, each CER within a study was reviewed for relevance of the intervention and comparator. We considered whether the intervention matched the package in Rwanda, including the screening and treatment approaches.

In step 1c, final CERs were selected for each cancer and each package (basic, core, and enhanced). This included giving geographic preference to studies from lower-middle income countries instead of upper-middle income studies; selecting the best match intervention and comparator for each package if there were many to choose from; and ensuring the final CER selection approach was consistent across cancers. Additionally, we recalculated CERs to ensure that the average cost-effectiveness ratio (ACER) was used. This enabled consistent ranking of interventions against a null comparator. The extracted data from Tufts was used to recalculate the ACER, and when necessary, this was validated against the original study. In some instances, we recalculated an ACER based on the comparator of a study. For example, if the comparator of the study matched one of our packages, we divided the costs by the effects of that comparator to recalculate the ACER.

In step 2, final CERs were adjusted for purchasing power parity (PPP) and scored. We adjusted for PPP to standardize across geographies, using the following formula:

$$CER_{Rwanda} = CER_{Country\ X} * \frac{GDP\ per\ capita\ PPP_{Rwanda}}{GDP\ per\ capita\ PPP_{Country\ x}}$$

Then, each CER was assigned between one and three stars, based on three transferability factors: geographic relevance, relevance of the intervention/comparator, and quality (Table 1). Quality is measured using the rating approach applied in the Tufts registry, scored by Tufts reviewers on a scale of 1 to 7, with 1 being the lowest quality and 7 being the highest. The score accounts for the following principles: transparency, sufficient time horizon, appropriate discount rate, disaggregated costs and effects; appropriate characterization of uncertainty; clear reporting of utility weights; performance of subgroup analysis, and quantification of non-health effects (27).

Table 1: Scoring cost-effectiveness ratios

Measure	Measurement approach	3*	2*	1*
Geographic relevance	Country/ income level	Rwanda or other African country	Lower-middle income country	Upper-middle income country
Relevance of intervention/ comparator	Reviewers' interpretation	Exact match	Partial match	No match
Quality	Tufts quality scoring framework	4-7	2-4	1 or unscored

In Step 3, CERs were ranked by cost-effectiveness and accompanied by the star rating.

Expert elicitation

To fill gaps where CERs were not available in the literature, we undertook a process of SEE, guided by standard and local approaches to SEE(21,28). These approaches are typically used to elicit inputs to CEAs (e.g. costs, health gains), so we adapted these methods to elicit the output of CEAs, the ICER. A group of

twelve cancer experts, hereafter referred to as 'the cancer experts', were nominated by the Ministry of Health to support the full HBP design process and participated in SEE. Their expertise is listed in Appendix 4.

A Delphi approach was used for elicitation of effectiveness, and subsequently CERs. First, an estimate of individual effectiveness was elicited for all interventions being assessed. Experts were divided into small groups with a facilitator and were asked to rate interventions as low effectiveness (the patient would survive for less than six months after intervention); medium effectiveness (the person would survive between 6 months – 5 years); or high effectiveness (the person would survive more than 5 years). Each group agreed a rating by consensus. Second, these estimates were combined with other data from the broader HBP assessment on each intervention and shared with experts to elicit CERs. This included a detailed explanation of each intervention; a unit cost per case based on local costing data; and the CERs that were available for other interventions from Tufts for reference. Third, experts were asked to individually score each service for cost-effectiveness using the descriptions in Table 2. Experts then shared their scores within the same group, and the group discussed a consensus score. Finally, all experts were convened and presented with the full list of scores for validation.

The potential range of CER for each category reflects a rough estimate of thresholds based on gross domestic product per capita (GDP pc)(29). CERs elicited from this process were assigned to each category as follows: 1 = US$ 2502 (3x GDP pc); 2 = US$ 1668 (2x GDP pc); 3 = US$ 834 (1x GDP pc); and 4 = US$ 417 (0.5x GDP pc)(29,30).

Table 2: Cost-effectiveness categorization

Category	Level of cost-effectiveness	Typical characteristics	ICER range
1	Not cost-effective	High costs & low effects	> $2502 (3x GDP pc)
2	Potentially not cost-effective	High costs & medium/high effects Medium costs & low/medium effects	$834 - $1668 (1-3x GDP pc)
3	Potentially cost-effective	Medium costs & high effects Low costs & low/medium effects	$417 - $834 (0.5-1x GDP pc)
4	Very cost-effective	Low costs & high effects	< $417 (0.5x GDP pc)

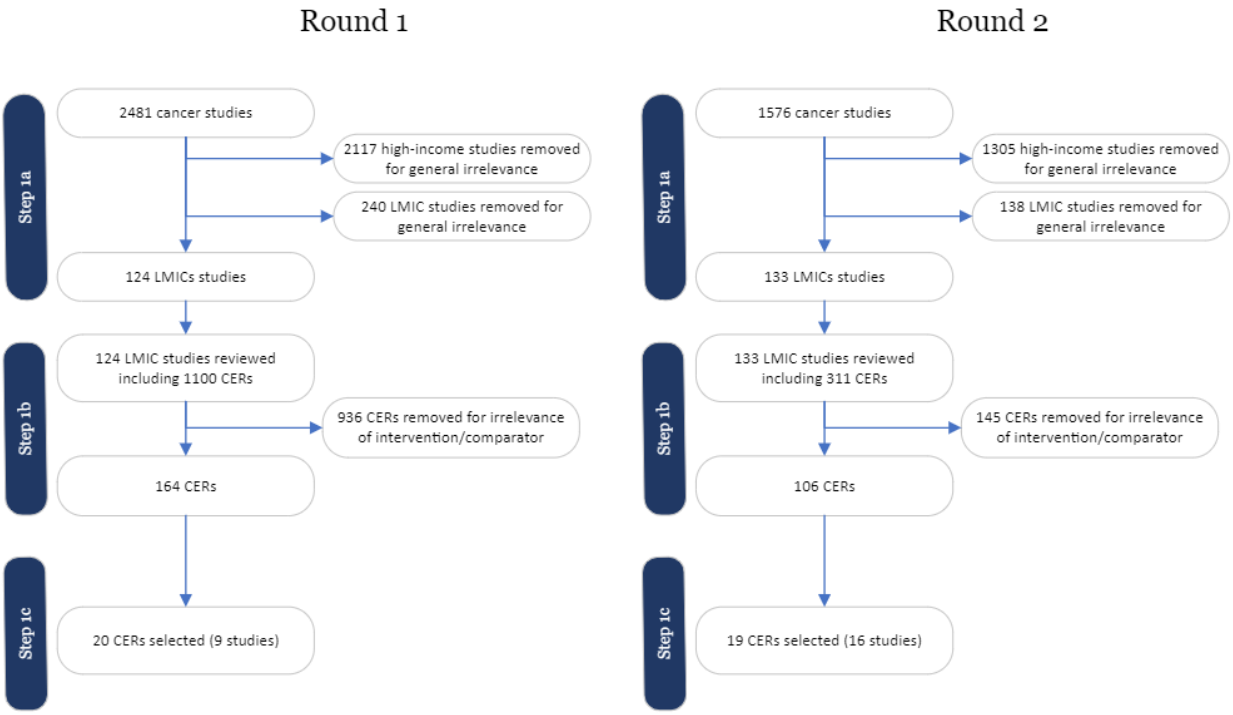
GDP pc = gross domestic product per capita

Results

Cost-effectiveness ratios from the literature

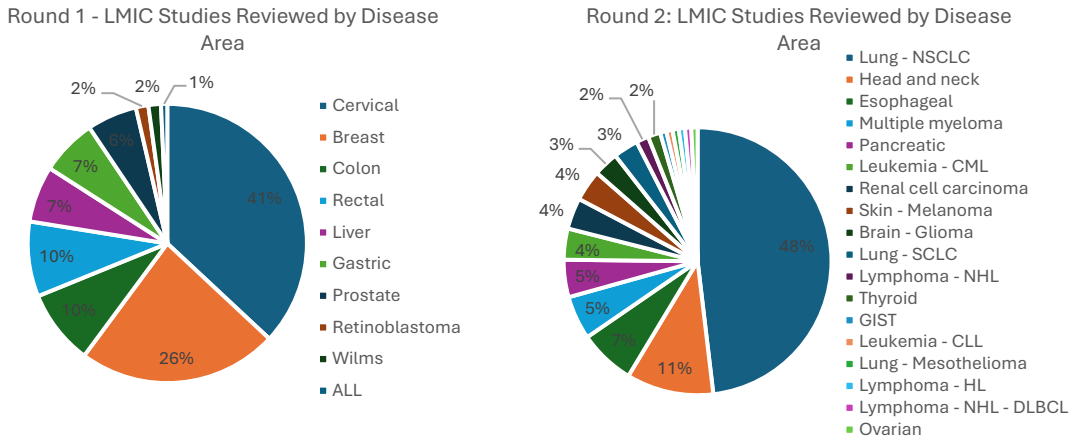
In round one, we sought CERs for basic, core, and enhanced packages for ten cancers (n=30, where a CER was sought for basic, core, and enhanced for each cancer) and prevention for one cancer (HPV vaccination, n=1). Cancers included breast, cervical, gastric, colon, rectal, prostate, liver, Wilms, retinoblastoma, and acute lymphoblastic leukemia. We identified 2481 cancer studies in the Tufts Registry for review. Of these, 124 from LMICs were selected for inclusion in step 1a. These 124 studies contained 1100 CERs, and 164 CERs we selected in step 1b. In step 1c, a final list of 20 CERs from 9 studies were included (n=20/31). In round two, we sought CERs for the remaining 39 cancers (n=117). We identified 1576 studies. Of these, 133 from LMICs were selected for inclusion in step 1a. These 133 studies contained 311 CERs, of which 106 were selected in step 1b. Finally, 19 CERs from 16 studies were selected in step 1c (n=19/117). This process is summarized in Figure 1, and a list of all studies included in Appendix 5.

Figure 1: Cost-effectiveness ratios selected



We found a clear bias towards certain cancers in the studies selected at the end of step 1a in both rounds (Figure 2). In round 1, most studies were focused on cervical and breast cancer, with far fewer studies on the remaining 8 cancers. In round 2, nearly half of all studies were for non-small cell lung cancer (NSCLC). Moreover, we only found studies on 19 of the 39 cancers in this round, meaning that for the remaining 20 cancers, no cost-effectiveness evidence was available at all. In narrowing the CERs from step 1a to step 1c, we were more likely to find exact matches in the cancers with more studies, and partial matches where there were very few to choose from.

Figure 2: LMIC Studies Reviewed by Disease Area



The 39 CERs selected are summarized in Table 3. Exact matches were found in 20 CERs, and partial matches found in 19 CERs (A). Geographically, 17 were from lower-middle income countries and 22 were from upper-middle income countries (B). The Tufts quality score in the studies ranged from 1 to 7 (C). Quality scores were unavailable for 14 CERs, as Tufts does not quality score all studies, all of which were from lower-middle income countries. Ultimately, all CERs scored two or three stars (D).

Table 3: Cost-effectiveness ratios from the literature and transferability scoring

Round	Cancer and Level	Cost-effectiveness ratio (2021 USD/DALY)	(A) Intervention and comparator Exact Match = 3* Partial Match = 2* No Match = 1*	(B) Geographic relevance Rwanda or Africa = 3* LMIC = 2* UMIC - 1*	(C) Quality score 4-7 = 3* 1-4 = 2* 1 or unscored = 1*	(D) Average Score (*, **, ***)
1	Cervical - Prevention	212	Exact Match	Rwanda		**
1	Gastric - Basic	381	Exact Match	UMIC	6.0	**
1	ALL - Basic	432	Partial Match	LMIC		**
1	Wilm's Tumour - Basic	445	Partial Match	Africa		**
1	Retinoblastoma - Basic	459	Partial Match	Africa		**
1	Colon - Core	495	Partial Match	Africa		**
1	Rectal - Core	495	Partial Match	Africa		**
1	Cervical - Basic	644	Exact Match	Africa		**
1	Breast - Core	645	Exact Match	Africa		**
1	Colon - Enhanced	650	Exact Match	Africa		**
1	Rectal - Enhanced	650	Exact Match	Africa		**
1	Cervical - Enhanced	655	Exact Match	Africa		**
1	Gastric - Core	672	Exact Match	UMIC	6.0	**
1	Cervical - Core	811	Partial Match	Africa		**
1	Gastric - Enhanced	916	Exact Match	UMIC	6.0	**
1	Prostate - Basic	1,006	Exact Match	UMIC	5.0	**
1	Prostate - Core	1,403	Exact Match	UMIC	5.0	**
1	Breast - Enhanced	1,445	Exact Match	Africa		**
1	Breast - Basic	1,600	Partial Match	Africa		**
1	Prostate - Enhanced	2,881	Exact Match	UMIC	1.0	**
2	Lymphoma - NHL - DLBCL - Basic	23	Exact Match	Africa	4.0	***
2	Thyroid - Basic	50	Exact Match	UMIC	4.0	**
2	Lymphoma - NHL - DLBCL - Core	450	Exact Match	Africa	4.0	***
2	Esophageal - Core	473	Partial match	UMIC	6.0	**
2	H & N - Core	814	Partial Match	UMIC	6.0	**
2	Lymphoma - HL - Enhanced	893	Partial Match	LMIC	5.5	**
2	Lung - NSCLC - Enhanced	999	Partial Match	UMIC	5.0	**
2	Lung - SCLC - Enhanced	3,065	Partial Match	UMIC	4.0	**
2	Pancreatic - Enhanced	3,609	Partial Match	UMIC	5.0	**
2	Lung - Mesothelioma - Core	3,808	Exact Match	UMIC	5.0	**
2	Leukemia - CML - Core	4,265	Partial Match	UMIC	5	**
2	Renal cell carcinoma - Enhanced	4,537	Exact Match	UMIC	5.0	**
2	Brain - glioma - Core	4,584	Partial Match	UMIC	6.0	**
2	Brain - glioma - Enhanced	4,584	Partial Match	UMIC	6.0	**
2	Skin - Melanoma - Enhanced	6,431	Partial Match	UMIC	5.0	**
2	Multiple myeloma - Enhanced	10,714	Partial Match	UMIC	5.0	**
2	Lung - Mesothelioma - Enhanced	16,523	Exact Match	UMIC	5.0	**
2	Esophageal - Enhanced	17,922	Exact Match	UMIC	5.0	**
2	Ovarian - Enhanced	43,708	Partial Match	UMIC	5.5	**

Acronyms: USD – United states dollar; DALY – disability-adjusted life year; NHL – non-Hodgkin's lymphoma; ALL – acute lymphoblastic leukemia; DLBCL – diffuse large b-cell lymphoma; H&N – head and neck; HL – Hodgkin's lymphoma; NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer; CML – chronic myeloid leukemia

Elicited cost-effectiveness ratios

In round two, we elicited the remaining 98 CERs from the cancer experts. We received responses for 83 CERs, some of which were counted for two cancers as indicated in the footnotes of Table 4. Those without response were for cancers that had no local incident cases, or those where there was no treatment assigned to a specific package (e.g. a cancer was stratified by experts to only have a basic and

enhanced package, but no core package) (n=15). Values for each CER were assigned following the approach set out in the methods.

Table 4: Elicited cost-effectiveness ratios

Cancer and Level	CER		
Esophageal - Basic	417	Lymphoma - NHL - DLBCL - Enhanced	1,668
Skin - Melanoma - Basic	417	Ovarian - Core	1,668
Adrenal tumors - Basic	417	Adrenal tumors - Core	1,668
Anus - Enhanced	417	Brain - brain tumors - Core	1,668
Uterine – Enhanced*	417	Uterine – Core*	1,668
Kaposi sarcoma - Basic	417	Kaposi sarcoma - Enhanced	1,668
Neuroblastoma - Core	417	Leukemia - ALL - Basic	1,668
Penile - Basic	417	Leukemia - AML - Core	1,668
Penile - Enhanced	417	Leukemia - AML - Enhanced	1,668
Skin - Non-melanoma - Basic	417	Leukemia - CLL - Basic	1,668
Vulva/Vagina - Basic	417	Neuroblastoma – Enhanced	1,668
Lung - NSCLC - Core	834	Renal pelvis carcinoma – Basic*	1,668
Lymphoma - HL - Basic	834	Renal pelvis carcinoma – Enhanced*	1,668
Lymphoma - HL - Core	834	Vulva/Vagina - Core	1,668
Multiple myeloma - Basic	834	H & N - Enhanced	2,502
Ovarian - Basic	834	Leukemia - CML - Enhanced	2,502
Renal cell carcinoma - Basic	834	Pancreatic - Basic	2,502
Skin - Melanoma - Core	834	Pancreatic - Core	2,502
Thyroid - Core	834	Thyroid - Enhanced	2,502
Anus - Basic	834	Adrenal tumors - Enhanced	2,502
Anus - Core	834	Bone - Enhanced	2,502
Bone - Basic	834	Brain - brain tumors - Enhanced	2,502
Bone - Core	834	Leukemia - ALL - Core	2,502
Brain - brain tumors - Basic	834	Leukemia - ALL - Enhanced	2,502
Uterine – Basic*	834	Leukemia - AML - Basic	2,502
Germ cell tumors - Basic	834	Leukemia - CLL - Core	2,502
Germ cell tumors - Core	834	Leukemia - CLL - Enhanced	2,502
Gestational/Placenta - Basic	834	Skin - Non-melanoma - Enhanced	2,502
Gestational/Placenta - Core	834	Vulva/Vagina - Enhanced	2,502
Kaposi sarcoma - Core	834	Neuroendocrine tumors - Basic	2,502
Lymphoma - NHL - T-cell - Basic	834	Neuroendocrine tumors - Core	2,502
Neuroblastoma - Basic	834	Neuroendocrine tumors - Enhanced	2,502
Penile - Core	834	Soft tissue sarcoma – Enhanced	2,502
Renal pelvis carcinoma – Core*	834	Multiple myeloma – Core	-
Skin - Non-melanoma - Core	834	Renal cell carcinoma - Core	-
Soft tissue sarcoma - Basic	834	Germ cell tumors - Enhanced	-
Soft tissue sarcoma - Core	834	Gestational/Placenta - Enhanced	-
Brain - glioma - Basic	1,668	GIST – Basic	-
H & N - Basic	1,668	GIST – Core	-
Leukemia - CML - Basic	1,668	GIST – Enhanced	-
Lung - Mesothelioma - Basic	1,668	Lymphoma - NHL - T-cell - Core	-
Lung - NSCLC - Basic	1,668	Lymphoma - NHL - T-cell - Enhanced	-
Lung - SCLC - Basic	1,668	Thymoma/thymic carcinoma* – Basic	-
Lung - SCLC - Core	1,668	Thymoma/thymic carcinoma* – Core	-
		Thymoma/thymic carcinoma* - Enhanced	-

"-" : either no incident cases were reported, or no treatment was included in this package
*Note: each of the following includes two cancers for which CERs were sought: thymoma/thymic carcinoma (n=2), uterine (corpus uteri + endometrial) (n=2), renal pelvis (renal pelvis carcinoma + urothelial (n=2)

Discussion

In this paper, we sought CERs for 148 cancer packages for 49 cancers. Our analysis found 39 CERs in the published literature and elicited 83 CERs from the cancer experts. In general, we found more exact matches to our full packages of services in the more common cancers in round one. In round two, we found more partial matches focused on specific drugs at specific points in the treatment pathway. Ratios

from the published literature ranged from 23 USD/DALY for the diffuse large b-cell lymphoma basic package to 43,708 USD/DALY for the ovarian enhanced package, after adjusting for PPP. Only two CERs were assigned three stars, because they were exact matches from studies from the African context; the remaining CERs were assigned two stars. Expert-elicited CERs included 11 packages which were considered very cost-effective, 19 which were considered not cost-effective, and the remainder were potentially cost-effective. It is possible that the experts were more generous in their CER evaluations than the literature, as they identified proportionately more interventions which they considered very cost-effective, and few which they considered not cost-effective than the published literature.

We estimate that the analytical time to complete the cost-effectiveness assessment was three to four months for a team of eight people working part-time. Having access to the Tufts registry's pre-extracted data was critical to expediting the assessment, as were the cancer experts who participated in the elicitation of missing CERs. Conducting the assessment built local capacity in systematic reviewing and reviewing of CEAs.

This study is the first of its kind focused on assessing the cost-effectiveness of many cancers at once to inform HBP design. It adds to the existing HBP literature by providing details on how and why assessment methods were selected, and how the cost-effectiveness assessment was conducted. Our detailed reporting of the expert elicitation of CERs is a particularly unique addition to the HBP literature, as many economic evaluations have used expert elicitation to elicit components of a CEA, but our approach is the first to apply the same methods to eliciting ICERs entirely.

Further enhancements could have been made to our approach. We could have strengthened the PPP adjustment by splitting tradeable and non-tradeable goods and adjusting the latter for PPP(31), or recalculated CERs with local costs. We could have also conducted a quality review of studies that we

included but were not quality reviewed by Tufts. However, in adapting mostly for time constraints, these additions were not possible.

Drawing from this experience, we can also make a few recommendations for the producers and reviewers of economic evaluations.

Reporting of CEAs could be refined for use in HBPs. In Rwanda, the cancer experts were interested in focusing on curative, early-stage treatment. However, CEA evidence on this type of treatment was sparse. Packages of care that were reported often covered stages I-IV, and recalculating CERs for a package of stages I-II or I-III was not possible. Study authors could consider reporting the costs and effects of each stage and groups of stages separately. Additionally, reporting units of costs and health effects in studies was inconsistent. Ideally, clearer reporting of costs and QALYs or DALYs per patient per year, size and definition of the study population, and total QALYs or DALYs averted per year would be consistently reported to enable accurate recalculations. More broadly, there is an obvious need for more CEAs to be done in LMICs, on LMIC priority topics.

Improvements could also be made to the reviewed data from Tufts, to avoid going back to original studies. Reporting of interventions was sometimes unclear. We would recommend more comprehensive intervention descriptions that include screening type, treatment method, drug(s) delivered, and the line of treatment (first line, second line) for cancer. Additionally, reporting of *incremental* CERs (ICERs) versus *average* CERs (ACERs) was inconsistent and should always be clarified.

Ultimately, while cancer is a well-studied topic in other countries, transferring CEAs from various jurisdictions for HBP design is challenging and fraught with uncertainty. Existing literature is disproportionately focused on a small subset of cancers, so our methods had to be adapted to respond

to the dearth of data for other cancers. This would have been true even if we had included the broad literature from high-income countries, which similarly focused on a small subset of cancers and is disproportionately incremental which is less useful for HBP design. The uncertainty of this approach creates a risk of sub-optimal decision making which should be clearly communicated in appraisal proceedings.

Conclusions

This cost-effectiveness assessment reviewed 49 cancers and demonstrates the feasibility of combining review with expert opinion to obtain CER estimates. Our study is the first of its kind to assess the cost-effectiveness of so many cancers at once for the purpose of HBP design. Moreover, it is the first HBP study to report methods of expert elicitation of CERs in detail, which should improve replicability of these methods in the future.

Acknowledgments

The authors would like to acknowledge the valuable contributions of all cancer experts who contributed to this process.

5.4 Epilogue

Using the methods articulated in Chapter 4 helped to select the assessment methods for 49 cancers and reflect on why decisions were made through the assessment based on the interplay between time, data, and capacity constraints. Chapter 4 summarizes four assessment methods: expert opinion, review, model adaptations, and new model. It was broadly used to knock out the possibility of model adaptation or new model, due to time constraints and lack of available data. This led the team to agree on a review of existing literature using the Tufts database. When confronted with no data at all, expert opinion was used to fill gaps to minimize the additional time spent on analysis.

Due to policy makers' time demands, we chose to assess the ten most prevalent cancers initially. In this round, a review was sufficient, as I identified cost-effectiveness evidence for nine of the ten cancers. The tenth was liver cancer, which experts deemed cost-ineffective and low priority. The subsequent assessment of 39 cancers was more challenging. Many of the cost-effectiveness studies identified were from upper-middle income countries (predominately China) and focused on very specific components of cancer care. Cost-effectiveness evidence for each of the basic, core, and enhanced packages were more uncommon in this round due to overall data scarcity. For 20 of the cancers, I found no cost-effectiveness evidence at all which required conducting expert elicitation. Interestingly, the HBP literature reviewed in Chapter 3 did not specify clearly the expert elicitation methods to inform HBP design, so I designed a bespoke approach based on the SEE literature. Each of these shifts demanded flexible and pragmatic methodological adaptations as the assessment progressed.

Additionally, a key component of the assessment was capacity strengthening. I built in training on rapid review and expert elicitation for the local assessment team. Capacity strengthening was an integral part of establishing local ownership of priority setting methods but was time consuming throughout. Balancing policy makers' demands to get things done quickly and teaching the team at the same time

was a challenge. In instances where time was too short, I focused on developing the new methods or finishing the assessment work in lieu of further training to ensure the work could be completed in time.

The experience reported in this paper, particularly instructions on clear methods for SEE and how to navigate different types of CEA for different disease areas would be valuable additions to the guidance in Chapter 4.

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Chapter 6: Cost and cost-effectiveness of cancer services packages in low- and middle-income countries: a case study of Rwanda

6.1 Prologue

The second part of applying the aHTA framing from Chapter 4 is presented here in Chapter 6. It uses the cost-effectiveness results from Chapter 5 as an input to the broader HBP assessment for cancer and presents the results in the form of potential cancer package scenarios.

Using the assessment of cost and cost-effectiveness with expert-elicited coverage rates, I modelled different scenarios of cancer packages with varying levels of cost and health effects in Excel. This is different from most other HBP exercises which use pre-existing HBP prioritization or optimization tools. Using Excel to develop the scenarios reflects the ethos of my framework in Chapter 4 because the design was centered on locally relevant methods rather than a tool with pre-defined method. Building scenarios in Excel was simply a transparent tool that fit well with the methods chosen.

This chapter combines my work on scenarios with a much broader assessment of the HBP against nine criteria. In the overall cancer assessment, I was responsible for: designing and leading the assessment of cost-effectiveness and burden of disease; supporting the assessment of other criteria; designing, executing, and refining scenarios including synthesis/elicitation of key inputs e.g. coverage rates; estimating the budget for cancer and budget impact of cancer packages; and submitting this work for ethics approval in the UK and Rwanda.

As part of reporting results of the HBP assessment in Rwanda, I coordinated the writing of a summary report, which was submitted to the Minister of Health for approval of the committees' recommendations. I have drawn on some components of this report in this chapter to complement my work. This includes contributions from Stella Umuhoza and James Humuza (University of Rwanda, School of Public Health) on the background in Rwanda; Rob Baltussen (Radboudumc) on the prioritization process; Andres Madriz-Montero (London School of Hygiene and Tropical Medicine) on costing methods; Cindy Muhoza (Rwanda Social Security Board and HBP committee member) on the committee's recommendations; and Inga Mumukunde (Clinton Health Access Initiative) on the next steps. Anna Vassall (London School of Hygiene and Tropical Medicine) provided feedback and input across the report and scenarios development. Additionally, Inga Mumukunde and four research assistants participated in trainings on and the assessment of cost-effectiveness including Jean Marie Sindambiwe, Isabelle Ndishimye, Valentine Uyisabye, and Felix Nzeyimana (University of Rwanda, School of Public Health). The chapter as presented here is a draft which will eventually be expanded and refined and co-authored with the individuals listed herein.

6.2 Cover sheet

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SECTION A – Student Details

Student ID Number	2100817	**Title**	Mrs
First Name(s)	Cassandra		
Surname/Family Name	Nemzoff		
Thesis Title	Methods, application, and risk of 'adaptive' health technology assessment		
Primary Supervisor	Anna Vassall		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Lancet Global Health
Please list the paper's authors in the intended authorship order:	Stella Umuhoza & Cassandra Nemzoff (joint first), Andres Madriz-Montero, Rob Baltussen, Inga Mumukunde, Regis Hitimana, Cindy Muhoza, Alexis Rulisa, Jean Marie Sindambiwe, Isabelle Valois, Felix Nganji, Thierry Zawadiz Muvunyi, Cyprien Shyirambere, Rose Gahire, Marcel

	Bahizi, Corneille Ntihabose, Andrew Mirelman, Ina Kalisa, James Humuza & Anna Vassall (joint last)
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	For this paper, I led the cost-effectiveness and burden of disease assessment with support from SU, JMS, and IV, and the development and revision of the cancer package scenarios. AMM led the costing with support from SU, IM, JMV, and IV. FN, TZM, and FN, TZM, CS provided expert inputs including coverage rates and proposed cancer packages for the committee. RB led the appraisal process which was supported by AM and IK. AV led the overall assessment with support from CN. AV and JH were the overall project leads. RH was the policy lead. AR, CM, RG, and MB contributed to the final recommendation as committee members. I wrote the first draft, and revised it based on feedback from co-authors.

SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	1 September 2024

6.3 Paper

Costs and cost-effectiveness of cancer service packages in low- and middle-income countries: a case study of Rwanda

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Abstract

Background: While the National Comprehensive Cancer Network has developed clinical guidelines for resource-constrained settings, there remains a gap in guidance on how to select cancer services for coverage under national health insurance schemes. Facing increasing pressure to cover non-communicable diseases, the Government of Rwanda recently embarked on a two-year effort to prioritize cancer services. This paper presents the costs and cost-effectiveness of different cancer packages to inform Rwanda's Community Based Health Insurance (CBHI) scheme.

Methods: To assess and appraise potential cancer services to be covered under Rwanda's CBHI scheme, the government convened a newly formed HBP appraisal committee; assessment team; and ad hoc committee of local cancer experts. A cost and cost-effectiveness analysis of alternative packages of cancer services was conducted, using a combination of secondary data and expert input.

Findings: Of the 148 cancer interventions assessed, 15 were found to be very cost-effective, 69 were found to be potentially cost-effective, and the remainder cost ineffective. The recommended cancer package in Rwanda is estimated to cost $16.4 million, treat 5,700 patients, and avert almost 40,000 disability-adjusted life years.

Interpretation: Investing in the most cost-effective interventions by focusing on specific cancers yields the highest health effects. The second-best alternative is to focus on early stage, curative care for all cancers. The Ministry of Health in Rwanda adopted the latter, combined with expanded screening for some cancers. This reflects a preference for prioritizing services that ensure equity for all patients.

Introduction

Cancer is of growing concern in low- and middle- income countries (LMICs), as nearly 70% of all cancer-related deaths in 2020 were in LMICs(1). However, it is unclear what the most appropriate and affordable cancer service package is in resource-constrained settings, to include as part of health benefits packages (HBPs) for universal health coverage (UHC)(2). Historically, HBP prioritization has focused on communicable diseases, but in recent years LMICs have faced a rise in non-communicable diseases (NCDs) necessitating their inclusion in HBPs as well(3).

However, there is limited evidence to support the prioritization of cancer services in LMICs. One of the nine volumes of Disease Control Priorities (DCP) focuses on cancer, but only includes cost-effectiveness evidence on six cancers for which available prevention and treatment options are considered cost-effective in an LMIC setting(4). Additionally, global literature on the cost-effectiveness of cancer services is housed in the Tufts cost-effectiveness analysis (CEA) registry, though the evidence is disproportionately from high-income countries(5,6). The National Comprehensive Care Network (NCCN) provides a set of guidelines that are 'stratified' into basic, core, and enhanced packages for 16 cancers(7,8). These adapt the NCCN's standard guidelines for the United States to varying levels of resources including human resources, infrastructure, technology, and drugs. NCCN has also produced 'harmonized' guidelines designed by providers and government officials to reflect specific regions. The harmonized guidelines for Sub-Saharan Africa covers 43 cancers which represent 90% of the region's incidence cases, though these guidelines are not stratified(8). There is little understanding of how any of these resources can be used to set national priorities on cancer(9).

As part of a broader effort to improve the financial sustainability of its community-based health insurance (CBHI) scheme and expand access to key services, the Government of Rwanda recently sought to prioritize services for 49 cancers. The priority setting process assessed interventions against multiple

criteria, while also ensuring that evidence was prepared in a timely way to respond to policy maker demand(10,11). A key output of the HBP assessment was the evidence review and assessment of the costs and cost-effectiveness of potential cancer package options.

This paper reports on the process, methods and results of this assessment, and the final package adopted for Rwanda.

Methods

Setting and process

Rwanda's CBHI HBP covers more than 90% of rural households and informal workers(12). It has improved access to care and provided financial protection particularly to the poor and vulnerable, through management under the Rwanda Social Security Board (RSSB). Despite the extensive coverage, RSSB continues to face the challenge of balancing CBHI financial sustainability with requests for coverage of new services(13).

To help with this challenge, the priority setting process in Rwanda was established through a 2021 Ministry of Health (MoH) Ministerial Instructions (MI), "Determining the methodology for CBHI – health benefits package (HBP) design"(14). This legal framework outlined nine decision criteria for prioritization of services for CBHI: cost, effectiveness, cost-effectiveness, budget impact, financial risk protection, feasibility, vulnerable groups, and life-threatening conditions. It also established a 17-member, multi-stakeholder HBP committee responsible for appraising the evidence and making recommendations.

Following the MI, the priority setting process was initiated with the first topic being cancer services. The assessment and appraisal process were guided by the concept of evidence-informed deliberative processes (EDPs)(15). This best practice framework is a practical and stepwise tool for priority setting which has the dual aim of optimizing the legitimacy of benefit package decisions, and related outcomes

in terms of decision criteria. To support the process, the mandated HBP committee was established, alongside an assessment team and ad hoc committee. The assessment team comprised local and international experts and was tasked with generating evidence for and supporting capacity building of the HBP committee. The ad hoc committee was comprised of local cancer experts (hereafter referred to as 'the cancer experts') and was convened to provide expert opinion on key criteria and develop preliminary recommendations for the HBP committee. A detailed overview of the prioritization process is in Appendix 1.

Describing and specifying services

Two resources were used to structure the 49 cancers being assessed (Appendix 2). The Rwanda MoH provided draft National Cancer Guidelines which were supplemented by the NCCN resource-stratified guidelines for 16 cancers(16,17). Combined, these were used to stratify a basic, core, and enhanced package for each of the 49 cancers in Rwanda, in line with the definitions used by NCCN. The basic package is an essential package of services needed to provide a minimal standard of care; the core package adds services to the basic which provide major health improvements and are not prohibitively expensive; and the enhanced package adds services to the core which provide lesser improvements in health but are prohibitively expensive(7). The cancer experts critically reviewed the existing stratified guidelines for 16 cancers to ensure their relevance to local clinical practice, and further stratified interventions for the remaining cancers for which no stratification was available. A summarized version of the stratification in tables is in Appendix 3.

Criteria assessment

Cancer interventions were assessed against the nine criteria from the MI. Two main criteria were evaluated quantitatively: cost and cost-effectiveness. Budget impact and financial risk protection were calculated from the costs. Burden of disease was also measured quantitatively. Feasibility, vulnerable

groups, life-threatening conditions, and effectiveness were evaluated using expert opinion. Below we detail the methods for costs and cost-effectiveness, and an overview of the methods for all criteria is outlined in Appendix 4**.**

Cost was estimated as a unit cost per case for each the basic, core, and enhanced package and was derived for each cancer using local costing data. Two sets of costs were developed: a health sector cost and an RSSB cost. The health sector cost reflects the package's full cost to the health sector, including those incurred by RSSB and MoH. The primary source of these costs was a recent MoH costing study on all services in the health system. This was supplemented by drug costs. These came from Partners in Health, a non-governmental organization which provides a substantial amount of cancer care in Rwanda, and other local sources. The RSSB cost reflects only the cost of the package borne by CBHI. The primary source of these costs was the RSSB tariff.

To evaluate cost-effectiveness, cost-effectiveness ratios (CERs) were first sourced using a review in the Tufts CEA Registry, an online database of more than 12,000 CEAs(18). A standard systematic review search strategy was applied that included the cancers being studied and the drugs to treat them. Studies were selected using the Welte knock-out criteria including relevance of the intervention and comparator; geographic relevance, giving preference to LMIC studies; and quality(19). Where no CEA was available, gaps were filled using structured expert elicitation. The cancer experts participated in a Delphi approach where they reviewed the already estimated unit cost per case combined with expert-elicited values of health effects. They then made an estimation of whether a cancer package was 'highly cost-effective', 'likely cost-effectiveness', 'likely cost-ineffective', or 'not cost-effective'(20).

Cancer package options

The total annual budget impact and potential health impact of different cancer package options were estimated and compared with the budget constraint. Package options were initially developed as a

collaboration between the assessment team and the cancer experts. Two rounds of assessment were undertaken, to first pilot the assessment methods with a small set of cancers and then assess the remaining cancers. The first round ("round one") was for 10 cancers, and the subsequent for the additional 39 cancers ("round two").

An iterative approach with the cancer experts was taken to prepare the package options for appraisal. First, an illustrative set of potential options were developed as Excel graphs and presented to the cancer experts. These scenarios demonstrated some broad possible choices, including for example, investing in the basic package for all cancers; the core package for all cancers; or investing in the most cost-effective cancers first. The purpose of this phase was to illustrate general variations in costs and health effects between scenarios.

Then, cancer experts were asked to propose revisions to the options. This included providing estimated feasible levels of coverage expansion for each cancer and each package. It also included revising the scenarios to what was deemed feasible clinical practice in the Rwandan setting. For example, changes included: varying which of the basic, core, and enhanced packages should be covered for each cancer; covering earlier stages of cancer only; including or excluding major screening programs; including or excluding high-cost drugs which were covered by donors; and investing in the most cost-effective interventions first. These were presented and adjusted in several iterations of scenarios for each round.

Budget impact and potential health impact

Current billing systems could not estimate expenditure by disease area, so the budget constraint was estimated using current cancer provision. This was done by multiplying the estimated health sector unit cost per case times the current estimated number of patients treated for each package. The cancer experts were requested to estimate the latter, and this was considered the status quo.

For each package option, the cancer experts reviewed ‘presenting’ and ‘projected’ incidence to estimate potential expansion of coverage. Presenting incidence included the number of new patients presenting at facilities, as reported in the Rwanda Cancer Registry(21). Projected incidence included the estimated number of new patients in the country annually, as projected by the Institute for Health Metrics and Evaluation (IHME)(22). Coverage was estimated by dividing presenting incidence by projected incidence.

The health sector unit costs were multiplied by varying increased coverage rates per cancer to estimate the budget impact of each package. Adjustments were sometimes made per scenario. The estimates of health impact were derived not by detailed population modelling, but by using the estimates from the secondary literature on cost-effectiveness and multiplying the effect for one person by population coverage. Total health effects were estimated by using the cost-effectiveness ratio to estimate the effect size per person.

Results

Individual results of the two main criteria, costs and cost-effectiveness, as well as coverage rates are provided in Appendix 4, Table 20, Table 21, Table 22, Table 23.

Package options that combine round 1 and round 2 are presented in Figure 1. This includes the 49 cancers, with each a basic, core, and enhanced package, plus cervical prevention in the form of HPV vaccination (n = 49*3 + 1 = 148 packages).

Four scenarios are presented. Strategy 1 is a point estimate of the status quo, reflecting the current provision of care. For the ten most common cancers, experts estimated that 100% of currently treated patients (“presenting” incidence) receive the basic package; 25% receiving basic also receive core; and 0% receive enhanced. For the remaining less common cancers, the cancer experts estimated that 90% of presenting incidence receive basic; 70% receiving basic receive core; and 20% receiving core receive

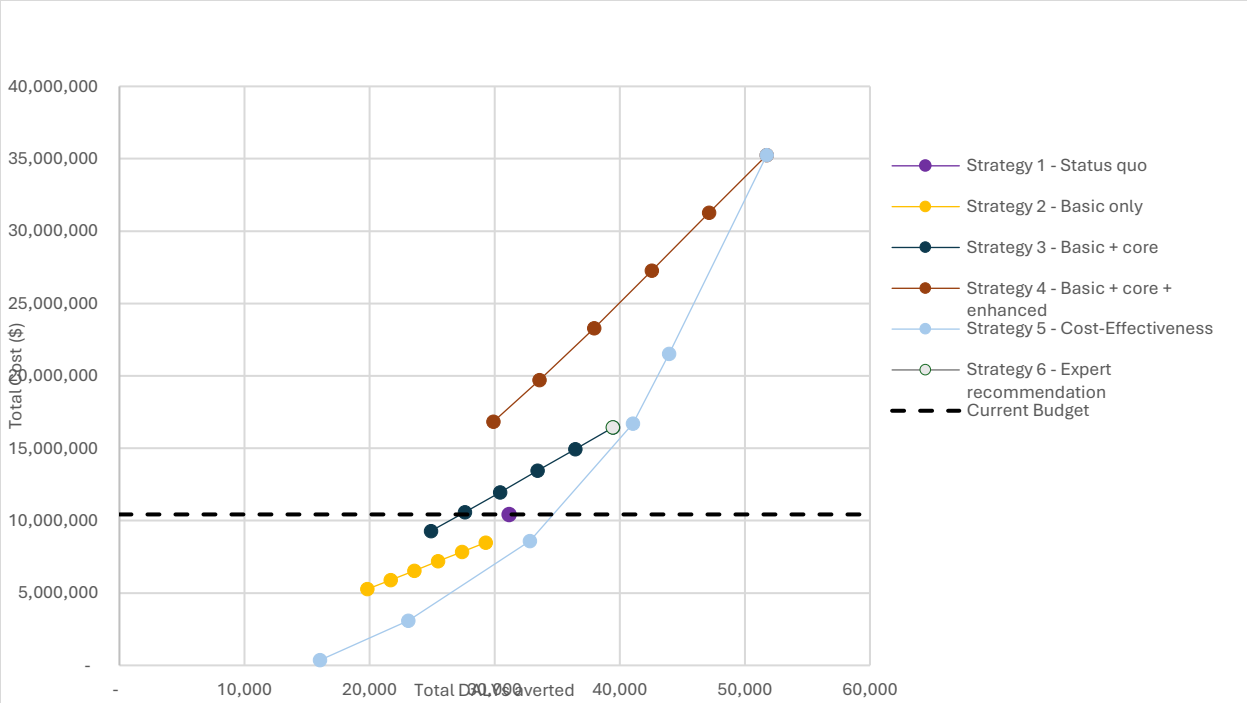
enhanced. Together, the total estimated cost of currently provided cancer treatment was 10.4 million (M) United States dollars (USD), and it averts 31,000 disability-adjusted life years (DALYs).

Strategies 2, 3, and 4 are all designed in the same way. The maximum cost and DALYs averted for each strategy use the experts' recommendation of expanded coverage rates. These vary by cancer and are documented in Appendix 5. Each of the lower points in each strategy reflect a 5% decrease in those coverage levels. This illustrates the impact on costs and health effects if the experts' suggested coverage levels are not immediately reached.

Strategy 2 covers the basic package for all cancers. The total cost of covering the basic package at experts' recommended coverage levels would be 8.4 M USD, or 1.9 M USD below budget, and avert 29,000 DALYs. Strategy 3 covers the core package for all but 11 cancers, as recommended by experts. The 11 cancers include: gastrointestinal stromal tumor, acute lymphomblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, small-cell lung cancer, non-Hodgkins' lymphoma (T-cell), multiple myeloma, pancreatic cancer, renal cell carcinoma, and thymoma/thymic carcinoma. The total cost of this package at the expert-recommended coverage rates would be 16.4 M USD, or 6.0 M USD above budget. It would avert 39.5 K DALYs. Strategy 4 covers the basic, core and enhanced package for all cancers, excluding the same 11 cancers. For illustrative purposes, we assume the coverage rates for enhanced are the same as those recommended for core. This would cost 35.2 M USD, which would require 24.8 M USD in additional funding and avert 51.7 K DALYs. Combined, these strategies illustrate that at the experts' recommended coverage levels, the basic package would be below budget, while adding the core or enhanced package would exceed the current budget but avert more DALYs than the status quo. The status quo, which combines a mix of the three packages, averts more DALYs than providing basic alone, but fewer than if the core or enhanced packages were added.

Strategy 4 adds the most cost-effective interventions first, up to the budget line. The lowest point reflects covering the single most cost-effective intervention, the second the 25 most cost-effective interventions, the third 33 interventions, the fourth 65 interventions, the fifth 80 interventions and the sixth all 148 interventions. Within the current budget, the 33 most cost-effective interventions could be covered, costing 9.8 M USD and averting 37,000 DALYs. In other words, adding the most cost-effective interventions first would avert 1,000 more DALYs than the status quo.

Figure 1: Cancer package options



Overall, the potential new packages are ordered by the additional health gain they provide. The basic package has the lowest health effect and adding the core and enhanced package increase the total DALYs averted. Covering the most cost-effective services first offers the maximum health gain.

Experts and the HBP committee explored several adaptations to these strategies to inform the final recommendation.

The first consideration was whether to include mass screening programs for breast, cervical, colon, and rectal cancers. Implementing the screening programs would diagnose patients at earlier stages, which would result in higher health gains and lower costs. Importantly, the costs assessed only included the lower cost of treating earlier stages; the cost of the screening program itself was excluded because it is paid for by a separate government department and was deemed irrelevant to RSSB.

The second consideration was whether to cover only stages I-III or I-II, rather than stages I-IV for the ten most common cancers. Treating stages I-III only offered an additional 800 DALYs averted compared with treating stages I-II but cost 40% more.

Finally, experts recommended removing the cost of one specific drug, imatinib. Imatinib is a high-cost cancer drug used to treat three cancers (chronic myeloid leukaemia, acute lymphoblastic leukaemia, and gastrointestinal stromal tumour) which has been donated to Rwanda for at least the past 15 years(23), and is expected to continue to be donated.

Final package, budget and potential health impact

Based on these scenarios and information provided on the additional seven criteria, the committee made its recommendation. The basic package was recommended for all cancers. The core package was recommended for most cancers, excluding the 11 cancers listed above. For the nine highest incidence cancers, the core package recommendation was restricted to stages I-III (excluding stage IV). Target coverage rates from the cancer experts were endorsed by the committee. The enhanced package was excluded entirely. This recommendation is represented in Figure 1 by the grey point. The recommendation would improve the health outcomes for cancer beyond what is currently being provided, though it would not improve health as much as implementing the most cost-effective interventions first. In doing so, it reflects the committee's desire to ensure equity of access to all cancer patients. The final package recommendation is summarized in Appendix 6.

The budget constraint compared with the budget impact of the committee's recommendation is summarized in Table 1 in 2021 Rwandan francs (RWF) and USD. For comparison, we present the current budget (A); 'basic only' scenario (B); the committee's recommendation (C), and the committee's recommendation plus enhanced (D).

The current estimated budget is 10.9 B RWF (10.4 M USD) (A), and the committee's recommendation would cost 17.1 B RWF (16.4 M USD) (C), requiring 6.3 B RWF (6.0 M USD) in additional funds (additional funds = C - A). If the basic package were funded first, it would cost 8.8 B RWF (B), which is 2.0 B RWF (1.9 M USD) under the budget (A - B). If the enhanced package were covered in addition to the committee's recommendation, it would cost 36.7 B RWF (35.3 M USD) (D) or require 25.9 B RWF (24.8 M USD) in additional funds (D - A). In all scenarios, the number of patients treated is estimated to increase from 4,100 to 5,700; the change in cost only reflects which package of service those patients receive (Table 1).

care.

Table 1: Summary of Budgets

Summary of budgets - Rwandan francs (United States dollars), annual				
	(A) Strategy 1 - Current budget	(B) Scenario 2 - Basic only	(C) Strategy 3 - Basic + core (committee's recommendation)	(D) Strategy 4 - Basic + core + enhanced
Health sector costs	10.9 B (10.4 M)	8.8 B (8.5 M)	17.1 B (16.4 M)	36.7 B (35.3 M)
DALYs averted	31,152	29,927	39,463	51,752

Discussion

Our findings reflect an iterative process of reviewing, prioritizing, and recommending cancer services to be provided by the CBHI HBP in Rwanda. Ultimately, the HBP committee recommended a cancer package focused on the basic and core packages of services to ensure equity of access across CBHI members. The possible cancer packages here are informed by a unique addition to the existing NCCN resource-stratified guidelines for 16 cancers: they include 49 cancers stratified for the Rwandan setting.

The cancer pilot took almost two years and set the foundations of a legitimate, institutionalized priority setting process in three main ways. First, it involved approximately forty stakeholders, including the multi-stakeholder HBP committee, the cancer experts, the assessment team, and numerous policy makers and development partners to deliver a robust priority setting process. This large cadre of stakeholders now have knowledge of priority setting processes and the capacity to carry out the assessment and appraisal. Second, the assessment team designed a set of standardized methods to evaluate nine criteria which can be replicated and refined in future prioritization processes. Third, standard operating procedures were developed as a means of solidifying and institutionalizing the process alongside the assessment methods which can be implemented in the future.

A few key lessons learned may inform future HBP prioritization processes in Rwanda and could benefit other countries doing the same.

First, data scarcity is a known challenge for HBPs. Despite expecting that cancer was a well-studied topic, substantially more guidance and evidence was available on the most common cancers than for rare cancers. This required the team to be pragmatic about using available local sources of data and supplementing with international evidence. Adaptations were made which came with their own challenges. For example, cancers with stratification from the NCCN were reviewed by experts for applicability to Rwanda, and cancers without stratification by the NCCN were stratified from scratch by

the cancer experts. This required training and iteration to finalize the stratification. Additionally, health effect data were unavailable for the scenarios, and were instead estimated by dividing the CER by local costs. This is a pragmatic but imperfect solution often employed in HBP design processes, though it is rarely reported clearly in the literature. The dearth of evidence overall also demanded extensive use of expert opinion, which alongside the assessment of other criteria, took more time away from clinical practice for the cancer experts. It is possible that the methods developed are specific to cancer and may need to be revised for future topics depending on the availability (or dearth) of data.

Second, the integration of donor funding into HBP prioritization remains unresolved. This assessment assumed that the cost of providing cancer services was the cost to the public sector and did not account for which services were funded by donors. The exception was imatinib, where the budget impact of it was so astronomical that it warranted special exclusion. Future prioritization processes may consider how to address donor funding more systematically.

Third, capacity building is central to institutionalizing priority setting. A key component of the cancer assessment was to train a local assessment team in evaluating each criterion and building the scenarios; training the HBP committee to appraise the evidence and the scenarios; and training the cancer experts in bridging clinical practice with priority setting processes. Over two years, capacity was built in these areas. As future topics are introduced, capacity will need to continue to be built to assess and appraise new topics.

Fourth, the evaluation and presentation of evidence could be iterated over time. Initially, evidence of the nine criteria were presented in evidence sheets (see Appendix 1, Figure 2 for a sample) alongside the package scenarios presented in this paper. The focus of appraisal was on the scenarios. Practically, the scenarios reduced the number of focal criteria from the nine in the MI to the two main criteria presented here. This is interesting because the scenarios reflect an intentional departure from pre-

established HBP 'optimization tools' which are complex and inflexible. Introducing a flexible, transparent, Excel-based tool allowed quick modification of the possible packages for appraisal and maybe a more dynamic appraisal process. In the future, it may be worth exploring whether all nine criteria are evaluated and how best they are presented.

Finally, cancer is one of many diseases that could be prioritized by CBHI. Due to data limitations, this exercise compared an estimated budget for cancer exclusively against the cost of a cancer recommendation. However, this does not account for the full resource envelope for health and how it might be most efficiently allocated across diseases. It may be worth exploring how to better estimate the full CBHI budget for future prioritization exercises and consider the allocative efficiency of the scheme as a whole.

Conclusion

The success of this pilot marks an important step towards institutionalising evidence-based, systematic priority setting in Rwanda. Moreover, this paper complements the existing HBP literature by presenting the results of the first assessment of many cancers completed in an LMIC.

Acknowledgments

The work contained in this paper would not have been possible without the input of many individuals. The authors would like to thank all the cancer experts who participated in the HBP design process; all 17 members of Rwanda's HBP committee who appraised the evidence and made the recommendations reported here; and additional contributions from the Rwanda Social Security Board, Ministry of Health, and various development partners including the Clinton Health Access Initiative, the World Health Organization, Palladium, and Management Sciences for Health.

6.4 Epilogue

The original expectation of Rwandan policy makers was to complete the assessment of cancer in 3-4 months. To meet these tight deadlines, the assessment team initially made the pragmatic choice of only assessing the top ten cancers. This was effective proof of concept: it allowed a test of aHTA methods and presenting them to the appraisal committee. However, when presented with the results, the Minister of Health requested that the remaining 67 cancers in the Rwandan guidelines (later grouped into 39 buckets) be assessed so that a recommendation could be made for all cancer treatment. Ultimately, a summary report of the assessment results and committee's recommendation was presented to the Minister of Health who approved it for implementation.

In total, completing the assessment of 49 cancers took two years. Even in selecting an aHTA approach which relied heavily on secondary data and expert opinion, it was time consuming. The dearth of data available to assess cancer was substantial, and assessment methods had to be constantly adapted and adjusted, including incorporating more expert opinion. Additionally, capacity strengthening was an important component of the process to ensure sustainability of priority setting in the future, but it took more time than anticipated. Because this was the first priority setting pilot in Rwanda, it required capacity strengthening of the assessment team to conduct the assessment; of the cancer experts to understand the priority setting process; of the HBP committee to understand the disease in question, the data within the analysis, and how to engage meaningfully in in priority setting processes; and of policy makers to review and consider the committee's recommendation.

Moreover, finalizing a recommendation with feasible coverage levels and budget impact was challenging. Many iterations were made of the scenarios to clarify the potential overall health and budget implications of different cancer packages. When I first presented the scenarios, I indicated how many services could be covered *within* the estimated budget, which reflected current expenditure. Through

the appraisal process, there was an interest in closing the gap between the cost of the recommendation and current expenditure. One important issue was that scenarios presented the *full cost* of each package at expert recommended coverage expansion rates (e.g. all basic and core packages covered). HBPs in some other countries have estimated costs for a coverage level that is lower or suggested full coverage of some interventions and cost-sharing for others.

I used the estimated opportunity cost threshold from secondary literature to indicate whether individual interventions were cost-effective or not and presented a scenario that invested in interventions in rank order of cost-effectiveness. However, both in the eventual decision and my observation during appraisal, this scenario was not discussed at length. I did observe substantial consideration around equity of access. One of my reflections was that if we had used cost-effectiveness as our primary criteria with an estimated threshold of .5x GDP per capita, fewer services would have been recommended.

The lessons summarized here could be added to the guidance in Chapter 4. This includes potentially testing assessment methods on a small set of services for proof of concept; accounting for the time it takes to build analytical capacity; and how to estimate and manage the budget in prioritizing interventions.

Overall, observing the process of supplying the evidence, presenting it and the subsequent deliberations, made me think about what the risks are for population health of such rapid processes. While there are many sources of risk for making wrong decisions, I was curious about making decisions based on imperfect data and if that risk could be communicated, and in doing so, whether recommendations would change to better align with existing or even predicted future resources.

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Chapter 7: Factoring uncertainty and risk into health service planning: an exploratory approach

7.1 Prologue

In this final results chapter, I extend the methods in Chapter 4, considering the context of Rwanda, and explore how going forward, aHTA design could be informed by explicitly considering uncertainty and the risk of making the wrong decision in rapid processes.

The interest in this chapter stemmed from my experiences in both developing analyses and observing the deliberations as presented in Chapter 5 and Chapter 6. Completing an HBP assessment that evaluated so many interventions raised the question of whether all interventions need to be assessed in the same way. Even though I applied standard aHTA methods defined in earlier chapters, and the Rwandans wanted a full assessment of all interventions, I wondered whether going forward some interventions that are either clearly highly cost-effective or not needed to be subject to the same level of assessment as those which sit at the margin. Additionally, in follow up to Chapter 6, the experience raised questions of whether better information could inform the risk of making decisions under the uncertainty of using aHTA.

There is a substantial literature in this area (explained further in the paper below) that looks at the value of more information. However, those methods in themselves require time, data and analytical capacity, so I wanted to explore if more feasible methods could be used to inform HBP assessment design. My ambition was to start to develop a novel method for designing HBP assessment methods to reflect uncertainty of the evidence for different interventions and the risk stemming from decisions based on it.

A window of opportunity opened at the close of the cancer assessment, when policy makers lamented that the assessment was time consuming, and they were under pressure to make many more decisions on many more topics. With the agreement of the HBP committee at the close of its final cancer appraisal, I sought to develop and pilot a very early stage of this framework to be considered for use in future assessments. This paper reports an exploratory approach to considering risk in designing assessment methods, with the aim that it may be further tested and developed at the start of future assessment designs in Rwanda or other countries.

In Chapter 7, I reviewed and adapted the framework for assessing risk; applied for ethics in the UK and Rwanda; collaborated with co-authors from various universities to adapt the framework; leveraged data from Chapter 5 and Chapter 6 to apply the framework to the cancer assessment; designed and conducted the survey; wrote the first draft; and presented preliminary results at Priorities 2024 in Bangkok. Full author contributions for this paper are included in the research cover sheet.

7.2 Cover sheet

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	2100817	**Title**	Mrs
First Name(s)	Cassandra		
Surname/Family Name	Nemzoff		
Thesis Title	Methods, application, and risk of 'adaptive' health technology assessment		
Primary Supervisor	Anna Vassall		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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Where is the work intended to be published?	TBD
Please list the paper's authors in the intended authorship order:	Cassandra Nemzoff, Sabine Grimm, Manuela Joore, Regis Hitimana, Andres Madriz-Montero, Sedona Sweeney, Stella Umuhoza, Rob Baltussen and Anna Vassall (joint last)
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	For this paper, I adapted the risk framework with inputs from AV, RB, SG, and MG. I populated the risk frame using data from my cost-effectiveness assessment in Chapter 5, and costing data from AMM in Chapter 6. IM and SU participated in the survey. AV was the project lead, and RH the policy lead. I wrote the first draft, and all co-authors provided feedback to the draft.

SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	1 September 2024

7.3 Paper

Factoring uncertainty and risk into planning for priority setting: an exploratory approach

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Abstract

Background: Cost-effectiveness analysis to inform health technology assessments (HTAs) is inherently uncertain, and as a result, subject to a risk of making the wrong decision. This risk is potentially exacerbated in countries that use 'adaptive' HTA (aHTA) methods to adjust for time and data constraints, particularly in assessments of many interventions at once for health benefits package (HBP) design. Current methods for assessing risk, such as value of information analysis (VOI), are research intensive and may not adequately capture the risk associated with decision making based on HBP assessments. The objectives of this paper were: 1) to develop and test an alternative, pragmatic method to evaluate the risk of using different aHTA methods for assessing cost-effectiveness; and 2) to use this evaluation to select the most appropriate aHTA methods for HBP assessments.

Methods: A four-step process was undertaken to develop and test our framework: conceptualization; adaptation; application; and selection. Conceptualization identified an existing framework that expands on VOI by illustrating different types of uncertainties in priority setting – the 'Appraisal of Risk Chart' (ARCH). Adaptation adapted the ARCH for HBP assessment design to chart the cost-effectiveness and risk of many interventions at once. Application tested the adapted framework on 148 cancer interventions recently assessed in Rwanda. Selection used a pairwise comparison survey to select which combination of three cost-effectiveness methods – expert opinion, rapid review, and modelling – was appropriate for HBP assessment based on local risk preferences.

Results: Of the 148 cancer interventions assessed in Rwanda, 30 were indicated on the ARCH as low risk because they were either very cost-effectiveness or very cost-ineffective and had a low risk score. The remaining interventions were considered higher risk because they had an ICER close to the threshold, a high budget impact, or a high likelihood of being wrong. Given a choice of methods, survey respondents selected a medium-risk assessment option combining two methods: rapid review and expert opinion.

Conclusion: These results suggest that it is possible to use an adapted version of the ARCH to determine HBP assessment methods based on local risk preferences.

Introduction

Priority setting methods are designed to inform resource allocation decisions for health(1). Central to these methods is the assessment of cost-effectiveness which weighs the costs and effects of different health interventions to prioritize those which maximize population health(2). This is often done in the context of health technology assessments (HTAs) that model cost-effectiveness and analyze budget impact(3).

Assessing cost-effectiveness is based on imperfect information which is subject to uncertainty(4). Standard uncertainty analysis accounts for uncertainties *within* a cost-effectiveness model, including parameter uncertainty, structural uncertainty, stochastic uncertainty, and heterogeneity(5). Uncertainty is often evaluated through statistical methods using deterministic or probabilistic sensitivity analysis(6).

Subsequent decisions based on uncertain information carry a risk of being sub-optimal(7). Risk combines the probability of being wrong and its consequence(8). A common framework for evaluating risk is value of information (VOI) analysis, which assesses whether collecting more information outweighs the value of making a decision based on current, uncertain information. In other words, it estimates the opportunity loss of making a decision under uncertainty(6,9). While VOI can be calculated alongside cost-effectiveness models, it is not routinely incorporated into decision making. This may be because it is time-consuming and disproportionately focuses on parameter uncertainty(10–12). Nevertheless, there a several papers in the literature which explain how to make VOI analysis computationally easier (13–15).

Countries aiming to achieve universal health coverage often work to prioritize health benefits packages (HBPs), evaluating the cost-effectiveness of many interventions at once. This necessitates 'adaptive' health technology assessment (aHTA) methods, which adapt for time, data, and capacity constraints, making use of evidence from other jurisdictions where possible(16). Cost-effectiveness methods for aHTA include expert opinion; rapid review of existing cost-effectiveness analyses (CEAs); and modelling, either through

adapting existing models or rapidly building de novo models(17). Rapid review is the most applied approach in HBPs, given the time constraints and the global availability of economic evidence(18).

Rapid reviews of existing CEAs are subject to additional uncertainties stemming from *transferring* cost-effectiveness models outside of their jurisdiction. Transferability refers to whether a study can be assessed for and applied to another setting(19). For example, structural uncertainty and price uncertainty are likely to arise if there are differences in health systems and differences in clinical practice across jurisdictions. There are no unique methods that quantify uncertainty of transferring evidence, and thus they are not routinely applied. At most, uncertainty of economic evidence in HBPs is considered when selecting cost-effectiveness studies by using simplified transferability checklists. For example, the Welte 'knock-out' criteria consider the relevance and quality of a study to understand its suitability for transfer(20,21).

The potential additional uncertainty of HBP assessments increases the risk of making a wrong decision. Evaluating this risk has rarely been done in the context of HBPs. One exception is Malawi, which implemented an adapted VOI framework using the sensitivity analyses of secondary CEAs. However, as with standard VOI, this approach only evaluated parameter uncertainty of the underlying data rather than the potential uncertainties from transferring evidence. Additionally, it was only possible to apply the framework to half of the target interventions due to inconsistent reporting of sensitivity analysis(22).

There is a missed opportunity to design HBP assessment methods based on risk. If we assume that all HBP assessments do a rapid review of existing evidence, a modified approach to VOI could help to determine whether an intervention without adequate existing evidence is low enough risk to use expert opinion or high enough risk to warrant modelling instead. Expert opinion would reduce the time and data needed but increase risk, whereas modelling would demand significantly more time and data but decrease risk. In other words, methods could be selected by explicitly trading off the key adaptations of aHTA methods – time and data – with the risk of making the wrong decision for each intervention. Additionally, a modified

approach could account for the risk preferences of those who make decisions based on the evidence produced by these methods.

The objective of this paper was to develop and test an alternative, pragmatic method to assess the risk of cost-effectiveness methods used in HBPs to inform assessment design.

The motivation for this work was the experience of designing a cancer service package in Rwanda. Rwanda has an established community-based health insurance (CBHI) scheme which covers over 80% of its citizens. The Government sought to ensure the financial sustainability of CBHI through an evidence-based prioritization process which includes the evaluation of cost-effectiveness, among other criteria(23). A recent pilot assessment prioritized 148 cancer interventions for 49 cancers. However, the cancer assessment took two years to complete and demanded significant data inputs. We thus wanted to explore whether it would have been possible to reduce this time by adjusting the aHTA methods used.

Methods

To develop and test our method for assessing risk, we took four steps which are summarized below: conceptualization; adaptation; application; and selection.

Step 1: Conceptualization

Our methods were informed by a review and framework developed by Grimm et al, which identified methods for communicating uncertainty and risk in priority setting(8). The review elaborated the shortcomings of VOI and sought to develop an alternative method for risk assessment and management that accounts for both quantified and not-quantified uncertainties. The approach proposes to facilitate the assessment of risk and related policy choices through using an 'Appraisal of Risk Chart' (ARCH), which graphically presents net benefit or loss, against potential risk(12).

In the ARCH, net benefit (y-axis) is drawn from evidence on cost-effectiveness. Risk (x-axis) includes the likelihood of a wrong decision and its impact. It combines the VOI with additional considerations for the likelihood of a wrong decision in the form of judgment on quantitative and qualitative uncertainties. To avoid information overload, not all uncertainties are included in this judgment. Rather, structural uncertainty, relative effectiveness, and generalizability of utility values were selected as the most relevant uncertainties to be incorporated into the ARCH(12).

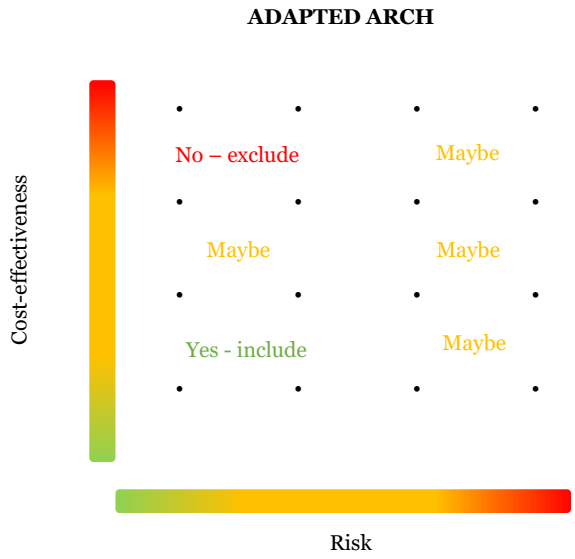
Based on this information, four quadrants of the ARCH suggest policy options for each combination of net benefit and risk. An intervention with net benefit and low risk would have a positive recommendation; one which has a net loss and is low risk would have a negative recommendation; and the uncertainty of any high-risk intervention, whether it is estimated to have a net benefit or net loss, would be mitigated using a managed entry agreements with price negotiations or further research(12). This approach is intended to inform a policy recommendation at the end of the evaluation, rather than to be an ex-ante tool for designing assessments.

Step 2: Adaptation

We sought to adapt the ARCH approach to inform the selection of aHTA methods in HBP design(18). We assume that a rapid review of existing cost-effectiveness evidence will be conducted, followed by a choice of whether to make a decision based on the current evidence, or to further evaluate an intervention using expert opinion or modeling before a recommendation can be made. The adapted ARCH is presented in Figure 1, followed by a detailed description of our adaptation.

Figure 1: Adapted ARCH

	y-axis	x-axis
Title	Cost-effectiveness	Risk
Measure(s)	Incremental cost-effectiveness ratio	Budget impact * risk score (relevance of intervention and comparator; geographic relevance; quality; unavailability)



We simplified the y-axis of the ARCH by changing it to use the incremental cost-effectiveness ratio (ICER) rather than net benefit. We indicated the midpoint of the y-axis as the cost-effectiveness threshold. Any ICER falling above the threshold reflects an intervention that is likely not cost-effective, and one below the threshold reflects an intervention which is likely cost-effective. In this way, countries which are uncertain about the threshold can consider whether to indicate multiple potential thresholds rather than tying the net benefit of each intervention to a single threshold.

The x-axis of the ARCH combines impact and risk. In the absence of formal VOI analysis, we use budget impact as an alternative to estimate interventions which may be high risk. Ideally, health impact would be included as well, but these data are more difficult to obtain to inform HBP design, so it was excluded. We also hypothesized that for an initial test of the ARCH, budget impact may be more intuitive to decision makers.

To estimate the likelihood of the wrong decision, we focused on the short list of uncertainties from the Welte knock-out criteria which include relevance of the intervention and comparator; geographic relevance, and quality(24). We then referred to the TRanparent Uncertainty Assessment Tool (TRUST), which provides a systematic approach to identifying sources of uncertainty(21). The TRUST tool considers

transparency, methods, imprecision, bias and indirectness, and unavailability(25). We reviewed whether the five TRUST aspects were well captured in the Welte knock-out criteria. Indirectness in TRUST reflects uncertainty related to transferability, which we assumed was captured well across the three Welte criteria. Quality from Welte was linked to the TRUST elements of transparency, quality of methods, and imprecision. This can be evaluated using existing checklists such as the CHEERS checklist, or simplified quality checklists such as that used by the Tufts CEA registry, a common source of secondary CEAs in aHTA(26,27). Finally, unavailability in TRUST did not link to the Welte criteria but allowed us to reflect instances where no cost-effectiveness estimate is available at all. Thus, our four uncertainty factors included the three Welte criteria and unavailability.

Finally, we examine the potential methodological implications for six areas of the ARCH. There are two places where the decision is obvious. In the low-risk quadrants, we assumed that where an intervention has an ICER which is highly cost-effective and falls below 1x gross domestic product per capita (GDP pc), it could be included without further analysis. For an intervention which is highly cost-ineffective with a threshold above 3x GDP pc it could likewise be excluded without further analysis.

In the remaining four areas of the ARCH, the decision is less obvious and may benefit from further information. This includes all three areas to the right of the chart, where uncertainty and budget impact are potentially high, and therefore a decision based on current information is risky. These areas are high-risk regardless of whether the ICER is considered cost-effective, possibly cost-effective or not cost-effective. The fourth area is where an intervention is low risk but has an ICER which falls between 1-3x GDP pc. This is because proximity of the ICER to the threshold increases the likelihood that the decision about whether an intervention is cost-effective or not is more uncertain therefore also risky. In these four cases, we assume that there are two additional methodological options: expert opinion or modelling. The selection of these methods should be based on comparing the additional costs of time and seeking data for assessment versus the potential risk of outcome in terms of budget impact.

Step 3: Application

We applied our method using a rapid review of cost-effectiveness evidence completed to support the development of a cancer service package in Rwanda. Each cancer was divided into three interventions: a basic, core, and enhanced package of care with increasing levels of treatment available, plus one prevention intervention, for a total of 148 interventions(28). Using the cost-effectiveness assessment of these interventions, we first sought to review where the interventions fell on the ARCH and how this could have influenced a potential change in methods to reduce the time and data needed.

To populate the y-axis of the ARCH, the ICERs from the cancer assessment were used. This included ICERs from the peer-reviewed literature and ICERs elicited from experts(28). We set four potential thresholds using the broad range of WHO-estimated thresholds as a guide(29), where: ICERs below 1 times gross domestic product per capita (GDP pc) we considered to be "green", or definitely cost-effective; ICERs between 1x GDP pc and 3x GDP pc were "yellow", or potentially cost-effective; and ICERs above 3x GDP pc were considered "red", or definitely not cost-effective. Importantly, we use these thresholds as an illustrative guide to provide broad categories for consideration. These should be adjusted to locally appropriate thresholds for each context, particularly given the well-known criticisms of the WHO thresholds.

We populated the x-axis of the ARCH with the budget impact and risk score. Budget impact was estimated by multiplying the unit cost per case times local incidence times an estimated 70% coverage rate from the cancer assessment. To calculate the risk score, we were guided by the International Conference on Harmonization (ICH) guidance on quality risk management(30). This guidance is used by pharmaceutical regulators and industry to make consistent risk-based decisions. In the ICH, various risk factors are scored, and the scores multiplied to estimate a total 'risk score'(31). The risk factors were the uncertainty factors from our adapted ARCH: relevance of the intervention and comparator; geographic relevance; quality; and

unavailability. The cost-effectiveness assessment of cancer documented these using a star system, where three stars is an intervention that is most transferable to the Rwandan setting and one star is the least transferable (28).

To calculate risk based on the ICH methodology, we first reversed these scores to give a 'risk score', so that 1 was the most transferable to the Rwandan setting and 3 was the least transferable (Figure 2). We then multiplied three scores for each intervention, such that the minimum risk score was 1% (1*1*1), and the maximum (3*3*3) was 27%. Interventions with no ICER were also assigned a 27% risk score.

Figure 2: Calculating the risk score

	Risk score		
Uncertainty factors	**1 (low)**	**2 (medium)**	**3 (high)**
Geographic relevance	Rwanda or other African country	Lower-middle income country	Upper-middle income country
Relevance of intervention/ comparator	Exact match	Partial match	No match
Quality	4-7	2-4	1 or unscored
Unavailability			No ICER available

Source: Adapted from Nemzoff et al. (28)

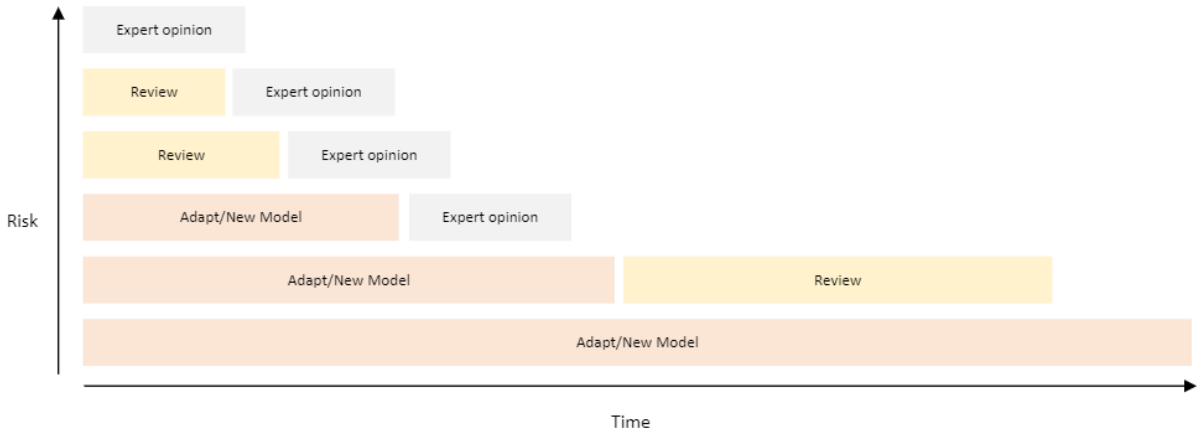
We then estimated the risk by multiplying the population-level budget impact by one plus the risk score. This is not a precise figure, but rather just reflect an indicative adjustment for risk. Together, the risk estimate is intended to illustrate that an intervention with a high budget impact and high risk score is riskier than an intervention with a high budget impact and low risk score. With this approach, we used Microsoft Excel to populate the adapted ARCH for all 148 cancer interventions. All data used from the cancer assessment to populate the ARCH is reproduced in Appendix 1.

Step 4: Selection

Last, we developed an approach to selecting aHTA methods for HBP design based on the populated ARCH which accounts for decision makers' risk preferences. In standard VOI, the cost of making the wrong decision would be compared with the cost of additional research to inform the choice of whether current information is sufficient for decision making, or more research is needed for an individual intervention(4). Rather than quantifying these costs, we defined methodological choice sets to guide the selection of aHTA methods based on the risk preferences of decision makers. Each choice traded off varying the time and data available against a relative estimate of risk. Time estimates for each aHTA method was based on a recent survey of HBP practitioners by co-authors(18). Data availability was based on the rapid review of available existing CEAs. Risk was measured relative to time, where the more time the choice takes, the less risky the choice is and vice versa. Then, instead of measuring the potential cost of each method choice, we developed a risk preference survey for decision makers in Rwanda. This allowed us to explore which methods were sufficient for decision making, based on local risk preferences.

Six choices for assessment methods were defined (Figure 3). To roughly mimic the cancer assessment, all six options assumed 150 interventions were being assessed. Of these, 50 interventions had available ICERs from the literature, and the remaining 100 ICERs were estimated using expert opinion(28). Three aHTA methods were possible: expert opinion, rapid review, or model adaptation/de novo model. We estimated the analytical time required as: one day per intervention for expert opinion; one week per intervention for review; and three months per cancer for new model(18). For modelling, we assumed that each cost-effectiveness model includes the basic, core, and enhanced package for a given cancer, covering three interventions for one cancer. Modelling all interventions would take the maximum time and carry the lowest risk, whereas eliciting expert opinion would take the least time and carry the highest risk. Any options in the middle would combine the aHTA methods to vary risk (Figure 3).

Figure 3: Assessment Options



The lowest risk option was to model all interventions. The second lowest risk option was to model the 100 interventions for which there was no cost-effectiveness data and review the literature for the remaining 50 interventions. On the opposite side, the highest risk option was to elicit expert opinion for all 150 interventions. In the middle, the remaining three options were defined based on varying risk and ordered by increasing demand on time and data. To define them, 50 interventions for which CEAs were available were categorized into three buckets based on the ARCH. 'Green' was defined as definitely cost-effective and low risk, with an ICER falling below 1x GDP per capita and the risk score falling below the median of all risk scores. 'Orange' was defined as uncertain cost-effectiveness and high risk, with an ICER falling between 1-3x GDP per capita and with risk falling above the median. 'Red' was defined as definitely not cost-effective, with an ICER above 3x GDP per capita and risk score falling below the median. The choice sets varied whether more intensive methods were completed only for the risky 'orange' interventions or all interventions. The numbers of greens, oranges and reds were rounded to the nearest 10 for simplification of the survey. The likely low risk of the green and red options reflects a situation where even if there is high uncertainty, it is unlikely that an uncertainty adjusted ICER would change the final recommendation. The full survey and time calculations for each option are summarized in Appendix 2.

The survey used a paired comparison approach to elicit risk preferences of decision makers to understand how their risk attitudes would influence their preference in methods. Paired comparisons rank a set of preferences by asking participants what their preference is between two options, across multiple

combinations of options. This is the same methodology used to estimate disability weights across multiple conditions in the Global Burden of Disease studies(32).

A small group of individuals who participated in the cancer assessment were invited to participate in the survey. Respondents included members of the assessment team, members of the national HBP committee, and development partners who participated in the process.

To introduce the survey, respondents were presented with the concept of trading off time and data with risk of completing assessment and asked to reflect on successes and challenges of the cancer assessment (Appendix 3). They were then introduced to the ARCH and presented with the adapted ARCH applied to the cancer assessment. Specific examples were provided, and time for questions allotted. The pairwise comparison approach was introduced, and each option of assessment methods in the survey explained. Surveys were completed individually and anonymously, using Google Forms. Results were assessed using the standard approach for pairwise comparisons; by summing the number of times each methodological choice set was selected to rank the preference of assessment methods.

Results

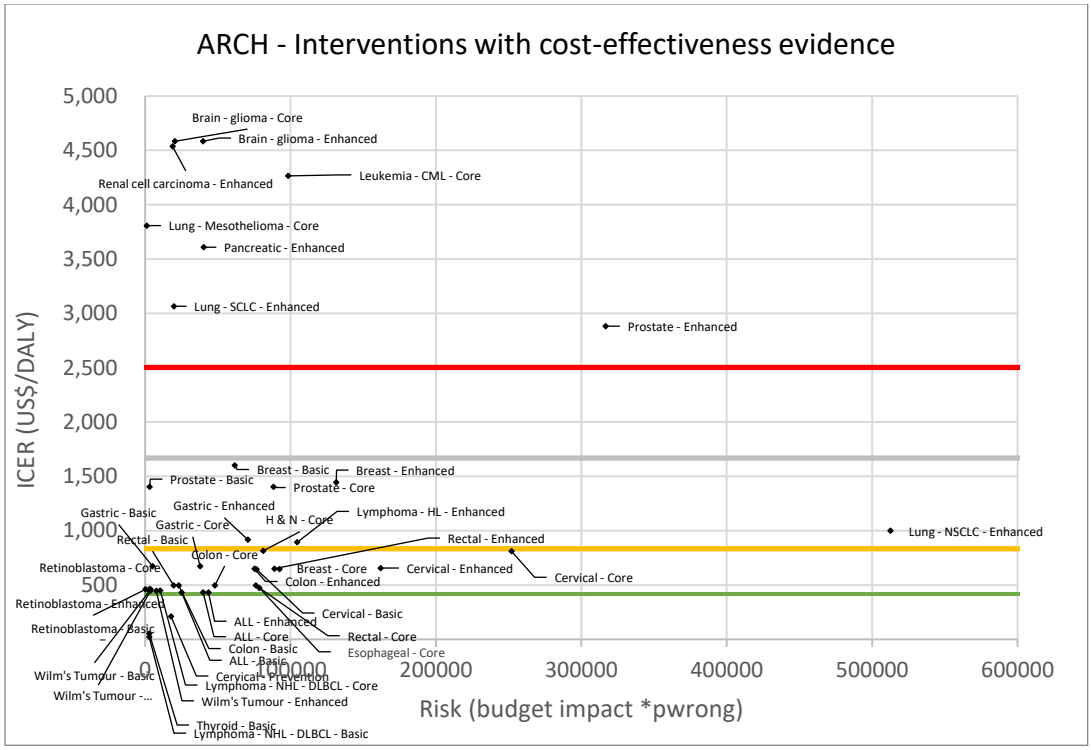
Application results

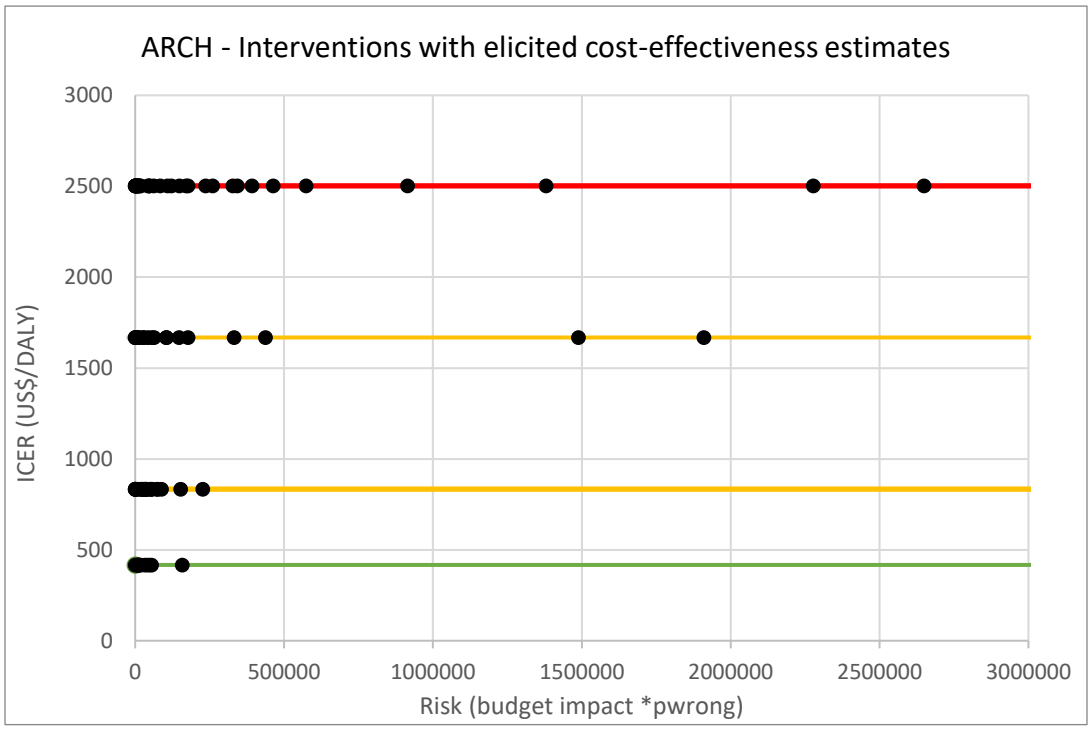
The adapted ARCH was applied to 148 cancer interventions and is presented in Figure 4. The top graph presents the 50 interventions for which the ICER was available from the literature, and the bottom graph presents the 98 interventions for which the ICER was elicited from experts. Each graph has four horizontal lines at .5x, 1x, 2x, and 3x GDP pc to illustrate the range of potential thresholds. In the bottom graph, the elicited ICERs had one of four values which corresponded to the same potential threshold values, depending on experts' judgment of whether the intervention was very cost-effective, potentially cost-effective, potentially cost-ineffective, or very cost-ineffective, respectively(28). Expert elicited values are included in Appendix 4.

Out of the 50 interventions with CEA information, 16 were categorized as ‘green’ and 6 categorized as ‘red’ (n=22). These interventions had an ICER below 1x GDP pc or above 3x GDP pc, respectively, and a risk score below the median risk of 40 K USD. These are the low-risk interventions, as cost-effectiveness can be considered relatively certain. The remaining 28 interventions were categorized as ‘orange’. These are higher risk because they fall in one of the three uncertain categories: they either have an ICER between 1-3x GDP pc or are higher risk with a higher budget impact and higher risk score. Risk is also driven by expected population coverage rates. For rare cancers with fewer cases, the population-level budget impact is lower than more common cancers and they are therefore more likely to fall in the low-risk category.

Of the 98 interventions without CEA information, 8 were categorized as ‘green’ and 13 categorized as ‘red’ (n=21). These also had an ICER below 1x or above 3x GDP pc, and a risk score below the median of 40 K USD. The higher number of ‘reds’ partially reflects interventions for which there is little cost-effectiveness information that are also more likely to have fewer cases. Thus, the overall budget impact is lower, so for interventions with an ICER exceeding 3x GDP pc, the decision to exclude is clear.

Figure 4: Application of the ARCH





Selection results

Successes of the cancer assessment reported by survey respondents included the completion of the cancer assessment and recommendation to the Minister; building local capacity; and meaningfully engaging clinicians who were key to the prioritization process. There were also a few main challenges. Participants noted that the assessment took about two years, which was much longer than the original three to four months expected. Data was scarce; existing data needed to be refined to suit the cancer assessment, and data gaps were filled with international data and expert opinion. Also, cancer was a new and difficult topic. Rwanda was the first country to assess so many cancers in depth to inform an HBP assessment. Due to this, analysts had to adapt methods over time.

The survey was completed after the general discussion, results of which are summarized in Table 1. Option 1 was the lowest risk option, and Option 6 the highest risk option. In between are the middle risk options which vary the methods for the 'greens', 'oranges', and 'reds' as described in the methods section. Respondents indicated a preference for Option 4 first, where all 50 interventions with CEA information were assessed using the rapid review method and 100 using expert opinion. The next preferred was Option 5, a review of 30 'orange' interventions and expert opinion for the remaining 120 interventions. Third, respondents preferred to shift to a lower risk option of assessing the same 30 'orange' interventions using modelling, and the remaining 120 again using expert opinion. The least preferred option was Option 1, modelling for all interventions.

Table 1: Survey results

Option	Rank	Time	Overall risk	Overview description
1	6	12.5 years	Very low risk	150 interventions: model cost-effectiveness for everything. 12.5 years.
2	5	9 years	Low risk	150 interventions: 50 rapid review in literature; 100 model cost-effectiveness. 9 years.
3	3	3 years	Low-medium risk	150 interventions: 120 expert opinion; 30 'oranges' model cost-effectiveness. 3 years.
4	1	18 months	Medium-high risk	150 interventions: 100 expert opinion; 50 rapid review in literature. 18 months.
5	2	14 months	High risk	150 interventions: 120 expert opinion; 30 'oranges' rapid review in literature. 14 months.
6	4	7 months	Very high risk	150 interventions: all expert review. 7 months.

The most preferred option (Option 4) reflects most closely the assessment method which was used for the cancer assessment. Overall, this indicates that it probably would not have been feasible to complete a riskier assessment that reduced the overall time and data needs for assessment. Nevertheless, if pressed to choose, the subsequent preferences indicate that respondents would be willing to conduct a slightly riskier assessment method to save time before switching to a less risky method to avoid the riskiest choice.

Discussion

This analysis re-conceptualized the ARCH with the aim of testing it for use in prospective aHTA methods selection. The adapted ARCH presented in this paper was intentionally simple, providing a relative estimate of risk. Applying the ARCH to the Rwandan cancer assessment demonstrated that 30 of the 148 cancer interventions could have been recommended for inclusion or exclusion based on obvious cost-(in)effectiveness and estimated risk. Survey results indicate that this type of approach would be acceptable, and indeed preferred, in the Rwandan context. These results show overall that it is possible to use the ARCH in planning the assessment of multiple health interventions.

The work presented in this manuscript is exploratory, and should be further expanded, adapted, and tested. There are several considerations, which co-authors plan to address with future refinement of the adapted ARCH.

First, the y-axis of the ARCH may be revisited. The approach presented here adapted the ARCH to include the ICER on the y-axis because it allowed consideration of more than one threshold. We also assumed this would be more intuitive to decision makers who had already been introduced to the concept of the ICER. Future iterations of the ARCH could revert to using net benefit on the y-axis as the original ARCH did, recalculated with multiple thresholds if a country sought to consider more than one threshold. This would allow for population-level considerations of both net benefit and risk, and could also avoid areas where there could be exceptions to the decision rules for the six areas of the ARCH. For example, our decision rule where an intervention is considered highly cost-effective and low risk suggests that we would generally deem it reasonable to include without further analysis. However, if the intervention offers extremely small and uncertain QALY gains, an ICER can easily shift from very high to very low, making this choice less straightforward.

Indeed, another exception to the decision rules could be where we considered an intervention with a high ICER and high budget impact to warrant further analysis. Upon further reflection, we considered whether the decision rule should be simply a 'no - exclude' in this case.

The risk axis (x-axis) of the ARCH only accounted for budget impact and four uncertainty factors to inform the likelihood of the wrong decision. This is partially because our adapted ARCH was applied retrospectively in a data-scarce environment, using the available data from an assessment of many cancer interventions. The method was intended to be intuitive: the higher the budget impact, the higher the risk, and the higher the likelihood of the wrong decision, the higher the risk. However, it was difficult to determine where the cut-off between low and high risk was using this methodology. We used the median

risk score as an indicative cut-off which worked for illustrative purposes. Moreover, our approach only accounts for the risk of spending too much on an intervention which is high-risk and highly uncertain. It does not account for the risk of not investing in an intervention which has a high health impact. It may obscure interventions which are both costly and highly beneficial, or equally, those which are both low cost and low benefit. For example, it does not reflect an intervention with high budget impact and high health impact being lower risk than one that has high budget impact and a low health impact.

Further, our uncertainty factors which informed the risk score reflect common uncertainty factors for HBP design. This still may not reflect the most important uncertainty factors for HBP design. 'Unavailability' especially simply reflected all interventions for which cost-effectiveness data were unavailable and assigned them all equally to the highest risk score. While some work has been done to synthesize existing approaches to evaluating uncertainty(33), more work could be done to review the most important uncertainty factors for HBP design, perhaps involving the expert opinion of HBP practitioners.

We envisioned that future adaptations of the ARCH would be done prospectively, and thus may face even stricter data constraints than our retrospective approach here. In cases where cost-effectiveness estimates and an estimated threshold are available for the topic and interventions under consideration, net monetary benefit could be estimated as the measure of impact using existing cost-effectiveness studies alongside our uncertainty factors. Alternatively, a rapid review of the existing cost-effectiveness data as we have here could be combined with expert elicitation on risk. The latter could include expert opinion on budget and health impact, and the likelihood of making a wrong decision. We are not aware of any examples where this has been done previously, and thus it would need to be carefully designed to clearly define the terms 'budget impact', 'health impact' and 'risk' and appropriately elicit their estimation.

Our approach also deviated from traditional VOI analysis. The adapted ARCH illustrates those interventions which are more uncertain and therefore riskier, which is similar to VOI, but partially done qualitatively.

Traditional VOI would have also estimated the cost of each methodological choice set, to determine whether more intensive aHTA methods were worth the effort. In our approach, the methodological choice set in the survey simply expressed the cost of the various aHTA methods in time (months) required to undertake the analysis, where the more time the approach took, the less risky it would be and vice versa. In addition, by asking the respondents for their preferences, we also included their risk perception. We chose this approach because data on the cost of conducting each methodological choice set was unavailable. Future iterations of the applied ARCH could seek to collect such data determine the cost of different aHTA assessment methods.

Finally, opportunities remain to refine the survey approach for use in the future. The survey sample size was small, which was adequate for the exploratory nature of this research. Future work could explore the risk preferences of the full 17-member HBP committee in Rwanda and other countries' decision makers to reflect the risk preferences of decision makers. If this approach is deemed acceptable, the methods could then be tested in future assessment design and documented as part of an overall priority setting process. It is important that this includes a definition of the type of interventions that can be subject to the ARCH. For example, the ARCH is designed for interventions which are not yet covered, rather than interventions in which the system has invested significant resources. Additionally, the survey was designed to mimic the cancer assessment. Cancer is interesting, because a small set of cancers have extensive cost-effectiveness evidence, but many cancers have no evidence at all. If the number of interventions or the type of interventions had been different (e.g. more or less cost-effectiveness evidence available), it may have yielded different results. An interesting test might be to conduct this type of survey both prospectively and retrospectively for the same assessment and compare results.

Conclusion

Evidence-based policy making is an uncertain science. Conceptualizing and applying an approach to considering the risk borne from this uncertainty can be useful for health planners to determine how they design assessments. Future work is needed to refine the adaptation of the ARCH to fit this purpose.

7.4 Epilogue

This paper is the first of its kind to propose an approach for considering risk in HBP assessment design. It presents a simplified mechanism for considering risk that could be applied to HBPs.

The application of the y-axis (cost-effectiveness) of the ARCH was straightforward. Rapidly reviewing the available cost-effectiveness data in Tufts was relatively easy. The application of the x-axis (risk) was slightly more challenging. Determining which uncertainty criteria were included was grounded in the literature, but it may be worth revisiting which uncertainties are most important and most easily communicated. Additionally, I used budget as the measure of impact because of data availability and ease of understanding, but further work is probably needed to better define the impact component.

While applying the framework retrospectively presented limitations, it has helped set the course for future work and provided several useful lessons. First, stakeholders were able to understand and use the framework to select aHTA methods. Second, I observed the stakeholders actively discuss and the risk around different interventions and how one could assess them as a result. While the total participants were only eight individuals, they comprised a mix of HBP assessment team members, HBP committee members, and development partners who were involved in the HBP prioritization process. Recurring challenges included the time it took to complete the assessment and the lack of data availability, exactly the challenges the framework was attempting to solve. Third, survey responses indicated that a medium risk option was preferred for assessment – to not take years to complete full assessments for everything, but at the same time to not take the minimum time to do an assessment with very limited data. This matched what had occurred.

My experience of developing and applying the framework presented many challenges, and further work is required to better understand risks, risk perception and the application in practice of such frameworks, compared to current gold standard methods such as VOI. As a result of this, led by my supervisors and

partners in Kenya, together with partners in Rwanda, I developed a work package as part of a large National Institutes for Health Research in the UK to further develop and test these methods over the coming 4 years.

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Chapter 8: Discussion

In the previous six chapters, I have explored and characterized existing aHTA methods, tested the application of aHTA to HBP design, and begun to explore the risks associated with using aHTA.

8.1 Summary of findings

In the absence of any clearly defined methods, Chapters 2, 3, and 4 explore and characterize aHTA methods. In Chapter 2, a rapid CEA on dialysis for acute kidney injury identifies areas where practitioners have adapted standard economic evaluation methods for CEA using the iDSI reference case as a guide. In Appendix 2: Adaptive health technology assessment to facilitate priority setting in low- and middle-income countries, I include a commentary that outlines my motivation to define and structure aHTA methods: while many practitioners are applying aHTA, at that time it was neither being done explicitly nor were the different methods fully described in the literature. This chapter enabled me to experience aHTA in practice. Chapter 3 identifies and characterizes five incremental aHTA methods for individual interventions using a systematic review of HTA agencies' aHTA methods: 'de facto HTA', 'rapid review', 'rapid cost-effectiveness analysis'; 'manufacturer-led submissions'; and 'transfers'. Chapter 4 applies the framework of methods defined in Chapter 3 to identify and characterize four sectoral aHTA methods used for HBP design using a scoping review of the HBP literature and a survey of its authors. The four sectoral methods include 'expert opinion', 'review', 'model adaptation', and 'new model'. The results of Chapter 4 are reported in a summary of existing aHTA methods for CEA in HBP design accompanied by a discussion of considerations about how to select aHTA methods. In summary, the first section of this thesis successfully characterizes a set of incremental and sectoral aHTA methods.

aHTA methods are applied in Chapters 5 and 6. Chapter 5 is a sectoral assessment of 49 cancers in Rwanda using aHTA methods: a combination of review of the Tufts CEA database and expert opinion.

Using an early version of results from Chapter 4, the review of the Tufts registry is first used as the preferred aHTA method. The initial review of Tufts highlights that while many studies are available on cancer, there is a substantial publication bias towards few, well-studied cancers. The addition of expert opinion is made to fill the gap in the cancer literature, as is often done in other HBP assessments(1). Cost-effectiveness results are summarized in league tables, separately for the 39 CERs from the peer-reviewed literature and the 83 CERs elicited from experts. Additionally, a comment I wrote for Lancet Global Health is included in Appendix 1: Aligning meta-regression analyses to policy makers' needs which complements Chapter 5 by exploring the limitations of meta-regressions as a source of CERs for HBPs. Indeed, Chapter 5 only identifies one CER predicted using meta-regression analysis, for HPV vaccination. In Chapter 6, the results of Chapter 5 are used to chart potential cancer package scenarios in Microsoft Excel. The scenarios were a central input to the Rwandan HBP committee's final recommendation.

Finally, Chapter 7 builds on Chapter 4 to introduce a novel method for evaluating risks of using aHTA. This includes both quantified and unquantified uncertainties. The results indicate that using the ARCH which articulates the risk of different aHTA methods can potentially help to guide the selection of methods in a systematic way.

8.2 Themes

The work in this thesis adds to the existing literature by improving our understanding of the role of and the methods used for aHTA in evidence-based decisions. In summary, this thesis contributes to the literature in four ways, summarized below.

aHTA methods clearly defined for the first time

First, this thesis presents a recommended characterization of aHTA methods with standardized and clearly defined terminology for each method. Despite a recent WHO survey which stated that 50 out of

127 country respondents indicated some type of rapid assessment methods, these methods were not specified in the survey(2). Rather, aHTA methods are developed and used for both incremental and sectoral analyses in siloes, drawing on varying sources of existing evidence and varying approaches to using the evidence. For example, the Canadian HTA agency's Rapid Response Service conducts rapid reviews of the existing literature; Ireland's NCPE conducts a rapid review of manufacturers' dossiers; and Ethiopia's HBP design work combined a review of the literature, estimating CERs using pre-existing WHO-CHOICE models, and expert opinion(1,3,4). My characterization is achieved through the analyses presented in Chapter 3 (systematic review) and Chapter 4 (aHTA methods in HBPs), in which key features of aHTA methods already used in HTA agencies and HBP practice are reviewed. The methods are described, defined, and articulated in terms of the time, data, and capacity needs of each.

Defining these methods is a first step in improving their replicability and helping to guide local decisions about methods selection. For example, if these had been available for the cost-effectiveness analysis of dialysis in Chapter 2, it would have enabled a structured discussion about the time, data, and capacity needed for each aHTA method and the trade-offs between them.

However, there remains heterogeneity within and across all aHTA methods used in HTA and HBP design. A greater understanding of this heterogeneity within the characterized methods would support improved guidance on each of the methods. More work is needed to fully report on the use of various methods under the characterized names. This work is already beginning to happen; since the publishing of my first BMJ commentary, the term 'aHTA' has been cited in the literature and used in various conference proceedings(5–9).

aHTA approach to make explicit choices about methods

Second, prioritizing 67 cancers with gaps in the literature necessitated aHTA methods. However, the existing methods and tools that collate cost-effectiveness evidence at a global level remain challenging to

apply in rapid HBP assessments. For example, a recent assessment from Pakistan explains that full modelling of multiple interventions was deemed not feasible, so re-running the systematic reviews in DCP to identify the best CERs for local context was piloted. However, due to inconsistent reporting and lack of detail, the analytical team was unable to re-run the reviews from DCP and instead decided to use the Tufts Registry because of its pre-extracted data and quality checks(10). Likewise, the cost-effectiveness evidence required for reviewing the 67 cancers in the Rwanda guidelines could not be completely sourced from the Tufts Registry, DCP, or WHO-CHOICE, separately or combined.

Developing and applying the framework in Chapter 4 adds a structured and transparent approach to the literature by presenting the methodological options for evaluating cost-effectiveness and the global data to support them. This can help to explicitly select the optimal approach for country contexts. An early version of the results of Chapter 4 sought to give a full description of each source of data, what it contained, and its limitations, and was used to select a review using the Tufts Registry for the cancer assessment. Recognizing the Tufts Registry would not have CERs for all cancers, the assessment team used the same framework to assume that expert opinion be used to fill gaps as is done in other HBP assessments.

The work in this thesis further builds on the existing literature by reporting the first clear, replicable methods for structured expert elicitation of cost-effectiveness ratios for HBP design. The scoping review and survey of HBP practice in Chapter 4 yielded little in terms of clear methods for expert elicitation(1,11–13). I therefore developed a de novo expert elicitation method for the remaining CERs, drawing on the general literature for structured expert elicitation(14,15). My approach used a Delphi method to elicit CERs using three sources of evidence: the 39 ICERs from Tufts for reference; estimated cost per intervention; and expert-elicited effectiveness estimates.

In summary, this thesis presents a clear framework which enables explicit choices of cost-effectiveness methods for HBP design based on time, data, and capacity constraints which could be used in any future HBP design project. It further presents the first clearly reported methods for expert elicitation of ICERs for HBP design.

Contributing to the empirical evidence base for dialysis and cancer

Empirically, this thesis contributes to the evidence base on dialysis for acute kidney injury and cancer.

Most cost-effectiveness studies on dialysis focus on chronic kidney disease, which renders patients dialysis dependent as discussed in Chapter 2. My CEA on dialysis instead focused on acute kidney injury from which patients can recover, following a short period of dialysis. Based on parameterizing this CEA and a recent systematic review on AKI-related cost-effectiveness studies, I am only aware of two other studies on the cost-effectiveness of dialysis for AKI in LMICs – in Argentina and Thailand(16–18). The study from Argentina focused on an elderly population, whereas my results are presented for a population 15-49 years old, and the study from Thailand compared continuous renal replacement therapy versus hemodialysis, whereas mine compared intermittent hemodialysis with peritoneal dialysis(16,17). My study is unique and adds to this very small evidence base. Moreover, it produces evidence on a topic identified as a priority to policy makers which is understudied elsewhere.

The cancer evidence presented in Chapter 5 and Chapter 6 contribute to the synthesized empirical evidence base on cancer. Current resources include the NCCN resource-stratified and harmonized guidelines for low-resources settings. The stratified guidelines (broken into 3 levels of stratification – basic, core, enhanced) are available for 16 cancers, though while the stratification is generally guided by principles of cost-effectiveness, they do not report cost-effectiveness evidence or CERs. The NCCN harmonized guidelines for Sub-Saharan Africa contain a single regionally recommended guideline for 43 cancers, which cover 90% of the incidence cancer cases in the region, but likewise do not include cost-

effectiveness evidence(19). Moreover, the harmonized guidelines are not stratified. DCP provides cost-effectiveness evidence for six cancers in its cancer volume, and WHO-CHOICE covers cost-effectiveness evidence for three cancers(20,21).

Chapter 5 and Chapter 6 add to these resources. First, the backbone of these analyses is a set of 148 interventions for 49 cancers which are locally stratified into the NCCN categories of basic, core, and enhanced. Chapter 5 is the first analysis of its type that reviews existing CEAs for these stratified interventions, which include all cancers found in the national cancer guideline. It identifies CERs for a total of 28 cancers, providing the first comprehensive overview of existing global evidence on the cost-effectiveness of cancer interventions to inform priority setting in an LMIC.

Based on this evidence, Chapter 6 is the first of its type to present different options of cancer packages for an HBP and compare the costs and health gains between them. Ministries of health and cancer centers in six African countries have endorsed the NCCN harmonized guidelines for Sub-Saharan Africa as the national standard of care(22), but the potential packages presented here are Rwanda-specific. Using this approach allowed for the flexibility of selecting the basic, core, or enhanced package for each individual cancer in the context of prioritizing and entire cancer package. Aside from the DCP chapter focused on six cancers, I am unaware of any other papers which present a potential HBP for cancer in an LMIC setting. Providing the stratification for 49 cancers, CERs, and potential packages tailored to an LMIC setting may prove useful to policy makers in other countries seeking to prioritize several cancers at once.

This body of work also highlights important gaps that remain in the evidence base. For example, the NCCN guidelines stratify 16 cancers (and harmonize a total of 43), though I observed in Rwanda that policy makers were still interested in stratifying and prioritizing all 49 cancers in their guidelines. In seeking cost-effectiveness evidence on these cancers, I found that very few studies in the published literature focus on the implementation of preventative and early stage, curative care for cancer which

DCP encourages(20). Rather, the existing CEAs on cancer included in the assessment are disproportionately focused on the incremental benefits of one drug versus another. Moreover, only 8-14% of economic evaluations are completed in LMICs(23). For LMICs like Rwanda seeking to implement a basic package of care for multiple cancers, I only found one study focused on multiple potential packages of care. A study from Ghana evaluated the cost-effectiveness of 11 potential cancer intervention packages for breast cancer(24).

In summary, this thesis provides empirical evidence on the cost-effectiveness of dialysis for AKI; the cost-effectiveness of interventions for 49 resource-stratified cancers; and the first reporting of a potential HBP package for cancer in an LMIC.

New methods for evaluating uncertainty of aHTA methods tested in an LMIC

Fourth, this thesis adjusts the current methods for uncertainty analysis to suit aHTA methods selection. Typically, uncertainty is quantified in a single CEA study using sensitivity analysis which focuses on parameter uncertainty(25). This is inadequate for sectoral HBP prioritization that assesses bundles of interventions using aHTA, because it does not account for the various potential uncertainties from transferring evidence.

Chapter 7 presents a novel approach for addressing multiple uncertainties in HBP design. This required considering which uncertainties were most important to include in evaluating the risk of different interventions, and which were possible to include in a data-constrained environment. Instead of a purely quantitative approach, it combines quantitative and qualitative dimensions to evaluate risk. The adapted ARCH includes qualitative measures of quality, relevance of the intervention and comparator, geographic relevance, and unavailability as uncertainty factors. These are combined with a quantitative estimate of budget impact to evaluate risk. In contrast to standard uncertainty analysis, which is applied to a single CEA, my approach is applied in a multi-intervention setting. It evaluates the risk of 148 cancer

interventions, enabling the evaluation of the methods for each in terms of risk. This approach was tested in an LMIC setting and is the first study I'm aware of that proposes the selection of aHTA methods a priori, and tests whether it would work in a live setting.

My approach requires a quick review of existing CEAs and budget impact estimates. This makes it feasible to use the framework to determine aHTA methods in a short period of time. However, it may be more difficult to apply prospectively, which I have not yet tested, and probably does not capture all the risks and complexities of evaluating many interventions at once. For example, using only budget impact for the impact component was intuitive and possible given the available data, but does not account for health impact. Depending on data availability, future iterations of the ARCH could include net monetary benefit as the measure of impact if secondary CEAs were available for most of the interventions considered, or alternatively, could use expert elicitation to evaluate the risk of different interventions. Additionally, it is possible that other transferability factors could be considered for inclusion in the framework, informed perhaps by a review or focus group on potential factors completed by HBP practitioners. The discussion in Chapter 7 elaborates these ideas of how the ARCH can be adapted in future and which data would be required.

Nevertheless, Chapter 7 is the first of its type which applies qualitative and quantitative uncertainty factors to evaluate the risk of assessing multiple interventions for HBP design.

aHTA research is expanding

My role and this PhD have been critical to identifying aHTA as an important area for both research and practice. I have presented this work widely, others are already applying this work, and a community around this field is developing. A recent comparison of full HTA and aHTA from India(5) builds on my characterization of aHTA methods and evaluates the validity and accuracy of results from aHTA compared with full HTA. An applied aHTA was published in India, and I have co-authored another paper

which is in review and reports results of 10 aHTAs completed for the Indian National Cancer Grid(26). Another forthcoming study, of which I was invited to co-author, is a cross-sectional analysis of the rapid reviews reported in the INAHTA database using my characterization of aHTA methods to provide more clarity and specificity on the methodological steps. The risk framework in Chapter 7 complements earlier and ongoing work on the benefits of aHTA: a study from Ireland estimated the number of appraisal days saved by doing aHTA for half of all technologies reviewed(27), and a forthcoming study from the National University of Singapore and HITAP will look at the return on investment (ROI) of aHTA, building on previous work on the ROI of full HTA(28). aHTA was also the topic of discussion for the latest ISPOR Regional Roundtable for Latin America in August 2024, focused on how to assess mid- to high-cost drugs and technologies that have a large population impact(29).

8.3 Areas of future research

aHTA methods and application remains a novel but growing field of research, and there are many possible future research directions.

Methods from low- and middle- income countries

The systematic review on aHTA methods in Chapter 5 highlighted formal aHTA methods found in mostly in HICs but mentioned the use of aHTA methods in several LMICs as well. For example, the Institute for Clinical Effectiveness and Health Policy (IECS) in Argentina has been practicing aHTA for the past 20 years, though under a different name. However, while I am aware of these methods, they were not captured in the scope of my review because the grey literature search sought formally published aHTA guidance and I did not identify any such guidance from IECS. A more detailed review or consultations with LMIC practitioners about their methods could be completed and compared with existing HIC methods.

Refined ‘triggers’ of aHTA

Likewise, the systematic review identified a set of potential ‘triggers’ for aHTA including urgency, certainty, and low budget impact. More work could be done to identify triggers for use in other contexts, including LMICs. This could be accompanied by guidance on how to select these triggers for use in national contexts. For example, it could identify which data are available to support the triggers, e.g. whether budget impact data are available to support a trigger based on low budget impact.

Testing and refining aHTA methods selection

The guidance for selecting cost-effectiveness methods for HBP design in Chapter 4 is based on completed HBP design work by practitioners. Further testing of the approach to selecting methods is needed in different jurisdictions to refine and expand how the considerations I presented might be applied in different contexts. Considerations may also vary depending on whether assessments are incremental or sectoral. Complementary research could be done to survey HTA practitioners doing incremental analyses to better understand the time, data, and capacity constraints considered in taking aHTA-like approaches for individual technologies. Together with the HBP work presented here, the trade-offs between incremental and sectoral analyses could be documented.

Additionally, this work was only designed for the selection of cost-effectiveness methods. New literature reviews could be completed to review methods and adaptations of how other criteria are assessed, and what the time, data, and capacity trade-offs of those are. Ultimately, a framework could be developed which considers the tradeoffs in time, data, and capacity between the assessment of all criteria. This framework, along with other components of this thesis and new research proposed here could potentially be used to inform a first reference case for aHTA methods.

Align priority setting methods and tools to policy maker needs

The application of methods in Chapters 5 (cost-effectiveness of cancers) and Chapter 6 (cancer package scenarios) call into question whether a broader effort to explore, refine, and align priority setting methods and tools developed mostly by HIC institutions with the context they serve is needed. This would require independently reviewing the existing global evidence, methods, and tools (e.g. Tufts, DCP, WHO-CHOICE) and comparing it to policy makers' needs to assess whether it is fit for purpose. There is a need to evaluate whether the existing tools and methods support collaborative global health research that is suited to national context or serve a global agenda. For example, identifying which topics are understudied but of most concern to policy makers could direct future research, rather than refining resources with already substantial data on well-studied topics (as in the case of meta-regression analyses). Perhaps a study could be done which maps available evidence, surveys policy maker demand, reports disease burden, and considers which interventions are donor-funded or government funded to help facilitate this decision. It could also be useful to include addressing simple methodological questions such as how many prioritization criteria should be used? The shift from nine criteria to two by focusing on cancer package scenarios in my Chapter 6 perhaps reflects the cognitive overload of too many criteria and leads to questions about how many criteria should be assessed(30). More work could be done to refine lists of criteria to match with the aHTA construct, considering how much time, data, and capacity are required for each and all collectively.

Better evidence to evaluate cost-effectiveness of health benefits packages for cancer

The evidence presented in Chapter 5 and Chapter 6 contribute to the empirical evidence base for cancer HBPs in LMICs. Improving the limitations of these data would improve future HBP prioritization exercises related to cancer. For example, cancer incidence rates drove my estimates of total costs of different

packages, and some of the potential cancer packages were revised to focus on stages I-II or I-III only. However, there was likely uncertainty in both the incidence rates reported in the cancer registry, and those predicted by IHME. Additionally, stage reporting was incomplete in the Rwandan cancer registry and had to be estimated and extrapolated using global studies. Better reporting of cancer incidence and staging of cancer could be done within Rwanda's cancer registry to inform future cancer package developments. Improving the reporting in cancer registries has indeed been made as a general recommendation for all LMIC registries by global cancer experts(31). Additionally, the cost-effectiveness evidence presented here only reflect the existing CEAs on cancer reported in the Tufts Registry and the expert opinion of Rwandan cancer experts. The cost-effectiveness of cancer has been studied much more in HICs than LMICs(20). Further work could be done to conduct more CEAs in LMIC contexts. This could ease the burden of transferring CEAs designed for HICs to an LMIC context. It would also better reflect packages of appropriate cancer care in LMICs which could include for example local costs, locally estimated disability weights, and discount rates that better reflect the economic growth of LMICs(31).

Moving ahead with priority setting in Rwanda

Results presented in this thesis are part of Rwanda's first formal priority setting exercise for which cancer was chosen as a priority. An important next step is the implementation of the cancer package, which is underway by the Ministry of Health and Rwanda Social Security Board. While I have not participated in the implementation process, I am aware it is ongoing due to several requests for information on the budget impact of the committee's final recommendation.

Cancer is one of many priority topics identified in a recent plan to ensure the financial sustainability of the CBHI scheme in Rwanda. In the evaluation of future topics, the approach reported in this thesis for selecting methods (based on risk), evaluating cost-effectiveness, and defining potential packages of care may be useful to again adapt for available time, data, and capacity in country. I hope that the co-

production of Chapter 5 (cost-effectiveness), Chapter 6 (cancer packages), and Chapter 7 (risk) has strengthened the local capacity to navigate the design of the next prioritization exercise. Through completing the prioritization of cancer and strengthening local capacity, future priority setting exercises in Rwanda will be well placed to support the CBHI sustainability agenda by ensuring CBHI covers services that reflect value for money and other locally important criteria. I plan to further support this through a 4-year National Institute for Health Research grant led by my supervisors, in which I included plans to advance the development of aHTA and advancement of the ARCH framework in Rwanda and Kenya.

Refine risk framework

More work needs to be done to refine the method for assessing the risk of aHTA and test its use. While Chapter 9 (risk framework) highlights that risk is not routinely considered in full HTA processes, I argue that considering risk is even more important for aHTA. Risks of using aHTA include that aHTA is used for technologies it is not well suited for (e.g. those with limited available evidence); it could be inappropriately used to replace full HTA; and relatedly, it could be used in this way to evaluate many interventions unsuited for aHTA at once with substantial impact on public health schemes. Future research to refine the risk framework could help to rectify some of these concerns. This could include focusing on the optimal approach for measuring impact, as Chapter 9 only focuses on budget impact. It could also explore which types of uncertainties are most important, and options for measuring them quantitatively or qualitatively. Local risk preferences of decision makers in the priority setting process could be assessed and contribute to any refinement of the method. Finally, further testing whether the ARCH is feasible in different contexts for the practice of selecting methods is needed.

Notably, this thesis was completed under the international Decision Support Initiative grant from the Bill and Melinda Gates Foundation. The shift in focus from incremental analyses to HBPs reflects the changing policy landscape in Rwanda. Had this shift not occurred, I may have focused my thesis work

more on aHTA for rapid CEAs, building on the dialysis assessment. I may have also had more time to focus on quantifying the trade-off between aHTA and full HTA, an aim I never quite explored. However, this shift allotted me the opportunity to make linkages between incremental and sectoral approaches to priority setting, and more importantly, to have an applied thesis that responded to policy demand.

Overall, additional practical papers that clearly explain why aHTA methods were selected, how they were conducted, and any challenges in applying the method could benefit practitioners in nascent priority setting systems.

8.4 Limitations

Limitations are discussed within the chapters of this thesis, but here I summarize what I consider to be the most important limitations and those which stretch across my thesis.

The dialysis results in Chapter 2 do not answer questions about whether to provide dialysis at lower levels of care, which has been used in other contexts to improve the availability and cost-effectiveness of dialysis provision(32). Formal aHTA methods are defined in Chapter 3 using methods mostly from HICs, which may not be ideal for LMICs. There also remains heterogeneity across aHTA methods, so my definitions should not be viewed as prescriptive. The approach to selecting aHTA methods in Chapter 4 is based on HBP practitioners' experience but may not yet be optimal because it still needs to be tested and refined. Cost-effectiveness results for cancer in Chapter 5 are disproportionately based on expert opinion, which is likely uncertain. For those CEA studies which were included, in many cases I used an ACER of the intervention or the comparator, which is pragmatic but imperfect. The cancer packages in Chapter 6 provide broad potential packages of services but because of the many CER estimates from expert opinion, and indeed health effects estimated from existing ICERs and local costs, the health effects are likely uncertain. The risk framework in Chapter 7 still needs to be tested a prori, rather than after an assessment as was done in this chapter.

Additionally, there are several limitations of the entire thesis. The work presented herein was carried out in a live policy context. My methods and results are synthesized in the thesis, but reflect iterative adjustments made throughout the project based on testing, learning, and changing requests from the cancer experts and policy makers. Additionally, these methods have been developed for many cancer interventions; the same iterative process of developing and refining new methods may be required for new topics if they are also understudied in LMICs. The definitions and frameworks presented here are based on the literature but have not yet been fully tested by practitioners. These have not been substantially contested, and as previously mentioned, are starting to be applied in the literature. However, I have not been able to formally test whether the methods presented are acceptable to other practitioners. The *incremental* aHTA methods would benefit from more clarity to improve their replicability, an aim I am starting to support with co-authoring the cross-sectional analysis of rapid HTA reports from INAHTA. Additionally, one of my main motivations was to develop methods which encouraged locally owned decisions. The application of the definitions and framework for *sectoral* analyses would benefit from being used and refined in several contexts, as I was not able to fully test whether my methods could be used for this purpose, or formally test the acceptability and feasibility of using these methods for local practitioners. It is possible that the methods I summarize are biased towards those which are published in the literature, which makes testing the acceptability and feasibility even more important. Based on my own experience building the methods and simultaneously strengthening capacity, further modifications may need to be made to adjust for the available number of people and skills available for working on prioritizing the HBP at any given time. Finally, I have not tested the risk of aHTA versus full HTA methods which would require further adjustments to the risk framework.

8.5 Conclusion

aHTA has been practiced for many years by many practitioners, but in an ad hoc way. The work of this thesis contributes to the establishment and formalization of aHTA as a discipline, which can be used in any country seeking to improve the efficiency of their priority setting system. aHTA is in a nascent development phase with many unanswered questions. I hope to continue my work in this space, partially through the NIHR grant I have mentioned which focuses on 'what works' in HBP design and includes the further advancement of the ARCH framework, and hopefully in other projects as well. As part of this work, I am keen to continue testing and refining methods that focus on the available time, data, capacity in any priority setting system.

8.6 References

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Chapter 9: Appendices

Appendices – Chapter 1

Appendix 1: Aligning meta-regression analyses to policy makers' needs

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Striving for Universal Health Coverage (UHC) and the current global economic crisis means that many countries are having to prioritise funding for health. These challenging decisions need to be informed by evidence of what works and what is cost-effective. In The Lancet Global Health, Fiona Silke and colleagues(1) report a new meta-regression analysis of cost-effectiveness evidence that will contribute to this effort. In their analysis, Silke and colleagues produced incremental cost-effectiveness ratios (ICERs) for 14 health interventions for HIV/AIDS, tuberculosis, malaria, and syphilis across 128 countries.

The data produced in Silke and colleagues' analysis is one of several resources that collates cost-effectiveness estimates for use by national decision makers. Other important sources are Disease Control Priorities (DCP), which synthesises ICERs for a set of essential, cost-effective services for low-income and middle-income countries (LMICs) by income-level; WHO's CHOosing Health Interventions that are Cost-Effective (WHO-CHOICE)(2), which produces ICERs for 20 disease areas for different regions, with the option of modelling country-specific estimates; and the Tufts University Cost-Effectiveness Analysis Registry (CEA Registry), which collates approximately 11 000 global cost-effectiveness studies.

Meta-regression analyses add to this space by quantitatively extrapolating country-specific ICERs. Only two similar analyses have been done previously, for HPV and rotavirus vaccinations(3,4). However, the potential for new meta-regressions is limited because they depend on the availability of multiple studies per intervention. Silke and colleagues' sample ranged from 57 articles for antiretroviral therapy for HIV to just five articles for treatment of drug-susceptible tuberculosis. This range reflects a skewed global evidence base. Generally, few cost-effectiveness studies are from LMICs, and they tend to focus on communicable diseases, whereas high-income countries have a substantial evidence base that is mostly focused on non-communicable diseases. A vacuum remains for policy makers wanting to make evidence-based decisions on under-studied topics.

Silke and colleagues explored differences across ICERs from different countries using four covariates: gross domestic product (GDP) per capita, disease burden, efficacy, and cost of traded goods (e.g., drugs). However, these covariates might not capture the full uncertainty of cost-effectiveness estimates. For example, the studies included exclusively used disability-adjusted or quality-adjusted life-years, which are standard outcome measures that enable comparison across diseases. The literature on HIV/AIDS is expansive, however, many such studies were excluded from this analysis because of their heterogenous outcomes. Additionally, the covariates used might not fully capture setting-specific drivers of cost-effectiveness. Fundamentally, the intervention in each cost-effectiveness study varies by country. For example, in cancer, one study's intervention might be a specific drug, and another study's might be a package of early-stage cancer treatment that includes that drug. Silke and colleagues recognised this limitation, excluding seven interventions in HIV/AIDS prevention due to inconsistent definition. DCP, WHO-CHOICE, and Tufts University CEA Registries similarly use different nomenclatures. Ultimately, countries need to understand whether the cost-effectiveness estimates from meta-regression analyses are of better quality and more certain than simply identifying a single study with an intervention that matches local clinical practice and using a standard checklist to determine how relevant it is to the local context.

For a domestic policy maker seeking to use estimates from this study, interpreting the authors' league tables should also be done cautiously. League tables rank interventions in order of cost-effectiveness so that they can be added preferentially until the budget is exhausted. Uncertainty intervals are provided around the cost-effectiveness estimates to account for uncertainty, but they overlap across interventions, making it difficult to determine the true cost-effectiveness ranking. The uncertainty intervals highlight which interventions need more specific estimates, but also a major limitation in the underlying data.

Furthermore, the 14 interventions assessed in this meta-regression analysis are a subset that had data available and are recommended by the Global Fund to Fight AIDS, Tuberculosis and Malaria, but do not include all possible interventions in a typical tuberculosis or HIV/AIDS programme budget. Moreover, interventions that were defined as cost-saving (i.e., decreased costs and improved health simultaneously) were excluded because predicting their cost-effectiveness is not meaningful. The final decision of what interventions should be provided, as the authors indicate, needs to be determined by use of the league tables alongside a cost-effectiveness threshold. A threshold is the ICER that interventions need to fall under to be affordable within current budgets but is notoriously difficult to estimate for each country.

Silke and colleagues provide two estimated thresholds: one as GDP per capita, as suggested by WHO, and a country-specific estimate determined using data from Pichon-Riviere et al.(5). However, the combined uncertainty of the estimates and the threshold complicate decision making(6).

The added value of this study is the production of several additional ICERs using meta-regression analysis, the models for which will accelerate the completion of future meta-regressions. At the same time, the study highlights that there are still gaps in the evidence base for under-studied diseases that might be priorities for policy makers seeking to spend domestic funds. The research community might consider where future analyses can be most impactful, perhaps focusing on areas with an increasing burden of disease but little evidence of cost-effectiveness (e.g., early stage, curative cancer care). I congratulate the authors on this impressive undertaking that contributes valuable evidence for global priority setting and raises as many questions as it answers.

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Appendix 2: Adaptive health technology assessment to facilitate priority setting in low- and middle-income countries

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Introduction

Traditional Health Technology Assessment (HTA) is a policy-based research process which aims to improve the efficiency and equity of the healthcare system with the limited financial resources available in healthcare(1). In various countries, traditional HTA has been 'institutionalized' – through the development of dedicated agencies with accepted norms and rules that guide explicit priority setting – over years or decades. These agencies use time-consuming, data intensive and systematic methods and processes which require health economics expertise and resources to make recommendations on how to allocate finite resources(2).

There is a growing appetite for HTA and its eventual institutionalization in low-and-middle income countries (LMICs) driven in part by the World Health Organization's (WHO) recommendation for it to be a critical component to achieving universal health coverage(3). While there are notable LMIC exceptions of introducing and institutionalizing HTA (e.g. Thailand, Colombia, Brazil, and India), others are constrained by limited technical and administrative capacity, paucity of data, time, and governance structures to carry out HTA(4).

A more pragmatic approach which we define in this paper as "adaptive HTA" (aHTA) is one which uses various expedited or flexible methods and processes that are 'fit-for-purpose' and could help to tackle some of these challenges faced by LMICs. Here, we suggest how policy makers, researchers, clinicians, and donors can collaborate and support the development and uptake of aHTA for LMICs to enable expedited evidence-based decision making in these countries as one part of the journey towards HTA institutionalization.

What is adaptive health technology assessment?

Ideally, all health policy decisions should involve the use of HTA processes and methods which offer quality, context-specific, and locally relevant evidence. However, where the 'gold standard' of HTA is not

immediately possible, countries may seek to expedite or adapt some aspects of the HTA approach(5). The broad concept of adaptive HTAs is not new, having been used in high-income countries including in the United Kingdom (UK), Canada, and the European Union(6,7). These approaches are largely focused on expedited processes to respond to time constraints, for example, in the case of a new technology or a public health emergency(8). However, there are limited examples from LMICs transferring the same types of approaches, as LMICs are more likely to be constrained not only by time, but also by capacity, resources and data. Hence there is a need for HTA processes, methods, and analytics that can be adapted to suit LMIC HTA constraints.

We seek to define adaptive HTA (aHTA) as a blanket approach for HTA methods and processes which are fit-for-purpose and focused on context-specific practicality considerations. Methodologically, aHTA may leverage or adapt available international data, economic evaluations, models, and/or decisions from the published literature or established HTA agencies to expedite policy decisions whilst adequately accounting for concerns of transferability and uncertainty(9). The aHTA process should be pragmatic, though still informed by key HTA principles such as transparency, independence, consultation, and contestability.

There is no 'one-size-fits-all' approach to aHTA as no two health systems are alike, but generally components of traditional HTA can be modified or adapted pragmatically to suit LMICs' needs (Table 1). Hence, aHTA may benefit LMICs which either have a nascent HTA agency or not one at all, and do not receive HTA submissions from pharmaceutical companies. In circumstances where an LMIC does have an active HTA agency with adequate capacity to appraise evidence, it may be feasible to receive pharmaceutical dossiers as part of the HTA process.

Table 1: Methods and trade-offs for adapting traditional health technology assessment in low- and middle-income countries

	Traditional HTA	Adaptive HTA in LMICs*	Trade-offs
Timeline	8-12 months +	1 – 6 months	• Level of comprehensiveness • Speed
Topic selection	Detailed topic selection process with established criteria and fits government priorities	No process *or* Opportunistic process *or* Minimal criteria	• Identifies low-hanging fruits • Local relevance • Range of topics
Analysis	De novo economic evaluation (e.g., cost-effectiveness analysis)	Price benchmarking *or* Literature reviews *or* Adapted economic evaluation *or* Outsourced economic evaluation	• Accuracy • Quality • (Un)certainty • Builds capacity • Leverages available data
Data sourcing	Local studies + primary data collection and systematic literature review/meta-analyses as needed	Pragmatic / sources known to authors	• Level of comprehensiveness
Appraisal	Multi-stakeholder group guided by agreed principles appraises evidence and makes policy recommendations	No appraisal *or* Modified appraisal process	• (Sub)optimal decisions • Level of HTA system improvement and health system strengthening
Implementation	Wide ranging policy changes could include adjustment to health benefits packages, essential medicines lists (including appropriate indications), price negotiations, reimbursement decisions, clinical guidelines, care pathways, and quality standards. *		• (Sub)optimal allocation of resources • Mobilizes HTA institutionalization

Figure 1 demonstrates potential different approaches for each step of a traditional HTA versus an adapted HTA for the LMIC context. Depending on the adaptation(s) selected, a range of potential trade-offs could be associated with each of these steps which should be considered when using aHTA, as well as the alternative of using no evidence at all.

**While aHTA and traditional HTA can inform similar policy decisions, aHTAs cannot be used for all technologies, as discussed below.*

Adaptive health technology assessment methods

There are numerous aHTA methods which vary by scope, approach, complexity, and mix of data sources used depending on contexts-specific constraints(10). The loosely categorized examples below demonstrate the breadth of these approaches which we are aware of in LMICs.

Expedited Process: The Filipino HTA guidelines set out a rapid review process for public health emergencies(11).

Adaptation of International Data Sets: The World Bank's Health Interventions Prioritization (HIP) Tool and Disease Control Priorities have consolidated international evidence on burden of disease, cost, and cost-effectiveness which have been adapted to inform benefits package design in Afghanistan, Armenia, Cot d'Ivoire, Eswatini, Pakistan, and Zimbabwe(12,13).

Literature Reviews and Synthesis: In Vietnam and Romania aHTAs gathered and synthesized international evidence on safety, clinical efficacy/effectiveness, cost-effectiveness, and clinical guidelines for high-cost drugs. Potential savings from rational use of medicines were then calculated(14,15).

Price Benchmarking: Also in Romania and Serbia 'indirect' cost-effectiveness analyses compared a set of high-cost drugs to a gross domestic product-adjusted list price in benchmark countries (e.g. UK, United States, Australia) to ascertain the maximum value at which each medicine might be cost-effective locally(15,16).

Modeling: In South Africa, a UK model was adapted to evaluate early breast cancer treatment using the Mullins checklist – a model adaptation tool(17). Similar model adaptations were done in Tunisia and Jordan(18,19).

Notably, these are analyses which have been carried out as one part of the HTA process, though the extent to which they have influenced policy or been implemented may be varied, or absent (e.g. Romania)(9).

Limitations of using adaptive health technology assessments

The primary incentive for using aHTA in LMICs is to serve policy makers who may be short on capacity, resources, time, or bandwidth to take decisions for various government processes such as budget

negotiations, ministerial and parliamentary meetings, procurement contracting, and tariff negotiations(20). In such situations pursuing an aHTA approach represents a practical and useful option; rather than taking up to one to two years for a full HTA process from topic selection to implementation as is perhaps usual under more traditionally applied HTA frameworks, aHTA provides relevant evidence quickly and reduces the domestic analytical burden.

However, aHTA also has its limitations, the most important of which is transferability of international data and information to the local setting, a process which can increase the uncertainty of results. Even for topics which are well studied in other countries, the evidence is often from high- or middle-income countries that have different health systems, healthcare costs, patient characteristics, burdens of disease, value judgements, and provider/clinical practice norms than the country under study(21). This is further complicated if the evidence used comes from countries where the HTA recommendations are linked with academic and commercial in confidence data (such as the UK), as well as by the publication bias towards technologies with positive cost-effectiveness results. If not adequately acknowledged in the appraisal process using available approaches for assessing transferability with the right expertise in health economics, reliance on misinterpreted international evidence risks leading to sub-optimal decision making(9,22). Furthermore, if evidence for many technologies is quickly reviewed without such expertise, it could result in a disproportionate number of cost-ineffective technologies being covered, putting unnecessary pressure on the sustainability of public finances as it did in Romania using a rapid "scorecard approach" (23).

In addition to transferability, aHTAs can generally only be conducted on topics for which international data and/or models are available. For topics which are not well-studied globally, de novo collection of local data is required. Depending on the topic and availability of locally relevant data, aHTA may also demand substantial local clinical expertise to understand local health system constraints, clinical pathways and outcomes, all of which are critical to transferring evidence from other jurisdictions.

Furthermore, aHTA may not build the needed wide-ranging capacity – in epidemiological and medical statistics, health economics, HTA processes, evidence appraisal, and translation of economic evidence to policy – or create the incentives for building capacity to support HTA institutionalization(9). If countries rely solely on aHTA as an approach to priority setting despite its limitations, sustainable HTA infrastructure and processes may never be built and reliance on development partners may continue.

Finally, while the HTA process has been undertaken in many LMICs and adapted in various ways, publications which detail HTA modifications, benefits, pitfalls, and lessons learned are limited. Moreover, we are not aware of any publication which assesses an aHTA approach against a more traditional one to empirically understand these benefits and pitfalls.

Benefits of using adaptive health technology assessment as a 'tool' in the toolbox

The limitations of aHTA make it clear that while it can offer some relevant and adequately nuanced evidence, which is better than no evidence at all, it is not a replacement for traditional HTA approaches, even those based on more expedited processes but still requiring significant expertise (e.g. NICE's Single Technology Appraisal). Rather, it is possible that aHTA, if fit-for-purpose, could be a permanent tool in a larger HTA toolbox as it already is in many countries, and support the long-term uptake of HTA. We have found through our work at the international Decision Support Initiative that *doing* HTA rather than *talking* about HTA is a useful and impactful means of sensitizing key stakeholders on the processes and analytics required for good HTA. Through lived experiences, aHTA can spark demand for future HTAs and uncover key data gaps that need to be addressed for use in HTA.

Furthermore, aHTA saves time by identifying 'low-hanging fruits,' – well-studied technologies which are known to be cost saving, highly cost-effective or very cost-ineffective internationally – minimizing the amount of effort required for review. This can allow resource space to be made available for the conduct of more intensive HTAs dedicated to local priorities and technologies that are not well studied in other

countries or those that are well studied but there is greater uncertainty about their marginal benefits and costs. Local capacity building can then be a much greater feature in the conduct of such HTAs.

For the future, aHTA requires developing processes, governance structures, and analytics that can be leveraged to support a fully institutionalized HTA model. In multiple countries, aHTA has created the impetus for small HTA 'core teams', mini topic selection processes, and appraisal processes which can be directly built upon for HTA institutionalization. Policy makers are also keen to incorporate local data into the aHTA, including for example, cost, epidemiology and coverage rates, which in turn demands locally relevant, more complex, analysis(24). In the first instance, there are a few initial steps that researchers, policy makers, and donors could take to support the uptake of aHTA:

- For HTA practitioners, write and publish peer-reviewed examples of aHTAs for global knowledge sharing, detailing where HTAs were adaptive, how they were modified, and strengths, weaknesses, and lessons learned.
- For researchers, develop, test and validate a set of standardized approaches for conducting aHTAs in LMICs – drawing on lessons learned from other LMICs' HTA journeys – articulating strengths, weaknesses, and uncertainty of each approach and identifying necessary skill sets for implementation.
- For policy makers, leverage aHTA as one mechanism for evidence-based decision making, identify priority topics for aHTA and those which demand more detailed analysis, build processes and governance structures which include aHTA, or even develop a 'reference case' for the conduct of aHTA.
- For clinicians, develop clinical practice guidelines, pathways, and health benefit packages that are more cost-conscious and informed by aHTA approaches at least initially, which are updated subsequently if evidence from a traditional HTA becomes available.

- For donors, support the uptake of aHTA and long-term HTA institutionalization through making key investments such as capacity building, model sharing, model databases, and ICER databases (e.g. Tufts Cost-Effectiveness Analysis Registry), as well as including HTA uptake as a key indicator for sustainability and aid transition.

Conclusion

Policy makers in many LMICs are often having to make health financing decisions for their available resources with limited information. Despite limitations, aHTA frameworks can offer evidence where there may otherwise be none whilst demonstrating the uses of HTA, uncovering gaps in data and capacity, and facilitating the use of HTA going forward.

Acknowledgements

The authors would like to thank the anonymous reviewers for their contributions to the manuscript.

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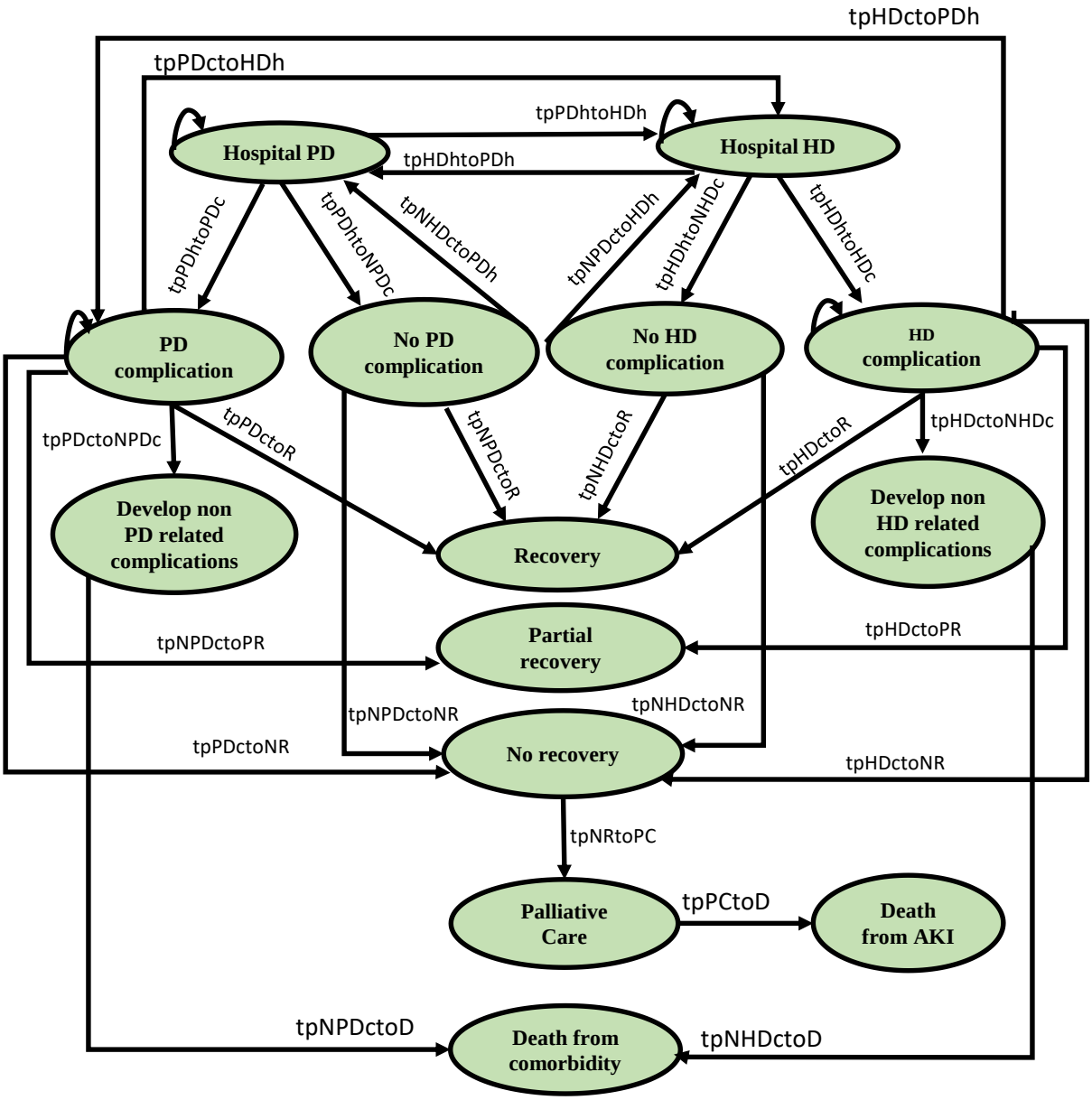
Appendices – Chapter 2

Appendix 1: Markov Model Structure AKI eligible for PD vs. HD dialysis



Appendix 2: Data collection

To drive the search strategy, the team developed an initial *high level* data summary with needs and potential sources for the HTA - as presented in Table 2 below - and shared it with key policy makers.

Table 2: Data Summary

Parameters	Potential Sources
Disease Burden	
Population	World Bank; Rwanda National Institute of Statistics
Prevalence	IHME; local observational studies
Mortality	WHO population life tables; demographic and heath survey (DHS); randomized control trials; local observational studies
Effectiveness	
Clinical effectiveness + quality of life	Systematic reviews of RCTs / RCTs; meta-analysis; systematic reviews; LMIC/LIC studies
Costs	
Costs of HD	Recently published cost analysis; national tariffs; personal communication
Costs of PD	Same as HD
Cost of palliative care	LMIC/LIC studies
Cost to patient	Patient surveys; hospital billing/claims; personal communication
Resource Use Data	
Resource Use (e.g. health staff time, facilities, consumables)	Prospective data collection/ local billing data; previous economic evaluations; personal communication

The initial data request was then expanded with iterative data collection based on the availability of local information and the willingness of local stakeholders to engage in the process and provide more detailed information. The search strategy was then based on a pragmatic approach, including the following steps:

1. The HTA developers reviewed an already completed iDSI review on dialysis requested by RSSB in early 2019 which summarized the available evidence on the costs and cost-effectiveness of dialysis for AKI patients with a focus on SSA and specifically, Rwanda.
2. Four local nephrologists and one international nephrologist expert on dialysis were identified. Consultation with these experts helped to unearth additional published and unpublished studies on clinical effectiveness and financing/costing studies in the field of dialysis of which experts had knowledge. These consultations also informed the structure of the model by clarifying the care pathway for patients with AKI.
3. Where there were data missing, the team drew on the iDSI network to source reliable dialysis models and studies. This included models and studies from Thailand's Health Intervention and Technology Assessment Program (HITAP), a core partner of iDSI, which has led important dialysis studies in Southeast Asia and are known to represent a reliable source of information to support this model development.
4. A simple literature search strategy supplemented the above information. It was designed and used to search two electronic databases: EMBASE (Ovid) and PubMed (Ovid). This simple search strategy combined terms for the interventions or comparators of interest with terms for the target condition (dialysis for AKI) as well as terms for CKD as it was not the target condition, but the authors expected it to be better studied than AKI. It was also focused on available studies in Sub-Saharan and/or East Africa, to establish whether there are more locally relevant studies than those sourced through the above methods.

Full details of the terms used in the literature search are presented below in Table 3.

Table 3: Search criteria

1	Dialysis OR PD OR HD OR peritoneal dialysis OR haemodialysis OR hemodialysis
2	AND AKI OR Acute Kidney Injury OR CKD OR Kidney Failure OR Chronic Kidney Disease OR Kidney failure
3	AND Test OR testing OR treatment OR test*
4	AND Cost OR Costs OR Costing OR Cost-effectiveness OR Cost-effectiveness analysis OR effect* OR effective* OR expenditure OR healthcare costs
5	AND Africa OR SSA OR Sub-Saharan Africa OR Rwanda OR Kenya OR Uganda OR Tanzania OR Burundi OR Malawi OR Mozambique OR DRC OR Democratic Republic of Congo

Additional terms:

- Past 10 years only
- No limits applied for study design or language

Appendix 3: Cost Summary and Breakdown

This appendix provides a detailed overview of costs included in each cost component and how they were calculated. All costs are expressed per patient and have been adjusted to 2022 RWF and current US dollars using the consumer price index (CPI) method (where adjusted costs = base year costs x (2022 CPI/base year CPI)), and the 2022 exchange rate US$ 1 : RWF 1031.

The table below provides an overview of costs which have been included in base case modelling, as well as the scenario.

Table 4: Costs

	Payer Perspective	Scenario
Sessions	18	5
PD Inputs	Direct medical costs; palliative care; dialysate; salaries; overhead	All costs @ 5 sessions
HD Inputs	Direct medical costs; palliative care; kits; salaries; overhead; depreciation	All costs @ 5 sessions

Direct medical costs

Direct medical costs for PD included the cost of a PD catheter, catheter insertion, anesthesia, drugs, consumables, labs, dialysate, and palliative care. These figures were provided by RSSB as a supplement to the RSSB 2018 dialysis costing study; lab costs for PD and HD were assumed to be equivalent. Direct medical costs for HD included drugs, HD catheter, HD kit, laboratory tests, other acts/procedures (catheter insertion, IV injection, medical fee, and wound dressing), other consumables not specific to the dialysis kit, and other laboratory tests (those not done by all facilities). These figures were sourced directly from the RSSB 2018 dialysis costing study. Both interventions were presented in that study as a session cost for a ‘new’ case and a session cost for ‘old’ cases. For each, we summed the cost of the initial ‘new’ session plus a ‘per session’ cost for the remaining 17 sessions modelled (and in scenario analysis, the remaining four sessions). The per patient direct medical unit cost for HD was calculated

using a straight line average of the total direct medical costs for provision across the four facilities where HD is delivered to CBHI patients (King Faisal Hospital (KFH), Rwanda Military Hospital (RMH), The University Teaching Hospital of Kigali (CHUK), and The University Teaching Hospital of Butare (CHUB)), while the cost for PD was sourced from the only hospital which provides PD services, KFH.

Direct non-medical costs

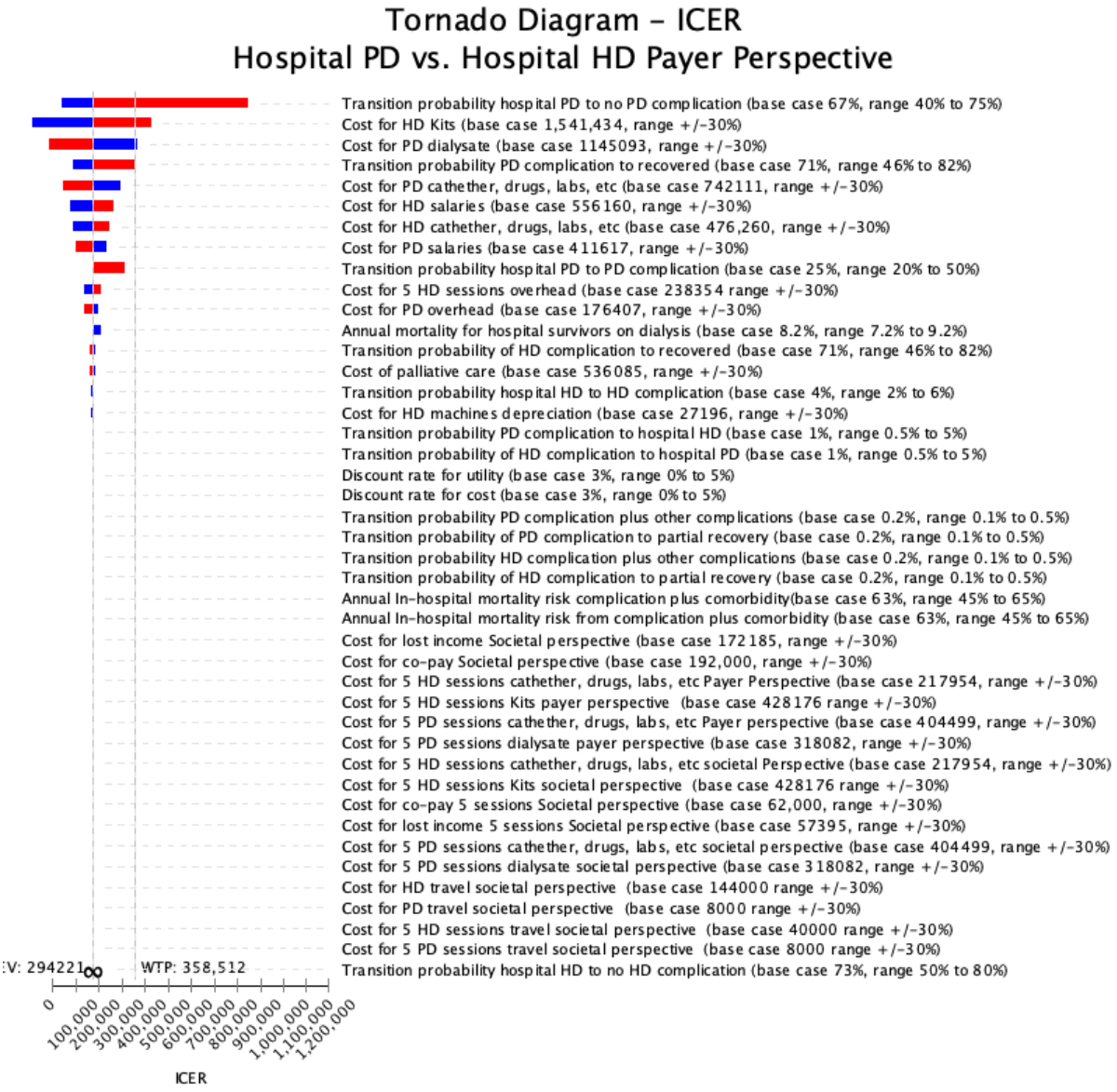
Both PD and HD incurred additional direct costs from salaries and overheads. Annual salary costs were calculated using a combination of staffing needs estimated by local experts and co-authors and salaries drawn from the 2019 Rwanda Health Labor Force Survey (which reported salaries in 2016 RWF). Staffing needs for PD and HD are summarized in Table 5 below. At CHUK, we assumed that 100% of each staff is allocated to HD services and used 2017-2018 patient volumes to calculate a unit cost per patient for staff. Then, due to uncertainty about staffing of PD services, we use the proportionate total cost of PD: HD services (74%) multiplied by the unit cost for HD services to estimate the unit cost for PD services (Table 5). Overheads were assumed to be 30% of total annual operating costs (staff + overheads).

Table 5: Staffing needs

Staffing Type	Salaries (2022 RWF)	PD (KFH)	HD (CHUK)
Nurses	5,645,725	2	4
Nephrologists	22,363,115	1	1
General Practitioners	13,616,805	1	1
Lab Technicians	5,645,725	0	1
Cleaning staff	960,769	1	1
Total costs (2022)		48,232,139	65,169,314
PD: HD proportion		74%	
Volume of HD patients			91
Per patient HD staff cost		530,024*	716,146**

**Per patient HD cost at CHUK * 74%*
***Total staff costs at CHUK ÷ 91*

Appendix 4: One-Way Sensitivity Analysis



Appendix 5: CHEERS Checklist

Table 6: CHEERS Checklist

Section	Item No	CHEERS checklist—Items to include when reporting economic evaluations of health interventions	Yes/ Partly/ No/ Unclear/ NA	Page #
Title and abstract				
Title	Q1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis," and describe the interventions compared	Yes	p1, line 1
Abstract	Q2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes	p2, lines 4-23
Introduction				
Background and objectives	Q3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance to health policy or practice decisions.	Yes	p3 lines 15-22
Methods				
Target population and subgroups	Q4	Describe the characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes	p6 lines 3-4
Setting and location	Q5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes	p6 line 3
Study perspective	Q6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes	p7 line 11-14
Comparators	Q7	Describe the interventions or strategies being compared and state why they were chosen.	Yes	p6, line 6-9
Time horizon	Q8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes	p6 line 1
Discount rate	Q9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Yes	p8 line 21-24
Choice of health outcomes	Q10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes	p8 line 17
Measurement of effectiveness	Q11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Yes	
	Q11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.		p8 line 12-16
Measurement and valuation of preference-based outcomes	Q12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Yes	N/A
Estimating resources and costs	Q13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with alternative interventions. Describe primary or secondary research methods for valuing each resource item regarding its unit cost. Describe any adjustments made to approximate to opportunity costs.	Yes	p7 line 20- p8 line 7
	Q13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item regarding its unit cost. Describe any adjustments made to approximate to opportunity costs.		
Currency, price date, and conversion	Q14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Yes	p8 line 8-10
Choice of model	Q15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show the model structure is strongly recommended.	Yes	p7 line 2-3
Assumptions	Q16	Describe all structural or other assumptions underpinning the decision-analytical model.	Yes	p7 line 5-9

Analytical method	Q17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	Yes	p7 line 17-19
Results				
Study parameters	Q18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Yes	Table 2
Incremental costs and outcomes	Q19	For each intervention, the report means values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes	Table 3
Characterizing uncertainty	Q20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Yes	
	b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Yes	p11 lines 7-14, p12 lines 4-10
Characterizing heterogeneity	Q21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Yes	p10 lines 13-18
Conclusion				
Study findings, limitations, generalizability, and current knowledge	Q22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge	Yes	p14 lines 4-13, p15 lines 1-6
Source of funding	Q23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	Yes	p19 lines 17-18
Conflicts of interest	Q24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of journal policy, we recommend authors comply with the International Committee of Medical Journal Editors recommendations	Yes	p19 line 15

Appendices – Chapter 3

Appendix 1: Reviewed HTA Agencies/Departments

Table 7: HTA agencies and departments

Country	HTA Network/List	HTA Agency/Department Name
Argentina	RedETSA	Centro Universitario de Farmacologia -CUFAR. Universidad de La Plata
Argentina	RedETSA; INAHTA	Instituto de Efectividad Cllinica y Sanitaria - IECS
Argentina	RedETSA	National Commission for Health Technology Assessment (CONETEC) - Ministry of Health
Argentina	RedETSA	Red Argentina Pública de Evaluación de Tecnologías Sanitarias (RedARETS)
Armenia	WHO	SCDMTE
Australia	WHO	Pharmaceutical Benefits Advisory Committee (PBAC) and Medical Services Advisory Committee (MSAC)
Austria	WHO; INAHTA	Gesundheit Österreich GmbH and Austrian Institute for HTA
Bangladesh	WHO	None
Belarus	WHO	THE REPUBLICAN SCIENTIFIC AND PRACTICAL CENTER OF MEDICAL TECHNOLOGIES, INFORMATIZATION, MANAGEMENT AND ECONOMICS OF PUBLIC HEALTH (РНПЦ М)
Belgium	WHO; INAHTA	Belgian Health Care Knowledge Centre (KCE)
Benin	WHO	Direction de la programmation et de la prospective (DPP) et Direction des hôpitaux
Bermuda	RedETSA	Bermuda Health Council
Bhutan	WHO	Essential Medicine and Technology Division, Ministry of Health
Bolivia	RedETSA	Ministerio de Salud (Unidad de Medicamentos y Tecnología en Salud)
Brazil	WHO; RedETSA	CONITEC - National Committee for Technology Incorporation
Canada	WHO; RedETSA	CADTH
Cape Verde	WHO	Direction Generale de la Pharmacie et du Medicaments
Chile	RedETSA	Departamento de Evaluación de Tecnologías Sanitarias y Salud Basada en Evidencia (ETESA/SBE) - Ministerio de Salud de Chile
China	WHO	China National Health Development Research Center
Colombia	WHO; RedETSA	Instituto de Evaluación Tecnológica en Salud (IETS)
Costa Rica	RedETSA	Casa Costarriquense de Seguro Social and Ministerio de Salud Costa Rica
Croatia	WHO	Agency for Quality and Accreditation in Health Care and Social Welfare
Cuba	RedETSA	Cuba - Ministerio de Salud - Departamento de Innovación y Evaluación de Tecnologías Sanitarias
Cyprus	WHO	Pharmaceutical Services, Ministry of Health
Denmark	WHO	Danish Health and Medicines Authority
Dominican Republic	RedETSA	Superintendencia de Salud y Riesgos Laborales (SISALRIL)
Ecuador	WHO; RedETSA	Coordinación General de Desarrollo Estratégico en Salud - Dirección Nacional de Inteligencia de la Salud - Ministry of health.
El Salvador	RedETSA	Unidad de Evaluación de Tecnologías Sanitarias - Ministry of Health
England	INAHTA	National Institute for Health and Care Excellence
Estonia	WHO	Department of Public Health, University of Tartu
Finland	WHO; INAHTA	Finnish Coordinating Center for HTA (FinCCHTA) and FIMEA
France	WHO; INAHTA	Haute Autorite de Sante (HAS)
Georgia	WHO	State Regulation Agency for Medical Activities

Germany	WHO; INAHTA	Iqwig - Institute is the Foundation for Quality and Efficiency in Health Car
Germany	WHO; INAHTA	The Federal Joint Commission - G-BA
Guatemala	WHO; RedETSA	Unidad de Plan /SIGSA/OPS-OMS/OSAR
Honduras	RedETSA	Agencia de Regulación Sanitaria de Honduras (ARSA)
Hungary	WHO	OGYÉI ETF TEI
India	WHO	HTAIn
Indonesia	WHO	Komite Penilaian Teknologi Kesehatan (Komite PTK)
Iraq	WHO	N/a . Ministry
Ireland	INAHTA	National Centre for Pharmacoeconomics (NCPE)
Italy	WHO; INAHTA	AGENAS
Jamaica	WHO	National Surveillance Unit
Japan	WHO	Central Social Insurance Medical Council (Chuikyo)
Jordan	WHO	N/A
Kazakhstan	WHO; INAHTA	Республиканский центр развития здравоохранения
Lithuania	WHO	State Health Care Accreditation Agency under the Ministry of Health
Luxembourg	WHO	Ministère de la Sécurité sociale
Malaysia	WHO; INAHTA	Malaysian Health Technology Assessment Section (MaHTAS)
Mali	WHO	Cellule de Planification et de Statistique
Malta	WHO	Office of the Chief Medical Officer
Mexico	WHO; RedETSA	Centro Nacional de Excelencia Tecnológica en Salud (CENETEC)
Micronesia	WHO	Budget & Planning
Monaco	WHO	No agency
Mozambique	WHO	No agency
Netherlands	INAHTA	The National Healthcare Institute / Zorgininstituut Nederland
New Zealand	WHO	National Health Committee
Norway	WHO; INAHTA	The National system for introduction of new methods in Specialist Health Care and Norwegian Institute of Public Health (NIPH)
Panama	RedETSA	Gorgas Instituto conmemorativo GORGAS de estudio de la Salud.
Panama	RedETSA	Ministerio de Salud de Panama
Paraguay	RedETSA	Ministerio de Salud Publica y Bienestar Social
Peru	RedETSA; INAHTA	Instituto de Evaluación de Tecnologías Sanitarias e Investigación
Philippines	Other	Health Technology Assessment Council
Poland	WHO; INAHTA	Agency For Health Technology Assessment and Tariff Systems
Portugal	WHO	INFARMED ,Äì National Authority of Medicines and Health Products, I.P.
Republic of Korea	WHO; INAHTA	National Evidence-based healthcare Collaborating Agency (NECA)
Romania	WHO	National Drugs Agency
Russia	INAHTA	Center for healthcare quality and assessment control
Saint Vincent	WHO	Health Information Unit
Saudi Arabia	WHO	ICT
Scotland	Other	Scottish Medicines Consortium (SMC)
Serbia	WHO	Committee for HTA
Singapore	WHO; INAHTA	Agency for Care Effectiveness
Slovakia	WHO	The Working Group for Pharmacoeconomics, Clinical Outcomes and Health Slovak Ministry of Health Technology Assessment of the Slovak Ministry of Health

South Africa	WHO	Essential Drugs Programme
Spain	WHO	Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del Sistema Nacional de Salud
Spain	INAHTA	Instituto de salud Carlos III - Agencia de Evaluación de Tecnologias Sanitarias - AETS
Sweden	WHO; INAHTA	The Swedish Council on Health Technology Assessment (SBU)
Switzerland	WHO	Swiss HTA
Syria	WHO	Planning and international collaboration directorate
Thailand	WHO	Health Intervention and Technology Assessment Program
Tunisia	INAHTA	INEAS
Turkey	WHO	General Directorate of Health Research Department of HTA
Tuvalu	WHO	National Drug and Therapeutic Committee
Ukraine	INAHTA	Department of HTA at the State Expert Center of the Ministry of Health
Uruguay	INAHTA	Health Assessment Division of the Ministry of Public Health
USA	WHO; INAHTA	Agency for Healthcare Research and Quality
Wales	INAHTA	Health Technology Wales
Networks	BeNeLuxA, EUnetHTA, HTAsiaLink, INAHTA, RedETSA	

Appendix 2: Inclusion and Exclusion Criteria

Inclusion criteria

- Systematic reviews or methodological papers on the methods of aHTA (including rapid HTA)
- Papers on design/development/testing of new approaches to aHTA/rapid HTA which are not found in the grey literature search
- Papers focused on rapid/adaptive approaches to HTA which:
    - Reflect on strengths, weaknesses, or experiences
    - Gather perspectives from experts on aHTA methods
    - Detail the appropriateness or predictors for using aHTA instead of full HTA

Exclusion criteria

- Rapid HTA papers on horizon scanning or early HTA or orphan drugs
- Systematic reviews or meta-analyses of HTAs/economic evaluations on a specific topic/technology
- Papers about clinical practice of rapid technologies
- Papers on the history of HTA in a country
- Challenges and lessons learned for doing HTA/EE on a specific disease
- Applied or experiences of individual technologies' or hospitals' rapid cost-effectiveness analyses or rapid review methods or transferred HTAs
- Conference abstracts, meeting reports and summaries

Appendix 3: Published literature search strategy

Table 8: Search Strategy

#	Searches
1	Technology Assessment, Biomedical/
2	Technology transfer/
3	1 and 2 [MeSH only combination]
4	Technology Assessment, Biomedical/
5	Technology transfer/
6	4 or 5
7	Time Factors/
8	(rapid and (review* or process* or respons* or synthes* or assess* or evaluat*)).ti,kf.
9	(rapid adj3 (review* or process* or respons* or synthes* or assess* or evaluat*)).ab.
10	7 or 8 or 9
11	6 and 10 [MeSH and text word combination]
12	((health technology assessment? or HTA or HTAs) and (rapid or mini)).ti,ab,kf.
13	((health technology assessment? or HTA or HTAs) and (adapt* or adopt* or transfer* or translat* or reproducibility)).ti,kf.
14	((health technology assessment? or HTA or HTAs) adj6 (adapt* or adopt* or transfer* or translat* or reproducibility)).ab.
15	12 or 13 or 14 [Text word only combination]
16	3 or 11 or 15
17	limit 16 to yr="2006 -Current"
18	limit 17 to (english or portuguese or spanish)
19	("34635994" or "27673610" or "32113633" or "30975388" or "19126250").ui. [Relevant papers]

Appendix 4: Methods for development of taxonomy

While aHTA has been carried out by many practitioners, no standardized taxonomy has been defined to date. To add to the methods to develop the taxonomy from the main text, we provide the following additional information:

First, we extracted as much detail as possible from the grey literature on each aHTA approach. In the attached supplement, the relevant extraction categories include: the name (Grey Literature Part 1-J), details of the method (Grey Literature Part 2-G, Part 3-B-E), and source of aHTA conduct (Grey Literature Part 4-E). We noticed heavy emphasis on the aHTA methods and decided to narrow our scope to focus on that. We then went back and reviewed the full extraction to identify recurring adaptive characteristics and considered the names and methods to bucket them into the categories reported in results (Grey Literature 1-J-K, Published E-F). An extract of the country, name of the aHTA approach, and standardized aHTA name are summarized in the table below.

Table 9: Summary of aHTA names

Country of origin	Name of aHTA approach	Standardized aHTA name
Belgium	Rapid review	Rapid review
Canada	Summary with critical appraisal	Rapid review
Canada	Rapid Response Systematic Review and Meta-Analysis	Rapid review
Canada	Rapid Response Reference Lists and Summary of Abstracts Reports	Rapid review
Chile	Sintesis rapida de evidencia/rapid synthesis of evidence	Rapid review
Croatia	EUnetHTA HTA Adaptation Toolkit	Transfers
Denmark	Foreign HTA with comments; HTA - cancer drugs	Rapid review
UK	Interventional procedures	Rapid review
France	Rapid assessment method for assessing medical and surgical procedures	Rapid review
Hungary	Balanced assessment scorecard	De-facto HTA
Ireland	Rapid review	Rapid manufacturer submission
Malaysia	1) Mini-HTA 2) Rapid Review	Rapid review
New Zealand	Rapid/ Preliminary/Indicative HTA	Rapid CEA/CUA
Philippines	Rapid Review	Rapid review
Romania	De-facto HTA	De-facto HTA
Scotland	Abbreviated Submissions	Rapid manufacturer submission
Singapore	Medical technologies evaluation	Rapid manufacturer submission
Singapore	Drug and vaccine evaluation	Rapid manufacturer submission
South Africa	Technical review report	Rapid review, rapid CEA
Spain	Rapid HTA	Rapid review
European Union	Adaptation toolkit	Transfers
UK	Fast-track appraisal	Rapid manufacturer submission

Appendix 5: All Included Papers

Table 10: Included papers: grey literature

Grey literature						
#	**Agency / Department**	**Year**	**Country / Network**	Title	**aHTA Type**	**Source**
1	Belgian Health Care Knowledge Centre (KCE)	2017	Belgium	Method - Rapid Reviews	Rapid review	(26)
2	Canadian Agency for Drugs and Technologies in Health	2015	Canada	(Peer Reviewed) Summary with Critical Appraisal Process Rapid response systematic review and meta-analysis process Rapid Response Reference Lists and Summary of Abstracts Reports Process	Rapid review	(48–50)
3	Department of HTA and Evidence-Based Health - MoH Chile	2017	Chile	Methodological Manual - Rapid Synthesis of Evidence to Inform Health Policies	Rapid review	(52)
4	Agency for Quality and Accreditation in Health Care and Social Welfare	2011	Croatia	The Croatian Guideline for Health Technology Assessment Process and Reporting	Transfer	(63)
5	Danish Health and Medicines Authority	2008	Denmark	Health Technology Assessment Handbook	Rapid review, rapid manufacturer submission	(53)
6	National Institute for Health and Care Excellence	2016	England	Interventional procedures programme manual Guide to the process of technology appraisal	Rapid review, rapid manufacturer submission	(37,43)
7	Haute Autorite de Sante (HAS)	2007	France	Rapid Assessment Method for Assessing Medical and Surgical Procedures	Rapid review	(54)
8	National Centre for Pharmacoeconomics (NCPE)	2021	Ireland	Rapid Review Template	Rapid manufacturer submission	(56)
9	Malaysian Health Technology Assessment Section (MaHTAS)	2015	Malaysia	Health Technology Assessment Manual	Rapid review	(32)
10	National Health Committee	2015	New Zealand	Prescription for Pharmacoeconomic Analysis	Rapid cost-effectiveness analysis	(36)
11	Health Technology Assessment Council	2020	Philippines	Philippine HTA Methods Guide	Rapid review	(42)
12	Scottish Medicines Consortium	2021	Scotland	Guidance to submitting companies on abbreviated submissions	Rapid manufacturer submission	(57)
13	Agency for Care Effectiveness	2018/ 2021	Singapore	Medical Technologies Evaluation Methods and Process Guide Drug and Vaccine Evaluation Methods And process guides	Rapid manufacturer submission	(29,35)
14	Essential Drugs Programme	2021	South Africa	Health Technology Assessment Methods Guide to Inform the Selection of Medicines to the South African National Essential Medicines List	Rapid cost-effectiveness analysis	(30)
15	Spanish Network of HTA Agencies and Services of the National Health System	2011	Spain	Guideline for the Elaboration and Adaptation of Rapid Health Technology Assessment Reports	Rapid review	(51)
16	EUNetHTA HTA Adaptation Toolkit and Glossary	2011	EUNetHTA	EUNetHTA HTA Adaptation Toolkit and Glossary	Transfer	(86)

Table 11: Included papers: published literature

Published literature						
#	Authors	Year	Country	Title	Assessment Method	Source
1	Danko et al.	2017	Hungary; tried in Slovakia, Serbia, and Bulgaria	Balanced assessment systems revisited	Expert opinion	(87)
2	Almeida et al.	2021	Brazil	Opportunities to improve reporting of rapid response in health technology assessment	Literature/aHTA review	(77)
3	Featherstone et al.	2015	N/A	Advancing knowledge of rapid reviews: An analysis of results, conclusions and recommendations from published review articles examining rapid reviews	Literature/aHTA review	(33)
4	Hailey	2009	Canada, Spain, Australia, Brazil, USA	A preliminary survey on the influence of rapid health technology assessments	Survey	(83)
5	Hamel et al.	2021	N/A	Defining Rapid Reviews: a systematic scoping review and thematic analysis of definitions and defining characteristics of rapid reviews	Literature/aHTA review	(47)
6	Harker and Klijnen	2012	England, Belgium, Australia, Canada	What is a rapid review? A methodological exploration of rapid reviews in Health Technology Assessments	Literature/aHTA review	(79)
7	Kalo et al.	2012	England + Central-Eastern Europe	Transferability of National Institute for Health and Clinical Excellence recommendations for pharmaceutical therapies in oncology to Central-Eastern European countries	Literature/aHTA review	(76)
8	Kaltenthaler et al.	2011	England	The National Institute for Health and Clinical Excellence Single Technology Appraisal process: lessons from the first 4 years	Literature/aHTA review	(70)
9	Kaltenthaler et al.	2011	England	Evidence review group approaches to the critical appraisal of manufacturer submissions for the NICE STA process: A mapping study and thematic analysis	Literature/aHTA review	(84)
10	Kaltenthaler et al.	2016	England	The use of rapid review methods in health technology assessments: 3 case studies	Literature/aHTA review	(88)
11	Kelly, Moher and Clifford	2016	Australia, Canada, England, Korea, Malaysia, Netherlands, Switzerland, US	Quality of conduct and reporting in rapid reviews: an exploration of compliance with PRISMA and AMSTAR guidelines	Literature/aHTA review	(46)
12	Khangura et al.	2014	Canada	Rapid review: an emerging approach to evidence synthesis in health technology assessment	Expert opinion	(89)
13	Lopert, Ruiz, and Chalkidou	2013	Romania	Applying rapid 'de-facto' HTA in resource-limited settings: experience from Romania	Expert opinion	(65)
14	MacPhearson and Thompson	2017	Scotland	Experiences in Adapting European Network for Health Technology Assessment Rapid Reviews to Inform Local Decision Making	Literature/aHTA review	(75)
15	McIntosh et al.	2016	Scotland	The Healthcare Improvement Scotland evidence note rapid review process: providing timely, reliable evidence to inform imperative decisions on healthcare	Expert opinion	(82)
16	Murphy and Redmond	2017	Ireland	Rapid reviews with health-technology assessments in reimbursement systems - An examination of Ireland as a case study	Literature/aHTA review	(38)
17	Murphy and Redmond	2019	Ireland	To HTA or Not to HTA: Identifying the Factors Influencing the Rapid Review Outcome in Ireland	Literature/aHTA review	(72)
18	Nemeth et al.	2020	Eastern Europe	The transferability of health technology assessment: the European perspective with focus on central and Eastern European countries	Expert opinion	(90)
19	Nemzoff et al.	2021	LMIC	Adaptive health technology assessment to facilitate priority setting in low-and middle-income countries	Expert opinion	(13)
20	Pichon-Riviere et al.	2012	Latin America	Transferability of health technology assessment reports in Latin America: an exploratory survey of researchers and decision makers	Survey	(73)
21	Pieper et al.	2013	Croatia, Australia, Scotland, Germany, Belgium, England	Methodological approaches in conducting overviews: current state in HTA agencies	Literature/aHTA review	(74)
22	Radu et al.	2016	Romania	The Development of the Romanian Scorecard HTA System	Literature/aHTA review	(64)
23	Silva et al.	2018	Brazil	Rapid response in health technology assessment: a Delphi study for a Brazilian guideline	Survey	(34)
24	Perez, et al.	2017	European union	Methodological guideline for the efficacy and safety assessment of new pharmaceuticals: implementation of EUnetHTA's recommendations	Expert opinion	(31)
25	Varley et al.	2022	Ireland	The Utility of a Rapid Review Evaluation Process to a National HTA Agency	Literature/aHTA review	(44)
26	Wadmann and Kjejllberg	2019	Denmark	New model for prioritised adoption and use of hospital medicine in Denmark since 2017: Challenges and perspectives	Expert opinion	(55)
27	Watt el al.	2008	Australia	Rapid versus full systematic reviews: validity in clinical practice?	Literature/aHTA review	(91)
28	Ballard	2017	N/A	Risk of bias in overviews of reviews: a scoping review of methodological guidance and four-item checklist	Systematic review	(69)
29	Drummond	2015	Middle-income countries	Challenges Faced in Transferring Economic Evaluations to Middle Income Countries	Survey	(92)

Appendix 6: aHTA country examples

Rapid Review

The Canadian 'Rapid Response Service' has four RR products that provide information to national and regional ministries, health authorities and hospitals. The timeline ranges from five days for a summary of abstracts to three months for a rapid systematic review. The method uses limited literature searching and requires systematic reviewing skills. For the more comprehensive products, it also requires critical appraisal skills(48–50).

Rapid CEA

New Zealand's PHARMAC undertakes CEAs with varying levels of intensity, with the least intensive leveraging pragmatically sourced data and completed in less than two weeks. During this time, a basic economic model is built on opportunistically sourced data; tested to ensure its sufficiency; briefly documented to ensure replicability; reviewed internally; and could include reviews or basic amendments to external analyses. PHARMAC also takes submissions from industry, so this may limit the number of 'in house' rapid CEAs they undertake(36).

Rapid manufacturer submissions

England's Single Technology Appraisal is an abridged version of its full HTA which accepts submissions from manufacturers as the main source of data which are then reviewed by an independent evidence review group (ERG) and subsequently appraised by the National Institute for Health and Care Excellence (NICE). This process takes 35 weeks and requires manufacturers to present a decision analytical approach to clinical and cost-effectiveness(70). Generally, it requires critical appraisal skills to review the manufacturers' submission alongside technical review skills from the ERG.

Transfers

The EUNetHTA Adaptation Toolkit uses a modular template for transferring studies to first analyze relevance, reliability, and transferability(86). It can then use this information to facilitate local re-modelling of cost-effectiveness, as is done in Croatia(63). In other words, it improves the efficiency of HTA conduct by leveraging reports and transferable evidence from other jurisdictions to develop locally relevant HTA reports.

Appendix 7: PRISMA Checklist

Table 12: PRISMA-ScR Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-4
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	N/A
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	6 + Appendix
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5-7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	7, Appendix
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	7
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	7-8
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	9-15, Appendix
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9-15
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Table 1, Figures 2, 3, 4
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	15-16
Limitations	20	Discuss the limitations of the scoping review process.	17-18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	19
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Cover letter

Appendices – Chapter 4

The supplementary material for Chapter 4 is summarized in Microsoft Excel and is accessible via this link:

Chapter 4 - Supplement 1.

Appendices – Chapter 5

Appendix 1: Incidence of Cancer in Rwanda

Cancers highlighted in grey are those which were assessed in assessment one (where colon and rectal cancers are counted as two cancers).

Table 13: Cancer incidence

No	Cancer	Cases (2019)
1	Breast cancer	552
2	Cervical cancer	535
3	Prostate cancer	401
4	Stomach cancer	362
5	Liver cancer	258
6	Colon and rectum cancer	182
7	Adult Chronic myelogenous leukemia	148
8	Adult non-Hodgkin's lymphoma - DLBCL	148
9	Sarcoma	120
10	Head and Neck	97
11	Kaposi Sarcoma	60
12	Penile	51
13	Esophageal	49
14	Hodgkin Lymphoma	47
15	Wilms Tumor	40
16	Acute Lymphoblastic Leukemia	39
17	Retinoblastoma	39
18	Bladder	38
19	Gestational trophoblastic neoplasia (GTN)	35
20	Ovarian Bep	30
	Source: Rwanda Cancer Registry	

Appendix 2: Cancers assessed

Table 14: Cancers assessed

	Round 1		Round 2		
1	Cervical	1	Adrenal tumors	21	Lymphoma - NHL - T-cell
2	Breast	2	Anus	22	Multiple myeloma
3	Colon	3	Bone	23	Neuroblastoma
4	Rectal	4	Brain - brain tumors	24	Neuroendocrine tumors
5	Liver	5	Brain – glioma	25	Ovarian
6	Gastric	6	Esophageal	26	Pancreatic
7	Prostate	7	Germ cell tumors	27	Penile
8	Retinoblastoma	8	Gestational	28	Renal cell carcinoma
9	Wilms	9	GIST	29	Renal pelvis carcinoma
10	Acute Lymphoblastic Leukemia	10	H & N	30	Skin – Melanoma
		11	Kaposi sarcoma	31	Skin - Non-melanoma
		12	Leukemia – ALL	32	Soft tissue sarcoma
		13	Leukemia – AML	33	thymic carcinoma
		14	Leukemia – CLL	34	Thymoma
		15	Leukemia – CML	35	Thyroid
		16	Lung – Mesothelioma	36	Urothelial
		17	Lung – NSCLC	37	Uterine - corpus uteri
		18	Lung – SCLC	38	Uterine - endometrial
		19	Lymphoma – HL	39	Vulva/vagina
		20	Lymphoma - NHL – DLBCL		

Appendix 3: Search strategies

Round 1

Cancer OR Neoplasm OR Oncology OR Malignant OR Malignancy OR Metastatic OR Metastasis OR Tumor OR Tumour OR Nephroblastoma OR Wilms' tumor OR Wilms' tumour OR Lymphoma OR Leukemia OR Leukaemia OR Breast cancer OR Kaposi's sarcoma OR Prostate cancer OR Colorectal cancer OR Cervical cancer OR Liver cancer OR Gastric cancer OR Eye cancer OR Osteosarcoma OR Malignant gestational trophoblastic disease OR Head and neck cancer OR Abiraterone OR Anastrozole OR Bevacizumab OR Bleomycin OR Calcium folinate (leucovorin) OR Capecitabine OR Carboplatin OR Cisplatin OR Cyclophosphamide OR Cyclosporine OR Docetaxel OR Doxorubicin OR Fluorouracil OR Folinic acid OR Goserelin OR Hydroxycarbamide Tamoxifen Citrate OR Ifosfamide OR Imatinib OR Irinotecan OR L-asparginase OR Letrozole OR Melphalan OR Mercaptopurine OR Methotrexate OR Mycophenolate OR Oxaliplatin OR Paclitaxel OR Rituximab OR Sorafenib OR Trastuzumab OR Vincristine OR Zoledronate OR Zoledronic Acid

Round 2

Cancers

brain cancer OR brain metastases OR brain tumor OR brain tumour OR medulloblastoma OR head and neck OR oral cavity cancer OR hypopharynx OR laryngeal OR oropharyngeal OR nasopharyngeal OR nasal cavity OR sinus cancer OR squamous cell carcinoma OR thyroid cancer OR thyroid carcinoma OR lung cancer OR small cell lung cancer OR non-small cell lung cancer OR SCLC OR NSCLC OR soft tissue sarcoma OR skin melanoma OR skin cancer OR anal cancer OR epidermoid cancer OR esophageal cancer OR oesophageal cancer OR pancreatic cancer OR adenocarcinoma OR sarcoma OR gastrointestinal stromal tumour OR gastrointestinal stromal tumor OR GIST OR neuroendocrine tumour OR neuroendocrine tumor OR ureter cancer OR bladder cancer OR testicular cancer OR penile cancer OR ovarian cancer OR vulvar cancer OR vulva cancer OR uterine cancer OR endometrial carcinoma OR Gestational

trophoblastic disease OR vaginal cancer OR gallbladder cancer OR choriocarcinoma OR Hodgkin lymphoma OR Hodgkin disease OR non-Hodgkin lymphoma OR non-Hodgkin disease OR diffuse large b cell lymphoma OR Burkitt lymphoma OR leukemia OR leukaemia OR chronic myeloid leukemia OR chronic myeloid leukaemia OR CML OR CLL OR chronic lymphocytic leukaemia OR chronic lymphocytic leukemia OR multiple myeloma OR lymphoma OR adrenal cancer OR Adrenocortical carcinoma OR bone cancer OR osteosarcoma OR ewing sarcoma OR yolk sac OR mesothelioma OR gestational trophoblastic neoplasia

Drugs

5-FU OR 5FU OR Actinomycin OR Adriamycin OR Afatinib OR Alectinib OR Anastrazole OR Bendamustine OR Bevacizumab OR Bleomycin OR Bortezomib OR Capecitabine OR Carboplatin OR Chlorambucil OR CHOP OR Cisplatin OR Crizotinib OR CyBorD OR Cyclophosphamide OR Cytarabine OR Dabrafenib OR Dacarbazine OR Dactinomycin OR Dasatinib OR Denosumab OR Dexamethasone OR Docetaxel OR Doxorubicin OR EP OR Epirubicin OR Erlotinib OR Etoposide OR Exemestane OR Filgrastim OR Fludarabine OR FOLFIRINOX OR Gemcitabine OR GEMOX OR Hydroxyurea OR Ifosfamide OR Imatinib OR Irinotecan OR Lenalidomide OR Letrozole OR Leucovorin OR Mesna OR Methotrexate OR Mitomycin OR Nivolumab OR Oxaliplatin OR Paclitaxel OR Pembrolizumab OR Pemetrexed OR Prednisone OR R-CHOP OR Rituximab OR Temozolomide OR Topotecan OR Trametinib OR Vinblastine OR vincristine OR Vinorelbine

Appendix 4: Overview of cancer experts

Table 15: Cancer expertise

Type of expertise	**Number of experts**
NCD division manager	1
Medical oncologist	2
Radiation oncologist	1
Pathologist	1
Radiologist	1
Oncology pharmacist	1
Surgical oncologist	1
Oncology nurse	2
Cancer director – Rwanda biomedical center	1
NCD director – Rwanda biomedical center	1

Appendix 5: Studies included

The studies below are those which were included in the final cancer recommendation. Either the intervention or comparator is bolded for each – the bolded one is the intervention we included in assessment.

Table 16: Studies included

Round	Cancer and level	Author & Year	Title	Country	Intervention	Comparator
1	Breast - Basic	Zelle 2005	Costs, effects and cost-effectiveness of breast cancer control in Ghana	Ghana	**Treatment of breast cancer, stages I-IV**	None
1	Breast - Core	Zelle 2005	Costs, effects and cost-effectiveness of breast cancer control in Ghana	Ghana	**Biennial clinical breast examination (CBE) screening + Treatment of breast cancer, stages I-IV**	None
1	Breast - Enhanced	Zelle 2005	Costs, effects and cost-effectiveness of breast cancer control in Ghana	Ghana	**Biennial mammography screening + Treatment of breast cancer, stages I-IV**	None
1	Cervical - Prevention	Jit 2005	Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study	Rwanda	**Human papillomavirus (HPV) vaccination**	None
1	Cervical - Basic	Ginsberg 2012	Cost effectiveness of strategies to combat breast, cervical, and colorectal cancer in sub-Saharan Africa and South East Asia: mathematical modelling study	SSA	**Visual inspection for cervical cancer with acetic acid (VIA) at ages 35, 40, and 45 (with lesion removal) + cancer treatment**	None
1	Cervical - Basic	Kim 2006	Packaging health services when resources are limited: the example of a cervical cancer screening visit	SSA	**Visual inspection using acetic acid for cervical cancer**	None
1	Cervical - Core	Kim 2006	Packaging health services when resources are limited: the example of a cervical cancer screening visit	SSA	**HPV DNA test for cervical cancer**	None
1	Cervical - Enhanced	Ginsberg 2012	Cost effectiveness of strategies to combat breast, cervical, and colorectal cancer in sub-Saharan Africa and South East Asia: mathematical modelling study	SSA	**Smear test for cervical cancer detection every 5 years, ages 20-65 + HPV vaccine from age 12 + cancer treatment**	None
1	ALL - Basic	Fuentes-Alabi 2018	The cost and cost-effectiveness of childhood cancer treatment in El Salvador, Central America: A report from the Childhood Cancer 2030 Network	El Salvador	**Cancer treatment at the Hospital Nacional de Ninos Benjamin Bloom (HNNBB) in San Salvador**	None
1	Retinoblastoma - Basic	Renner 2018	Evidence From Ghana Indicates That Childhood Cancer Treatment in Sub-Saharan Africa Is Very Cost Effective: A Report From the Childhood Cancer 2030 Network	Ghana	**Pediatric oncology treatment center**	None
1	Wilm's Tumour - Basic	Renner 2018	Evidence From Ghana Indicates That Childhood Cancer Treatment in Sub-Saharan Africa Is Very Cost Effective: A Report From the Childhood Cancer 2030 Network	Ghana	**Pediatric oncology treatment center**	None
1	Wilm's Tumour - Basic	Fuentes-Alabi 2018	The cost and cost-effectiveness of childhood cancer treatment in El Salvador, Central America: A report from the Childhood Cancer 2030 Network	El Salvador	**Cancer treatment at the Hospital Nacional de Ninos Benjamin Bloom (HNNBB) in San Salvador**	None
1	Colorectal - Core	Ginsberg 2012	Cost effectiveness of strategies to combat breast, cervical, and colorectal cancer in sub-Saharan Africa and South East Asia: mathematical modelling study	SSA	**Colonoscopy at age 50 (with surgical removal of polyps)+ cancer treatment**	None
1	Colorectal - Enhanced	Ginsberg 2012	Cost effectiveness of strategies to combat breast, cervical, and colorectal cancer in sub-Saharan Africa and South East Asia: mathematical modelling study	SSA	**Colonoscopy screening every 10 years + cancer treatment**	None
1	Gastric - Core	Zhang 2019	Adjuvant Chemoradiotherapy for Gastric Cancer: Efficacy and Cost-Effectiveness Analysis	China	**adjuvant chemotherapy for gastric cancer**	None
1	Gastric - Enhanced	Zhang 2019	Adjuvant Chemoradiotherapy for Gastric Cancer: Efficacy and Cost-Effectiveness Analysis	China	**adjuvant chemoradiotherapy for gastric cancer**	None
1	Gastric - Basic	Zhang 2019	Adjuvant Chemoradiotherapy for Gastric Cancer: Efficacy and Cost-Effectiveness Analysis	China	**adjuvant chemotherapy for gastric cancer**	None
1	Prostate - Basic	Zhang 2016	Addition of docetaxel and/or zoledronic acid to standard of care for hormone-naive prostate cancer: a cost-effectiveness analysis	China	**Docetaxel + standard of care**	Standard/Usual Care
1	Prostate - Core	Zhang 2016	Addition of docetaxel and/or zoledronic acid to standard of care for hormone-naive prostate cancer: a cost-effectiveness analysis	China	**Docetaxel + standard of care**	Standard/Usual Care
1	Prostate - Enhanced	Aguiar 2018	Cost-effectiveness analysis of abiraterone, docetaxel or placebo plus androgen deprivation therapy for hormone-sensitive advanced prostate cancer	Brazil	**abiraterone + androgen deprivation therapy**	Standard/Usual Care- androgen deprivation therapy
2	Brain - glioma - Enhanced	Wu 2012	Subgroup economic analysis for glioblastoma in a health resource-limited setting	China	**Temozolomide and radiotherapy (TMZ + RT)**	Radiotherapy
2	Brain - glioma - Core	Wu 2012	Subgroup economic analysis for glioblastoma in a health resource-limited setting	China	**Temozolomide and radiotherapy (TMZ + RT)**	Radiotherapy
2	Esophageal - Enhanced	Zhang 2020	Cost-effectiveness analysis of nivolumab in the second-line treatment for advanced esophageal squamous cell carcinoma	China	**Nivolumab**	Standard/Usual Care-chemotherapy (paclitaxel and/or - unclear - docetaxel)
2	Esophageal - Core	Zhan 2019	Cost-effectiveness analysis of neoadjuvant chemoradiotherapy followed by surgery versus surgery	China	**Neoadjuvant chemoradiotherapy (vinorelbine + cisplatin) + surgery**	Standard/Usual Care- surgery alone

			alone for locally advanced esophageal squamous cell carcinoma based on the NEOCRTEC5010 trial			
2	H & N - Core	Yang 2020	Real-World Cost-Effectiveness Analysis of Gemcitabine and Cisplatin Compared to Docetaxel and Cisplatin Plus Fluorouracil Induction Chemotherapy in Locoregionally Advanced Nasopharyngeal Carcinoma	China	Gemcitabine + cisplatin --> cisplatin + intensity modulated radiotherapy	**Docetaxel + fluorouracil + cisplatin + radiotherapy**
2	Leukemia - CML - Core	Li 2017	Cost Effectiveness of Imatinib, Dasatinib, and Nilotinib as First-Line Treatment for Chronic-Phase Chronic Myeloid Leukemia in China	China	Dasatinib first	**Imatinib first**
2	Lung - NSCLC - Enhanced	Limwattananon 2018	Cost-effectiveness analysis of policy options on first-line treatments for advanced, non-small cell lung cancer in Thailand	Thailand	EGFR test; Afatinib M+/Platin M-	**Carboplatin + paclitaxel (and other platinum doublets)**
2	Lung - Mesothelioma - Enhanced	Zhan 2017	Cost-effectiveness analysis of additional bevacizumab to pemetrexed plus cisplatin for malignant pleural mesothelioma based on the MAPS trial	China	**Pemetrexed/cisplatin plus bevacizumab**	Standard/Usual Care- Pemetrexed/cisplatin
2	Lung - Mesothelioma - Core	Zhan 2017	Cost-effectiveness analysis of additional bevacizumab to pemetrexed plus cisplatin for malignant pleural mesothelioma based on the MAPS trial	China	Pemetrexed/cisplatin plus bevacizumab	**Standard/Usual Care- Pemetrexed/cisplatin**
2	Lung - SCLC - Enhanced	Zhou 2017	Cost-effectiveness analysis of sensitive relapsed small-cell lung cancer based on JCOG0605 trial	China	**Cisplatin, etoposide, irinotecan**	Standard/Usual Care- Topotecan
2	Lymphoma - HL - Enhanced	Hatam 2015	Cost-Utility Analysis of IEV Drug Regimen Versus ESHAP Drug Regimen for the Patients With Relapsed and Refractory Hodgkin and Non-Hodgkin's Lymphoma in Iran	Iran	**Ifosfamide, epirubicin and etoposide (IEV Treatment)**	etoposide, methylprednisolone, high dose cytarabine, and cisplatin (ESHAP Treatment)
2	Lymphoma - NHL - DLBCL - Core	Painschab 2021	Comparison of best supportive care, CHOP, or R-CHOP for treatment of diffuse large B-cell lymphoma in Malawi: a cost-effectiveness analysis.	Malawi	**R-CHOP (individual patient)**	CHOP (individual patient)
2	Lymphoma - NHL - DLBCL - Basic	Painschab 2021	Comparison of best supportive care, CHOP, or R-CHOP for treatment of diffuse large B-cell lymphoma in Malawi: a cost-effectiveness analysis.	Malawi	CHOP (individual patient)	**best supportive care, palliative treatment without chemotherapy (individual patient)**
2	Multiple myeloma - Enhanced	Cai 2019	Cost-effectiveness analysis on binary/triple therapy on the basis of ixazomib or bortezomib for refractory or relapsed multiple myeloma	China	**Bortezomib, Thalidomide, and Dexamethasone**	Bortezomib and Dexamethasone
2	Ovarian - Enhanced	Luealon 2016	Cost Effectiveness Analysis of Different Management Strategies between Best Supportive Care and Second-line Chemotherapy for Platinum-resistant or Refractory Ovarian Cancer	Thailand	**Gemcitabine + BSC**	Standard/Usual Care- Best supportive care
2	Pancreatic - Enhanced	Cui 2020	Cost-effectiveness analysis of nab-paclitaxel plus gemcitabine versus folfirinox in the treatment of metastatic pancreatic cancer in China	China	Nab-paclitaxel + gemcitabine	**Standard/Usual Care- fluorouracil + leucovorin + irinotecan + oxaliplatin (folfirinox)**
2	Renal cell carcinoma - Enhanced	Chen 2019	Cost-effectiveness Analysis of Pembrolizumab Plus Axitinib Versus Sunitinib in First-line Advanced Renal Cell Carcinoma in China	China	Pembrolizumab + axitinib	**Sunitinib**
2	Skin - Melanoma - Enhanced	Gao 2021	Cost-Effectiveness Analysis of Dabrafenib Plus Trametinib and Vemurafenib as First-Line Treatment in Patients with BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma in China.	China	**Dabrafenib**	vemurafenib
2	Thyroid - Basic	Corso 2014	Total thyroidectomy versus hemithyroidectomy for patients with follicular neoplasm. A cost-utility analysis	Colombia	Partial thyroidectomy	**Total thyroidectomy**
Note: the **bolded** intervention or comparator is what was used to calculate the ACER.						

Appendices – Chapter 6

Appendix 1: Summary of Process

The HBP revision process for cancer was designed and capacity strengthened during several workshops and HBP committee meetings in Rwanda (Nov 2021, March 2022, May 2022, August 2022, and November 2022). As this was the first time the HBP revision process was conducted, the design and preparation were also supported by a capacity strengthening workshop of key Rwandan actors to the Netherlands (September 2023) and several visits by international experts to Rwanda supported by the Bill and Melinda Gates Foundation and the World Health Organisation.

The HBP revision process was implemented through a series of workshops and expert / committee meetings throughout the pilot assessment period November 2021 - November 2023 (Table 17).

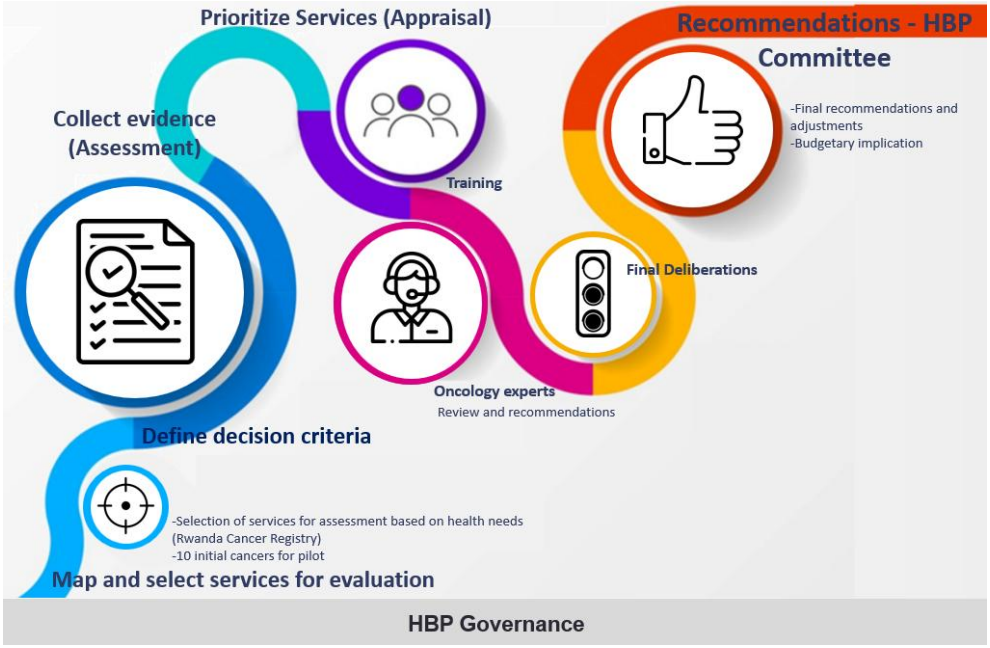
Table 6: Activities in the HBP revision process

Time	*Activity*	*Aim*
Nov 2021	*Inception workshop with all partners*	*Defining objectives, development of process and methods, training*
March 2022	*Inception workshop, follow-up*	*Sensitization and training of relevant concepts for all stakeholders*
May 2022	*1st HBP committee meeting*	*Further training on relevant concepts for the HBP committee. Detailed methodology training for assessment team.*
July 2022	*Assessment team workshop*	*Training and methods development*
August 2022	*2nd HBP committee meeting*	*Agreement on objectives, process and methods*
October 2022	*Assessment team workshop*	*Training, methods development and data analysis*
November 2022	*1st Expert meeting* *3rd HBP committee meeting*	*Technical recommendations on 10 cancers to HBP committee* *Recommendations on 10 cancers to MoH (not achieved)*
February 2023	*2nd Expert meeting* *4th HBP committee meeting*	*Revised technical recommendations on 10 cancers to HBP committee* *Recommendations on 10 cancers to MoH*
April 2023	*5th HBP committee meeting*	*Recommendations for 10 cancers to MoH, on basis of refined analysis*
June 2023	*Assessment team workshop-Cost-effectiveness*	*Training, method development and data analysis*
July 2023	*Assessment team workshop - Costing*	*Training, method development and data analysis specific to costing of services*
September 2023	*Workshop in Netherlands with all partners*	*Revisiting processes and methods, including planning capacity building*
November 2023	*3rd Expert meeting* *6th HBP committee meeting*	*Technical recommendations on 49 cancers to HBP committee* *Recommendations on 49 cancers to MoH*

Figure 1 shows a summary of the HBP revision process that involved several steps, as outlined in further detail below. The first step is establishing the governance structure.

Step A: Installing governance structure. Key stakeholders collaborated to design a governance structure for the HBP revision in accordance with the MI based on two connected stages of deliberation around priorities. The first stage convenes disease experts, in this case, 13 Rwanda-based oncology/ cancer experts, tasked with reviewing the technical aspects of a range of interventions for potential inclusion into the HBP, and coming to initial recommendations on inclusion. The second stage is the HBP committee, whose mandate (in the MI) is to interpret the recommendations of the disease experts in the broader context including fiscal space and social judgments and combine them into an overall set of recommendations to the Minister. The Minister of Health is then responsible for making the final decision to implement the HBP recommendations. The governance structure also included the Assessment team whose responsibility it was to provide, synthesize and present evidence for each service on the various decision criteria (see below) with regards to cancer to both the expert and HBP committees. Terms of reference were drafted and adopted for each entity in the governance structure endorsed by the Ministry of Health in the 2nd committee meeting in August 2022.

Figure 1: Summary of the HBP revision process for CBHI scheme in Rwanda



Step B: Map and select services for evaluation. The HBP committee agreed in their 2nd meeting in August 2022 that cancer services would be the first group of services for evaluation, for three reasons: cancer related morbidity and mortality represents a growing burden of disease for Rwanda; cancer is a high political priority and is aligned with health system needs and objectives; and there is increasing demand for additional cancer services to be covered by CBHI. Cancer incidence in the Rwanda Cancer Registry was reviewed, and it was decided to focus on an initial pilot cluster of ten cancers with the highest incidence, including the top three childhood cancers, for assessment. These included breast, cervical, prostate, colon, rectal, liver, gastric, acute lymphoblastic, leukaemia (ALL), Wilms' tumour, and retinoblastoma cancers. This was then followed up with the remaining 39 other cancers and completed in late 2023.

For each cancer, all services were mapped using the same approach. First, the services included for each cancer were informed by the National Cancer Treatment Guidelines and international protocols. Then the assessment team classified services into resource classes of 'essential', 'core' and 'enhanced'

services, following resource stratified guidelines developed by the National Comprehensive Cancer Network (NCCN). The assessment team also developed 'service descriptions' for each specific service. In a series of consecutive workshops, the cancer experts reviewed the proposed classification including service descriptions and made changes where necessary to reflect current clinical practice in the Rwandan context.

Step C: Defining decision criteria. The MI proposed a set of decision criteria for use in the HBP revision. As part of the HBP revision design these were condensed and the methods for assessment were discussed and agreed upon by the HBP committee in August 2022. The following nine criteria were selected: burden of disease, financial risk protection, effectiveness at population level, feasibility of implementation, cost, value for money (cost-effectiveness), vertical equity (priority to vulnerable groups / the worst off), total budget impact, and life-threatening conditions.

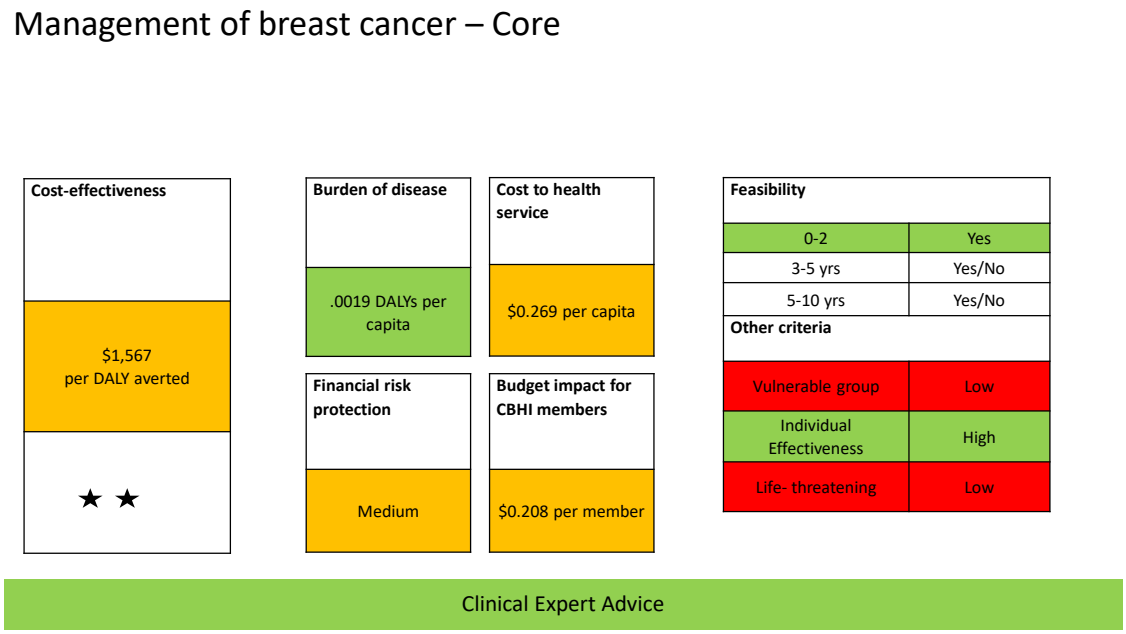
Step D: Collect evidence. The assessment team collected the available evidence on five criteria, for which quantitative data was available: cost of services (expressed as budget impact and cost to health system); cost-effectiveness, burden of disease, financial risk protection and budget impact. Data from Rwanda was used to the best degree possible, and international data was used when there were gaps. For the four other criteria, insufficient data was available to make a quantitative assessment, and these were qualitatively assessed during the appraisal stage using expert opinion of the cancer experts. All evidence was reviewed and validated by the cancer experts for 10 cancers in meetings in November 2022, February 2023 and for 39 other cancers in November 2023.

Step E: Appraise and prioritize services. The interpretation of the results of the assessment and the formulation of recommendations to the MoH was split into two sub steps as it requires making both technical judgments on cancers (sub step 1, involving cancer experts) as well as broader societal

judgements taking into account fiscal space and other constraints (sub step 2, involving the HBP committee).

Sub-step E1. The first sub-step involved the division of the 'essential', 'core' and 'enhanced' services, for each cancer, into categories of 'high priority,' 'medium priority' and 'low priority,' reflecting their relative importance for the cancer control and management in Rwanda. To arrive at these categories, the cancer experts interpreted the results of the assessment stage for each service and deliberated in two meetings in November 2022 and February 2023 on the first cluster of 10 cancers. The HBP Committee was allocated a trained facilitator, who had received instructions on how to follow a stepwise deliberative process. Discussion on each cancer started with an introduction, followed by a deliberative process for each service, which included reading of the service description, a round of clarification questions and answers, and an initial voting, in which each expert categorized the service as a high, medium, or low priority. Based on their votes, the facilitator invited each expert to share his/her argumentation followed by group deliberation. Subsequently, experts gave their last vote, and the rapporteur summarised the final voting results and argumentation. Several templates were available to facilitate this process, such as 'evidence sheets' (Figure 2) and 'criteria explanation sheet.' This led in November 2022 to an initial set of recommendations in which the oncology experts labelled all 'core' packages of cancer services as high priority and provided recommended coverage levels for each of these packages.

Figure 2: Sample evidence sheet



A second two-day expert meeting took place with the same oncologists, and this time they were presented with a budget estimate of their previous recommendations (i.e. from the November 2022 meeting). Two budget options were proposed by the assessment team: the current spending on cancer services, and the current spending plus 25%, again upon reflection with CBHI. The cancer experts were invited to provide more specific advice, i.e. to reallocate these budgets by changing the coverage of services (e.g. improve coverage of basic and/or core services); add or remove screening and/or change the allocation of services across cancers (e.g. spend less on some cancers in order to spend more on others). Deliberation led to a revised set of preliminary recommendations to the HBP committee.

In November 2023, a third meeting was held with the expert oncologists to develop preliminary recommendations for the second cluster of 39 cancers. In this meeting, the same approach as in the February 2023 meeting was employed. In that meeting, the expert oncologists eventually combined all

49 cancers and categorized the respective cancer packages in terms of priorities, i.e. assigning them to categories ‘low’, ‘medium’ or ‘high’ priority.

Sub-step E2. Over the course of several meetings in November 2022, February 2023 and November 2023, the HBP committee reviewed the cancer experts’ recommendations. As a basis for discussions, the assessment team developed several scenarios reflecting possible choices that the HBP committee could make, based on recommended services by the cancer experts, attainable coverage levels and available fiscal space. For each scenario, evidence on total health gains, coverage levels and budget impact were provided. The HBP committee eventually came to final recommendations on 10 cancers (in February 2023) and 39 cancers (in November 2023). This overview has integrated these final recommendations on a total set of 49 cancers.

Appendix 2: Summary of cancers

The full list of 49 cancers assessed is presented below in Table 18. The Rwanda Cancer Guidelines include 67 cancers. To adapt the assessment for time and data constraints, the 67 cancers were grouped into 49 cancers by local experts to reflect cancers with similar care pathways. These are the 49 cancers assessed and presented below.

Table 18: Cancers assessed

Round 1		Round 2		Round 2	
1	Cervical	1	Adrenal tumors	21	Lymphoma - NHL - T-cell
2	Breast	2	Anus	22	Multiple myeloma
3	Colon	3	Bone	23	Neuroblastoma
4	Rectal	4	Brain - brain tumors	24	Neuroendocrine tumors
5	Liver	5	Brain – glioma	25	Ovarian
6	Gastric	6	Esophageal	26	Pancreatic
7	Prostate	7	Germ cell tumors	27	Penile
8	Retinoblastoma	8	Gestational	28	Renal cell carcinoma
9	Wilms	9	GIST	29	Renal pelvis carcinoma
10	Acute Lymphoblastic Leukemia	10	H & N	30	Skin – Melanoma
		11	Kaposi sarcoma	31	Skin - Non-melanoma
		12	Leukemia – ALL	32	Soft tissue sarcoma
		13	Leukemia – AML	33	thymic carcinoma
		14	Leukemia – CLL	34	Thymoma
		15	Leukemia – CML	35	Thyroid
		16	Lung – Mesothelioma	36	Urothelial
		17	Lung – NSCLC	37	Uterine - corpus uteri
		18	Lung – SCLC	38	Uterine - endometrial
		19	Lymphoma – HL	39	Vulva/vagina
		20	Lymphoma - NHL – DLBCL		

GIST – gastrointestinal stromal tumor; H & N – head and neck; ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CLL – chronic lymphocytic leukemia; CML – chronic myeloid leukemia; NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer; HL – Hodgkin's lymphoma; NHL – non-Hodgkin's lymphoma; DLBCL – diffuse large b-cell lymphoma

Service Summaries

Cancer – First Round

February 2023

National Comprehensive Cancer Network®

Framework for Resource Stratification

outlines a rational approach for building cancer management systems to provide the highest achievable cancer care by applying available and affordable services in a logical sequence

Basic Resources	include essential services needed to provide basic minimal standard of care that improves disease-specific outcomes
Core Resources	include services provided in the Basic plus additional services that provide major improvements in disease outcomes (e.g. survival) and that are not cost prohibitive
Enhanced Resources	include services provided in the Core plus additional services that provide lesser improvements in disease outcomes and/or services that provide major improvements in disease outcomes but are cost prohibitive in lower resource settings

NCCN Framework™ - Guidelines for Treatment of Cancer by Type

Breast Cancer
- Basic Resources Version 3.2020 (Preliminary)
- Core Resources Version 3.2020 (Preliminary)
- Enhanced Resources Version 3.2020 (Preliminary)
- NCCN Guidelines Version 4.2022

NCCN Framework™: Basic Resources

CLINICAL STAGE | **WORKUP[a]**

T0–3,N1,M0 / T1–3,N0–1,M0 (If not considering preoperative systemic therapy) →

- **History and physical exam**
- **Imaging:**
  - **Diagnostic bilateral mammogram**
  - **Ultrasound as necessary**
  - Breast MRI[b] (optional), with special consideration for mammographically occult tumors
- **Pathology review[c]**
- **Determination of tumor estrogen/progesterone receptor (ER/PR)[c] status** and HER2 status[d]
- Genetic counseling if patient is at risk[e] for hereditary breast cancer
- Counseling for fertility concerns if premenopausal
- Pregnancy test in all women of childbearing potential[f] (If pregnant, see PREG-1)
- Assess for distress[g]

Consider additional studies only if directed by signs or symptoms of metastatic disease:[h]
- **Complete blood count (CBC)**
- **Comprehensive metabolic panel, including liver function tests and alkaline phosphatase**
- Bone scan indicated if localized bone pain or elevated alkaline phosphatase or sodium fluoride PET/CT[i] (category 2B)
- Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis
- Chest diagnostic CT with contrast (if pulmonary symptoms present)
- FDG PET/CT[j,k] (optional)
- *Chest x-ray*
- *Abdominal ultrasound*

NCCN Framework™: Enhanced Resources

CLINICAL STAGE | **WORKUP[a]**

T0–3,N1,M0 / T1–3,N0–1,M0 (If not considering preoperative systemic therapy) →

- **History and physical exam**
- **Imaging:**
  - **Diagnostic bilateral mammogram**
  - **Ultrasound as necessary**
  - Breast MRI[b] (optional), with special consideration for mammographically occult tumors
- **Pathology review[c]**
- **Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status[d]**
- **Genetic counseling if patient is at risk[e] for hereditary breast cancer**
- **Counseling for fertility concerns if premenopausal**
- **Pregnancy test in all women of childbearing potential[f]** (If pregnant, see PREG-1)
- **Assess for distress[g]**

Consider additional studies only if directed by signs or symptoms of metastatic disease:[h]
- **Complete blood count (CBC)**
- **Comprehensive metabolic panel, including liver function tests and alkaline phosphatase**
- **Bone scan indicated if localized bone pain or elevated alkaline phosphatase** or sodium fluoride PET/CT[i] (category 2B)
- **Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis**
- **Chest diagnostic CT with contrast (if pulmonary symptoms present)**
- FDG PET/CT[j,k] (optional)

Screening Program

	Basic	Core	Enhanced
Breast Cancer	Clinical Breast Exam (CBE)– Opportunistic and Symptoms	Clinical Breast Exam (CBE)– Biennial for women 40-69	Mammography – Biennial for women >40
Cervical Cancer	Visual inspection with acetic acid (VIA)- Every 5 years for women 30-65	Rapid HPV DNA Test - Every 5 years for women 30-65	Rapid HPV DNA Pap Smear - Every 5 years for women 30-65
Colorectal Cancer		FOBT/FIT - opportunistic screening	FOBT/FIT- Biennial for 50 to 75 years old Colonoscopy – every 10 years
Liver Cancer	Ultrasound AFP - patients at risk of HCC	Ultrasound AFP - patients at risk of HCC	Ultrasound AFP - patients at risk of HCC

Breast Cancer

	Basic	Core	Enhanced
Screening Program	Clinical Breast Exam (CBE)– Opportunistic and Symptoms	Clinical Breast Exam (CBE)– Biennial for women 40-69	Mammography– Biennial for women >40
Work-up (Diagnosis / Staging)	**Early breast cancer T0-3, N1, M0, T1-3, N0-1, M0** History and Physical Examination Imaging -Diagnostic bilateral mammogram -Ultrasound as necessary Pathologic review Determination of ER/PR status CBC, Comprehensive metabolic panel, pregnancy test Chest x-ray Cardiac ultrasound	**Early breast cancer T0-3, N1, M0, T1-3, N0-1, M0** +Abdominal± pelvic diagnostic CT with contrast or MRI +Chest diagnostic CT with contrast (if pulmonary symptoms present) +HER2 status **≥T2,M0 or ≥N1,M0 (If considering pre-operative therapy)** +Axillary assessment with exam consider ultrasound percutaneous biopsy of suspicious nodes + HER2 status	**Early breast cancer T0-3, N1, M0, T1-3, N0-1, M0** +bone scan if symptoms
Treatment	**Early breast cancer T0-3, N1, M0, T1-3, N0-1, M0** **Loco regional treatment** Total mastectomy + level I/II axillary dissection **Systemic Adjuvant Treatment** Adjuvant endocrine therapy (ER/PR status +-HER unknown -- node +- / favorable histologic type)	**Early breast cancer T0-3, N1, M0, T1-3, N0-1, M0** **Loco regional treatment** +Lumpectomy +surgical axillary staging +WBRT/RT to chest wall (+aux nodes) +regional nodal irradiation (aux nodes) **Systemic Adjuvant Treatment** +adjuvant chemotherapy (ER/PR + --HER unknown --node +- / favorable histologic types) **+Neo Adjuvant Therapy** (≥T2,M0 or ≥N1,M0)	**Early breast cancer T0-3, N1, M0, T1-3, N0-1, M0** **Loco regional treatment** +reconstruction **Systemic Adjuvant Treatment** +Adjuvant chemotherapy with trastuzumab
	Surveillance/Follow-Up		
	Palliative Care		

Cervical Cancer

	Basic	Core	Enhanced
Screening Program	Visual inspection with acetic acid (VIA) Every 5 years for women 3065	Rapid HPV DNA Test - Every 5 years for women 30-65	Rapid HPV DNA Pap Smear - Every 5 years for women 3065
Work-up (Diagnosis / Staging)	History and physical (H&P) Complete blood count (CBC) Cervical biopsy Pathologic review (Cytology - Pap smear or liquid based) Cone biopsy as indicated Colposcopy Liver function test (LFT)/renal function studies Imaging (chest x-ray) HIV and pregnancy testing	+Chest/abdomen/pelvic CT scan +Pelvic MRI	**Stage II–III** +PET CT
Treatment	**Pre-cancer/Early Stage IA1, IA2, IB, IIA** **Primary treatment (non fertility sparing)** Cryotherapy LEEP, CKC Hysterectomy Pelvic Lymph Node dissection **Stage IIB, III** Pelvic EBRT + concurrent platinum-containing chemotherapy + brachytherapy	**IB3 and Stage IIA2** +Pelvic EBRT + concurrent platinum-containing chemotherapy + brachytherapy	**IA, IB,IIA1** +Pelvic EBRT + concurrent platinum-containing chemotherapy + brachytherapy **IA1, IA2, IB1,IB2** +Trachelectomy
	Surveillance/Follow-Up		
	Palliative Care		

Colon Cancer

	Basic	Core	Enhanced
Screening Program		FOBT/FIT - opportunistic screening	FOBT/FIT- Biennial for 50 to 75 years old Colonoscopy– every 10 years
Work-up (Diagnosis / Staging)	Barium enema/radiography Ultrasound CBC, chemistry profile Chest/abdominal/pelvic CT Pathologic review	+Colonoscopy +MMR testing +CEA +MRI	+MSI testing
Treatment	Primary Treatment (if resectable) Colectomyh with en bloc removal of regional lymph nodes Resection Diversion **T3, T1-3 N1, T4 N1-2** Chemo (Capecitabine(6 mo) or 5-FU (6 mo))	Unresectable +Chemo (Capecitabine(6 mo) or 5-FU (6 mo))	**T3, T1-3 N1, T4 N1-2** +CAPEOX +FOLFOX +Radiotherapy
Surveillance/FollowUp			
Palliative Care			

Rectal Cancer

	Basic	Core	Enhanced
Screening Program		FOBT/FIT - opportunistic screening	FOBT/FIT- Biennial for 50 to 75 years old Colonoscopy– every 10 years
Work-up (Diagnosis / Staging)	Barium enema/radiography Ultrasound CBC, chemistry profile Chest/abdominal/pelvic CT Pathologic review Proctoscopy	+Colonoscopy +MMR testing +CEA +MRI	+MSI testing
Treatment	**Localized rectal cancer** Neoadjuvant therapy Chemo (Capecitabine(6 mo) or 5-FU (6 mo)) ↓ Transabdominal resection	**T1 N0** +transanallocal excision if appropriate Resection +Chemo **T1-2 N0** Resection Adjuvant therapy– after resection +Chemo (Capecitabine(6 mo) or 5-FU (6 mo)) + CAPEOX +RT **T3 T4 (M0)** NeoadjuvantChemo +RT → resection (if resectable)	+FOLFOX
Surveillance/FollowUp			
Palliative Care			

Liver Cancer

	Basic	Core	Enhanced
Screening Program	Ultrasound AFP - patients at risk of HCC	Ultrasound AFP - patients at risk of HCC	Ultrasound AFP - patients at risk of HCC
Work-up (Diagnosis / Staging)	Abdominal multiphasic CT Multidisciplinary evaluation (assess liver reserves and comorbidity) and staging: H&P FBC, LFT, RFTs, AFP, Hepatitis panel, PT or INR Chest CT Abdominal/pelvic CT Bone scan if indicated	+Abdominal/pelvic MRI	
Treatment	**Potentially resectable/operable** Hepatectomy (resection) or Ablation **Unresectable/ liver confined-inoperable** Ablation or supportive care	**Potentially resectable/operable** +arterially directed therapies **Unresectable/ liver confined-inoperable** +arterially directed therapies	**Potentially resectable/operable** +ERBT +bridge therapy (if fits UNOS criteria) +transplant (if fits UNOS criteria) **Unresectable/ liver confined-inoperable** +ERBT (if not transplant candidate) +bridge therapy +transplant +systemic therapy
Surveillance/FollowUp			
Palliative Care			

Gastric Cancer

	Basic	Core	Enhanced
Screening Program			
Work-up (Diagnosis / Staging)	H&P Barium swallow CBC and comprehensive chemistry profile	+Upper GI endoscopy and biopsy +Chest/abdomen/pelvic CT with oral and IV contrast +Radiography (abdominal ultrasound)	+Endoscopic ultrasound (EUS) +Endoscopic resection (ER) +HER2 +laparoscopy
Treatment	Best supportive care	**cTis or cT1a / Locoregional disease (cM0)** +Endoscopic mucosal resectionand lymphadenectomy +Distal, subtotal, total Gastrectomy **Locoregional disease (cM0)** +Endoscopic mucosal resectionalong with lymphadenectomy +Distal, subtotal, total Gastrectomy **Medically fit, resectable** +Perioperative chemotherapy (category 1) or Preoperative chemoradiation (category 2B) **Medically fit, unresectable** Chemoradiation or Systemic therapy	
Surveillance/FollowUp			
Palliative Care			

Prostate Cancer

	Basic	Core	Enhanced
Screening Program			
Work-up (Diagnosis / Staging)	P&H Digital rectal exam Testosterone, FBC, RFT and LFT	+Perform and/or collect prostate specific antigen (PSA) +Obtain and review diagnostic prostate biopsies +MRI +Abdominal ultrasound	
Treatment	**Low risk group** Active surveillance/ observation **Intermediate risk group** Active surveillance/ observation Androgen deprivation therapy **High** ADT/Observation	**Favorable Intermediate risk group** **Initial therapy Adjuvant** +ERBT or brachytherapy alone or ADT +Radical prostatectomy +PLND **Unfavorable Intermediate risk group** **Initial therapy Adjuvant** +ERBT +ADT or ADT +Radical prostatectomy +PLND **High/** **Initial therapy Adjuvant** +ERBT +ADT or ADT +Radical prostatectomy +PLND	**Very Low/ Low risk group** **Initial therapy Adjuvant** +ERBT or brachytherapy +RP ~~+ADT~~ **High/** **Initial therapy Adjuvant**
Surveillance/Follow-Up			
Palliative Care			

Wilm's Tumour

		Basic	Core	Enhanced
Screening Program				
Diagnosis / Staging	**Clinical**	History and Physical Examination		
	Laboratory	CBC, Blood Chemistry, Coagulation		+1p and 16q deletion
	Imaging	Chest X-ray, ultrasonography	+Abdominal/Chest CT Scan	
	Pathology		+Biopsy	
Treatment	**Surgery**	Nephrectomy and lymph node sampling	+Nephron-sparing neprechtomy	
	Chemo	Vincristine, Actinomycin (Doxorubicin)	+Doxorubicin Cyclophosphamide Etoposide Ifosfamide Carboplatin	
	Endocrine Therapy			
	Radiotherapy			+Radiation therapy
Surveillance/ Follow Up			H&P Imaging (x-ray/CT) Laboratory (monitoring for toxicities)	

Retinoblastoma

		Basic	Core	Enhanced
Screening Program				
Diagnosis / Staging	**Clinical**	History and Physical Examination	+Eye examination underanaesthesia	+fundus photograpy
	Laboratory	CBC, Blood Chemistry		+Ocular ultrasonography
	Imaging		+CT Scan	+MRI
	Pathology		+Bone marrow aspiration/biopsy Lumbar puncture for CSF cytology	
Treatment	**Surgery**	Enucleation	+focal laser therapy +cryotherapy +ablation	
	Chemo	Low dose Chemotherapy- Carboplatin, Vincristine and etoposide	+Standard dose Chemo	+Intravitreal chemotherapy
	Endocrine Therapy			
	Radiotherapy		+EBRT- all stages	
Surveillance/ Follow Up			H&P/ Eye examination under anesthesia Imaging (MRI) Laboratory (monitoring for toxicities)	

Acute Lymphoblastic Leukemia

		Basic	Core	Enhanced
Screening Program				
Diagnosis / Staging	**Clinical**	History and Physical Examination Testicular exam		
	Laboratory	CBC, Blood Chemistry, TLS, Hep B/C, Pregnancy, HIV		
	Imaging	Chest X-Ray, Cardiac US	+Testicular US +CT Scan (head, chest, pelvis, neck,abd)	+MRI
	Pathology	Bone marrow aspirate or peripheral blood smears, and H&E–stained core biopsy and clot sections, IHC	+Cytogenetic studies +Lumbar puncture	+Comprehensive flow cytometric immunophenotyping +molecular characterization
Treatment	**Surgery**			+Bone marrow transplantation
	Chemo	Multiagent Chemotherapy Oral prednisone prophase therapy		
	Endocrine Therapy			
	Radiotherapy		+EBRT- all stages	
Surveillance/ Follow Up			H&P Laboratory (CBC/monitoring for toxicities)	

Service Summaries

Cancer – Second Round

December 2023

Central nervous system (Meningioma)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Brain MRI -Laboratory: Basic lab tests	-Pathologic review: Biopsy ,tumor marker, Lab: IHC – GFAP, PR, Vimentin, EMA, S100,	
Management	Observation if asymptomatic	All stages: - Surgery: Total Excision - Post op MRI Post op Radiotherapy: - if incompletely excised (symptomatic Grade I, and II) – All Grade 3	Unresectable tumors: - Radiotherapy Recurrence: - Radiotherapy
Follow -up	-History and Physical Examination -Imaging: Brain MRI - Basic lab tests		

Central nervous system (Glioma)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Brain CT/MRI (recommended by the team of experts) -Laboratory: Basic lab test	Pathologic review – biopsy, tumor marker Lab: IHC - IDH2, GFAP	Molecular testing: BRAF, IDH mutation analysis, MGM, 1p/19q, EGFR, TP53 mutation analysis
Management	Observation low grade in location unamenable to surgery	All Stages: -If maximal safe: Gross total resection -If not safe or high grade: -Subtotal resection or open biopsy -Radiotherapy +TMZ -Post –op MRI	All Stages: -Targeted therapy with certain molecular alteration (for BRAF mutation positive): Dabrafenib Recurrence: • Surgery + Brain MRI for resectable disease • Biopsy +RT + temozolomide for unresectable disease
Follow-up	-History and Physical Examination -Imaging: Brain MRI - Basic lab tests		

Central nervous system (Intracranial and Spinal Ependymoma)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Brain/spine MRI -Laboratory: Basic lab test	Pathologic review – Lumbar puncture then CSF Analysis Lab: IHC – EMA, GFAP, S100, CD56, Synaptophysin	
Management		If maximal safe: - Gross total resection - Post op MRI If not safe: - subtotal resection or open biopsy - Radiotherapy - Post op MRI	Recurrence: • Surgery + Brain MRI for resectable disease • Biopsy +RT + temozolomide for unresectable disease
Follow-up	-History and Physical Examination -Imaging: Brain MRI -Laboratory: Basic lab test		

Head and Neck (Laryngeal)

	Basic	Core	Enhanced
Workup	-History and Physical Examination – with laryngoscopy/ Dental Evaluation -Basic Laboratory test -Imaging Chest X-ray -Pathologic review: - laryngoscopy-guided biopsy of the primary tumor. - FNA or biopsy of a neck mass	Laboratory: p16 and other IHC CK7, CK20, pancytokeratin , EMA, p63, P53, CD45, CD3, CD20, vimetin, Synaptophysin , mygenin , chromogranin, (cost 2) Imaging: CT scan and/or MRI head, neck and chest.	Imaging: PET SCAN Pathology: Tumor markers: EBV,
Management	**Stages I and II:** - Open partial laryngectomy - Neck dissection **Recurrence** • Laryngectomy • Neck dissection	**Stages I and II:** - radiotherapy alone. **Stages III-IVa** – Concurrent Chemoradiation (cisplatin) for organ preservation/ Total Laryngectomy and neck dissection. Adjuvant radiotherapy or chemo radiotherapy depending on surgical adverse effects (pathological features) - Induction systemic therapy (TPF) followed by RT or systemic therapy/RT **Recurrent and Stage IVb/ IVc** • Single agent systemic therapy	**Stages I and II:** - trans oral laser excision. **Recurrent and Stage IVb/ IVc** • Palliative RT
Follow-up	History and Physical Examination with laryngoscopy -Dental Evaluation -Imaging: Chest X-ray/ - Thyroid -stimulating hormones (TSH)	Imaging : CT scan and/or MRI of the head, neck	

Head and Neck (Nasopharyngeal)

	Basic	Core	Enhanced
Workup	-History and Physical Examination – with Nasopharyngoscopy/ Dental Evaluation -Imaging Chest X-ray - Laboratory test: basic lab, -Pathologic review: Nasopharyngoscopy guided biopsy of the primary tumor	Nutrition and speech evaluation, ophthalmology exam Laboratory: P16, other IHC (cost 2) Imaging: CT scan and/or MRI head, chest and neck.	Bone scan Pathologic review: - tumor markers: EBV
Management	Stages I –Radiotherapy alone Stages II-Ivb: Concurrent chemo/RT • Cisplatin • RT	Stages II-IVb – • Induction/adjuvant: docetaxel + cisplatin+5FU Recurrent or very advanced – chemotherapy single or combination therapy • Single agent: Capecitabine	Stage IVc: palliative care with systemic platinum-based combination chemo followed by RT
Follow-up	History and Physical Examination -Dental Evaluation -Imaging: Chest X-ray/ Thyroid -stimulating hormones (TSH)	Nutrition and speech evaluation, ophthalmology exam Imaging: CT scan and/or MRI head, chest and neck.	

Head and Neck (Oral cavity)

	Basic	Core	Enhanced
Workup	-History and Physical Examination - Dental Evaluation -Imaging: Abdo US, Chest X -ray -Laboratory: Basic lab test, -Pathologic review – FNA or biopsy	Imaging: MRI, CT Head and neck and chest Laboratory: HPV 16 and other IHC : pancytokeratin , P63, Desmin , SMA,mygenin , CD45, CD3, CD20, CD99, CD34,	Pathology: tumor markers:EBV
Management	-Surgery: resection for T1 -2 N0 and T3, N0; T1 -3, N1-3; T4a, N0-3 and recurrence	Concurrent chemo for positive margins T1-2 N0 and T3, N0; T1-3, N1-3; T4a, N0-3: • Cisplatin Radiotherapy for: - Positive margins T1-2 N0 - T3, N0; T1 -3, N1-3; T4a, N0-3	Radiotherapy for recurrent disease with concurrent chemo: • Cisplatin
Follow-up	History and Physical Examination Dental Evaluation Imaging: Abdo US, chest x -ray Thyroid -stimulating hormones (TSH)	Imaging: MRI, CT Head and neck and chest	

Gynecological (Vulva cancer)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Chest X -ray -Laboratory: HIV, FBC, LFTs, RFTs, -Pathologic review – biopsy - Cervical cancer screening: VIA	Imaging: CT scan, Pelvic MRI Laboratory: HPV (P16) screening, and other IHC: pancytokeratin , P63, P53, WT1, Cervical cancer screening: Pap smear & high risk HPV screening	
Management	Early-Stage IA/B, II (<4cm): Surgery • Partial superficial vulvectomy: T1a<1mm invasion • Radical partial vulvectomy & ipsilateral +/- bilateral (central lesions) inguinofemoral lymph node evaluation and/or lymphadenectomy: T1b >1mm invasion or T2 or T1 with unknown depth of invasion	Early-Stage IA/B, II (<4cm): • If positive margins - re-excision - adjuvant EBRT Locally advanced stage II (>4cm) to IVA and high risk: • EBRT+Concurrent chemotherapy (Cisplatin) • +/- selective Inguinofemoral lymphadenectomy	Recurrence: • Resectable: Partial or total radical vulvectomy +/- unilateral or bilateral inguinofemoral lymphadenectomy • Unresectable: EBRT+/ -Concurrent chemotherapy (Cisplatin): close or positive margins
Follow-up	-History and Physical Examination - Imaging: Chest X -ray -Laboratory: HIV, FBC, LFTs, RFTs,	Imaging: CT scan, Pelvic MRI	

Gynecological (Ovarian carcinoma)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Abdo US, Chest X -ray -Laboratory: basic lab tests, CA-125, AFP, CEA, B-HCG, CA-19	Lab: IHC : Pancytokeratin , CK7, CK20, CDX2, PAX8, WT1, ER, CD10, P53 Imaging: CT scan -Pathologic review –cytology, biopsy	Molecular testing: BRCA1 -2, BRAF Imaging: PET Scan
Management	Stage 1A/B Grade 1&2: - BSO and hysterectomy with surgical staging + Peritoneal lavage	Stage IA -IVA: - Cytoreductive surgery with surgical staging when possible (hysterectomy +BSO) - Adjuvant chemotherapy (Carboplatin + Paclitaxel) Stage III -IVA: - Neoadjuvant chemotherapy (Carboplatin + Paclitaxel)	For selected cases in stage III -IV: - Hormonal therapy: Letrozole 2.5mg once a day for 5 years Stage IVB: - Palliative Chemotherapy (carboplatin + paclitaxel) Recurrence: Chemotherapy • platinum -sensitive disease (Carboplatin + Paclitaxel) • Platinum resistant (Docetaxel + Gemcitabine)
Follow -up	-History and Physical Examination -Imaging: Abdo US, Chest X -ray -Laboratory: basic lab tests, CA -125	Imaging: CT scan	

Melanoma

	Basic	Core	Enhanced
Workup	History and Physical Examination laboratory : FBC, RFTs, LFTs, LDH Pathology: (Biopsy Excisional or incisional biopsy), punch biopsy	Lab: IHC: Pancytokeratin , Melan-A, HMB45, S100, SMA, CD45, CD34. Imaging :CT scan of the primary lesion, CT chest/ abdomen and brain to rule out metastasis.	Biochemistry :(BRAF&PD-L1)
Management	Stage0-IA :Wide Local Excision Stage IB, II, III(A): wide local excision +sentinel node biopsies. Recurrent Diseases: Surgery :Excisional or incisional biopsy		Stage IIIB -IV: (Unresectable disease) • Palliative Radiotherapy • palliative surgery -Adjuvant treatment with Dacarbazine or Pembrolizumab -Anti PD-1 monotherapy (Pembrolizumab) If BRAF V600 activating mutation is present: -Dabrafenib and Trametinib Radiotherapy Recurrent Diseases: -If unresectable same systematic therapy.
Follow -up	History and Physical Examination with ABCD changes and self-skin examination.		Imaging :CT scan of the primary lesion, CT chest/ abdomen and brain to rule out metastasis

Non –Melanoma cancer

	Basic	Core	Enhanced
Workup	History and physical examination. Biopsy Laboratory tests: Baseline RFT, LFT and FBC.	Imaging: CT or MRI for suspected Nodal and bone involvement Laboratory: IHC: pancytokeratine , CK7, CK20, synaptophysin,, chromogranin, desmin, mygenin , CD20, CD45, CD99, CD3	Laboratory: molecular tests
Management	Low Risks: -Surgery: standard excision with 4 -6m &post-operative margin assessment High risk/very high -risk -Surgery: lymph node dissection, excision with wider surgical margins and post -operative margin assessment	Low Risks: • RT High risk/very high -risk • RT	Low Risks: Surgery : Moh's surgery High risk/very high -risk -Chemotherapy concurrent : Cisplatin or Carboplatin -When Excluded Radiotherapy (Immunotherapy): Cisplatin and Capecitabine.
Follow -up	History and physical examination (including complete skin and regional lymph node exam) Laboratory: basic labs	Imaging: nodal basin US ,Chest X -Ray	MRI , CT

Bone Cancer(Osteosarcoma)

	Basic	Core	Enhanced
Workup	History and Physical Examination Imaging : skeleton X -ray Laboratory :basic Labs, LDH, Pregnancy test Pathology :surgical Biopsy	Imaging: CT and MRI of chest and Abdomen	Imaging: bone scan, PET scan Laboratory: SPEP Tumor markers :P53 ,IGF1,RB1,SATB2
Management	Low grade and High grade: - Surgery: wide excision -	Low grade: - Limb salvage surgery High grade: - Neoadjuvant (Cisplatin + doxorubicin, add all chemo) - to cost one - Limb salvage surgery - Adjuvant Chemo (Cisplatin + Doxorubicin, -MAP (high dose Methotrexate, Cisplatin and Adriamycin) - Ifosfamide , Cisplatin, and Epirubicin Then : AP get 70% , MAP get 15%, ICE get 15%	Metastatic and recurrence: -Surgery: Wide excision , Metastatectomy -Chemo: docetaxel +gemcitabine
Follow -up	History and Physical Examinations Imaging: skeleton X -ray Laboratory: basic labs	Imaging :CT Abdomen with contrast	Imaging: MRI

Kaposi Sarcoma

	Basic	Core	Enhanced
Workup	History and Physical Examinations Laboratory: basic Labs ,TB culture Test, pregnancy Test, HIV serology ,HIV VL, CD4 T -cell count. Pathology review: biopsy Imaging : Chest X -ray	Pathology review: Bronchoscopy pulmonary, we must change percentage to 2% of patients - Colonoscopy only for only 2% of patients - HHV8 and Laboratories IHC: CD31,34, CD68. Imaging: Chest CT ,CT pelvis , CT abdomen (for only 5%)	
Management	KS HIV negative: stage I&II (limited cutaneous) : - Surgery: excision KS AIDS positive: T0 disease: - Antiretroviral therapy (ART)	KS HIV negative: stage I&II (limited cutaneous): - RT KS HIV negative: Stage III - Chemotherapy (Paclitaxel with high dose dexamethasone) - Radiotherapy KS AIDS positive: - RT Patients with advanced cutaneous, oral, visceral or nodal disease: -Antiretroviral therapy (ART)+Radiotherapy -Chemotherapy (Paclitaxel with high dose dexamethasone)	KS HIV negative Stage IV: Chemotherapy : Liposomal doxorubicin 20mg/m2 q 2 weeks for 6 cycles
Follow -up	History and Physical Examinations Imaging : Chest X-ray, Laboratory: basic labs	Imaging: Chest CT ,CT pelvis , CT abdomen	

Mesothelioma(pleural)

	Basic	Core	Enhanced
Workup	History and Physical Examinations Imaging: CT of Chest Labs: Basic Labs Pathology review : Pleural biopsy echo guided, pleural fluid cytology	Imaging: MRI of chest Pathology Lung capacity assessment (Pulmonary Function test) Lab: IHC: Pancytokeratine , calretinin, CEA, TTF1, CK7, CK20, P63, S100, Melan –A, WT1	Imaging : Mediastinoscopy , Cardiac stress test
Management	Observation/supportive care		Stage I-IIIA: Chemotherapy : Ind chemo (cisplatin +pemetrexed) Stage I-IIIA: (surgery options): - Surgery (10%)– - Surgical resection - ,Pleurectomy, - Decortication - extrapleural pneumonectomy (EPP) -Post –EPP Radiotherapy Stage I- IIIA: targeted therapy: Anti PD-1: Nivolumab/ipilimumab, Anti PDL -1: pembrolizumab Stage IV: -Radiotherapy -Chemo (cisplatin+ pemetrexed + bevacizumab) Progression: -Cisplatin+ pemetrexed + bevacizumab
Follow -up	-History and Physical Examinations -Basic labs		Imaging **:** CT, MRI of Chest

Rhabdomyosarcoma(Adults)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -laboratory tests: basic lab, Liver and Renal function tests -Pathology: Core biopsy ,excisional biopsy, incisional biopsy -Imaging: plain X -ray	Imaging: CT and MRI of primary site and for staging Laboratory: IHC:Desmin , myogenin , SMA, CD99, pancytokeratine , EMA, CD45	Laboratory: Molecular testing: PAX3:FOXO1, PAX7:FOXO1
Management	Stage I, II & III -Surgery: tumor resection, - In some cases: Amputation, and excision of lymph nodes.	Staging I -II &III: - Limb Sparing Surgery - RT (to cost total dose) - Chemotherapy: Doxorubicin, Ifosfamide and Mesna; -Doses are: IV Doxorubicin 60mg/m2, Mesna at 600mg/m2 before Ifosfamide , Ifosfamide at 5000mg/m2 and Mesna post Ifosfamide infusion at 1250mg/m2, every 3 weeks for 6 cycles.	All stages: targeted therapy: ATR, KDM4B, PDGFRA inhibitor Stage IV: -Chemotherapy: Doxorubicin, Ifosfamide and Mesna; Doses are: IV Doxorubicin 60mg/m2, Mesna at 600mg/m2 before Ifosfamide , Ifosfamide at 5000mg/m2 and Mesna post Ifosfamide infusion at 1250mg/m2, every 3 weeks for 6 cycles. -Radiotherapy Recurrent disease: -Surgery -Radiotherapy - Chemo Gemcitabine and Docetaxel; Doses are: IV Gemcitabine 900mg/m2 (D1 and D8) and Docetaxel 75mg/m2 (D8 only) every 3 weeks for 6 cycles *disseminated diseases :* -Surgery (regional node dissection) -Palliative options – chemotherapy , RT(30GY) Surgery and observation (if asymptomatic)
Follow-up	History and Physical Examination Imaging : Plain X -ray, Laboratory: Basic Labs	Imaging: CT , MRI	

Adrenal Tumors

	Basic	Core	Enhanced
Workup	History and physical examination Laboratory: Basic labs& biochemistry examinations (to remove P53,TTF-1), norepinephrine, epinephrine, catecholamine Imaging: abdominal ultrasound Pathology review: Core needle biopsy image guided CT/US (50% each)	Laboratory: IHC : Ki-67, synapdophyn , chromogranin -A, pancytokeratine , S100, Gata3, vimentine , CD10, calretinin, NSE Imaging: MRI abdomen, CT abdomen	
Management	Stage I-III (Resectable): -Surgery : Adrenalectomy, bilateral adrenalectomy, Care for patients with Cushing disease following bilateral adrenalectomy		Stage IV (Unresectable/Metastatic): -Chemotherapy : Carboplatin + etoposide + mitotane + doxorubicin -Radiotherapy
Follow-up	History and physical examination Imaging: abdominal ultrasound Laboratory: Basic labs& biochemistry examinations	Imaging : MRI, CT abdomen	

Hodgkin Lymphoma

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Chest X -ray, Abdomen Ultrasound -Laboratory: FBC,RFT, LFT, LDH, HIV, pregnancy test Pathologic review : -Lymph node biopsy -IHC (CD15+,CD30+,PAX-5+,CD3-,CD20-,CD45-,CD79a-)	Imaging: CT scan chest, abdomen & pelvis, Echocardiogram -Other labs: Hep B&C -Flow cytometry Bone marrow exam, lumbar puncture, CSF.	PET SCAN (Added as it is an essential imaging in diagnostic even if it is not on the national guideline) -Ebstein-Barr virus -Pneumococcal & meningococcal vaccines
Management	All stages -Chemotherapy ABVD (Doxorubicin – Bleomycin - Vinblastine - Dacarbazine) 6 cycles	All stages -Chemotherapy ABVD 2 or 4 cycles +ISRT	Recurrence: - Lymph node biopsy - Chemotherapy: - DICEP : Dose Intensive Cyclophosphamide, Etoposide, Cisplatin for patients eligible for HDC-ASCT - Brentuximab vedotin (Bv) for patients eligible for HDC-ASCT) - Transplant
Follow-up	History and Physical Examination -Laboratory: FBC, LDH RFT, LFT, LDH	Imaging: CT scan chest, abdomen, pelvis, Chest X-ray, Echocardiogram	PET SCAN Lipid profile (Cholesterol, Triglycerides,….)

Non-Hodgkin Lymphoma (Cutaneous T-cell Lymphoma)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging :Chest X-ray -Laboratory: FBC, RFT, LFT, HIV -Pathologic review :-Skin biopsy with IHC	-Imaging: CT scan chest, Neck, abdomen, pelvis -Lab: LDH, Pregnancy, Sezary screen in peripheral smear -Pathologic review : -Bone marrow biopsy, Lymph node biopsy	- HTLV (human T -lymphotropic virus) - Flow cytometry
Management	T1-T2: Topical corticosteroids	T1-T2: -Radiotherapy (not in NCTG but in NCCN) -Total skin electron beam therapy (not in NCTG but in NCCN)	T1-T2: Brachytherapy (Added because it is the best management for cutaneous T-Cell Lymphoma & it will be soon provided in Rwanda) T3-T4: Chemotherapy (Doxorubicin, retinoids, interferons) Recurrence: - Chemotherapy - Radiotherapy
Follow-up	-History and Physical Examination -Imaging: Chest X-ray -Laboratory: FBC, RFT, LFT	Imaging: CT scan chest, Neck, abdomen, pelvis Lab: LDH, Pregnancy test, Sezary screen in peripheral smear	

Non-Hodgkin Lymphoma (Diffuse B-Cell Lymphoma)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Chest X -ray, Abdominal ultrasound -Laboratory: RFT, LFT, LDH, HIV, Pregnancy , Hep B&C -Pathologic review: Lymph node Biopsy IHC panel: CD20,CD3,CD5,CD10,CD21,CD45,BCL2,BCL6,Ki -67	Imaging: CT chest, Head and Neck, abdomen, pelvis ,-Echocardiogram -Pathologic review: – bone marrow biopsy, lumbar puncture, CSF cytology	PET SCAN -Other tests: IRF4/MUM1,MYC, Karyotype or FISH -Cell surface marker analysis by flow cytometry
Management	All stages -CHOP 6 cycles	Stage I-II: Non bulky: -RCHOP 3 or 6 cycles + ISRT Bulky: -CHOP 3 cycles +ISRT Re-staging with CT Scan Chest, Abdomen, pelvis Stage III-IV - CD 20+ or not done – RCHOP x 6 cycles - CD20 – CHOP x 6-8 cycles - CD 20+ or not done – Prephase: Rituximab + Prednisone - CD20 – ISRT	Bone marrow transplant Recurrence: -Second line therapy (RICE or DA -EPOCH) -Palliative ISRT
Follow-up	- History and Physical Examination - Labs: FBC,RFT, LFT, LDH	Imaging: CT scan chest, Head and Neck, abdomen, pelvis	PET SCAN

Non-Hodgkin Lymphoma (Peripheral T-cell Lymphoma)- From NCCN Guideline

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Chest X -Ray ,Abdominal ultrasound -Laboratory: FBC,RFT, LFT, HIV -Pathologic review: –Skin biopsy, Lymph node biopsy ,IHC		Imaging: CT scan chest, Head, Neck, abdomen, pelvis, Echocardiogram Other Labs: Human T-cell lymphotropic Virus test, Hep B&C , Pregnancy test, LDH Pathologic review :Bone marrow biopsy, lumbar puncture, CSF cytology, IHC panel, cell surface marker analysis by flow cytometry, EBV PET SCAN
Management			All stages: Chemotherapy Brentuximab vedotin + CHP(Cyclophosphamide , Doxorubicin and Prednisone) Partial remission: Radiotherapy Complete remission: Re-stage with imaging (CT of chest, abdomen, pelvis) Recurrence: - Chemotherapy with transplant intent (Rituximab + ifosfamide+ carboplatin+ Etoposide) - Chemotherapy without transplant (Rituximab + doxorubicin + Etoposide + Vincristine + Cyclophosphamide + Prednisone) - Bone marrow transplant
Follow-up	- History and Physical Examination -Labs: FBC,RFT, LFT		Imaging: CT scan chest, Head, Neck, abdomen, pelvis PET SCAN

Pediatric cancer - Neuroblastoma

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Abdominal, pelvic CT scan ,MRI -Laboratory: FBC, RFT, LFT, electrolytes, LDH, Ferritin, TSH, T4, Coagulation profile -Pathologic review:Biopsy ,IHC	Other Labs: Urine VMA/HVA	Labs:FISH ,IgG
Management	All stages Surgery: localized tumor - Tumor excision	All stages (Unrespectable tumor) -Chemo: Low risk :Etoposide ,Carboplatin,Cyclosphophamide,doxorubicin High risk: Etoposide ,Carboplatin,Cyclosphophamide ,doxorubicin, Vincristine. - Radiotherapy	All stages Bone marrow Transplant(NCCN) Recurrence: Surgery: - Tumor excision - Chemo: Etoposide ,Carboplatin,Cyclosphophamide ,doxorubicin, Vincristine. - Radiotherapy
Follow-up	History and Physical Examination Laboratory: FBC, RFT, LFT, electrolytes, LDH, Ferritin, TSH, T4, Coagulation profile , Urine VMA/HVA	Imaging: MRI	

Endometrial carcinoma

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging : -Abdominal -Pelvis ultrasound -Transvaginal ultrasound -Laboratory: FBC, RFT, LFT, HIV , PAP smear -Pathology: - Endometrial biopsy, curettage biopsy - IHC , Oestrogen receptor (ER) Lab test: BCG test (HBP committee recommended)	-Lab test: : CA 125 -Imaging: CT chest, abdomen, pelvis ,Hysteroscopy with biopsy -Pathology: lymph node biopsy	Imaging: MRI,PET Scan
Management	Suitable for surgery: - Total hysterectomy and bilateral salpingo -oophorectomy and Lymphadenectomy	Suitable for surgery: - Chemotherapy (Cisplatin + Carboplatin + Paclitaxel) Not suitable for surgery: - Brachytherapy - EBRT - Hormone therapy: Progesterone	Recurrence: - Chemo: carboplatin + Paclitaxel) - Palliative Radiation Therapy
Follow-up	-History and Physical Examination -Laboratory: FBC, RFT, LFT	-Imaging: CT chest, abdomen, pelvis	

Gestational Trophoblastic Neoplasia

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Laboratory: Basic lab tests, Serum β-hCG level, T3, T4, TSH - Imaging: Pelvic and abdominal Ultrasound, CXR - Pathology: curettage biopsy	-Imaging: CT chest, CT abdomen, CT pelvis, Brain CT or Brain MRI (If metastatic disease) -Pathology:IHC	
Management	Stage I or low-risk (WHO score <=6) Stage II or III: - chemo :Methotrexate - Hysterectomy	Stage IV or high -risk (WHO score ≥ 7) Stage II or III or resistance to single -agent - Chemo (Etoposide/Methotrexate/ leucovorin / dactinomycin / cyclophosphamide/vincristine) Recurrence & metastasis: - Surgery – hysterectomy - Pre-chemo evaluation (FBC), ALAT/ ASAT, and creatinine) - Chemotherapy : (Etoposide/Methotrexate/ leucovorin/dactinomycin/cyclophosphamide/vincristine)	
Follow -up	- History and Physical Examination - Laboratory: Serum β-hCG level - Imaging: Pelvic and abdominal Ultrasound		

Multiple Myeloma

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Laboratory: basic lab tests, peripheral blood smear, LFTs, Hep B&C, LDH, SPEP, SIFE, UPEP -Pathology: - bone marrow aspirates + biopsy - IHC - Imaging: whole body low dose CT(Skeletal survey)		-Imaging: whole -body MRI, Bone Scan ,PET (Skeletal survey) Other Labs: Flow Cytometry
Management	-Supportive treatment		All stages: ▪ Surgery (to remove single plasmacytomas) ▪ Chemotherapy: ○ Pre-transplant: Bortezomib/ lenalidomide/dexamethasone ○ Chemo for non transplant candidates: (Bortezomib+lenalidomide+dexamethasone) ▪ Radiotherapy ▪ Bone marrow transplantation ○ Post transplant chemo: VRD (Bortezomib (Velcade)+Lenalidomide (Revlimid)+Dexamethasone) ▪ Maintenance therapy (Lenalidomide or bortezomib) ▪ Recurrence: -Radiotherapy
Follow -up	-History and Physical Examination -FBC,LFTs,RFTs		Imaging: whole body low dose CT and whole -body MRI

Lung cancer (Small Cell Lung cancer(SCLC)

	Basic	Core	Enhanced
Workup	• History and Physical Examination • Lab tests: Full Blood Count (FBC), Electrolytes, liver function tests, renal function tests Pathology review: post biopsy, possibly with bronchoscopy and/or CT-guided biopsy, pleural fusion cytology	• Imaging: Chest, abdomen, pelvis CT scan, Brain MRI. Limited stage: • If pleural effusion is present – thoracentesis • unilateral marrow aspiration or biopsy for patients presenting with neutropenia or thrombocytopenia	Pulmonary function tests – during evaluation for surgery or definitive radiation therapy
Management			Limited stage • I-IIA –with chest CT negative: Lobectomy (preferred) • N0 – add systemic therapy • N1 – systemic therapy +/ - mediastinal RT • N2 – systemic therapy + mediastinal RT Patients who are medically inoperable: • Systemic therapy + concurrent or sequential RT Limited stage: • Poor performance status (3 -4) due to SCLC :systemic therapy +/ - concurrent or sequential RT • Poor performance status (3 -4) not due to SCLC :Individualized treatment including supportive care Extensive stage: - Extensive stage without localized symptomatic sites or brain metastases: • Good PS (0-2) OR Poor PS (3-4) due to SCLC: Combination systemic therapy including supportive care; • Poor PS (3-4) not due to SCLC: Individualized therapy including supportive care.

Lung cancer (Small Cell Lung cancer) continued

	Basic	Core	Enhanced
Workup			
Management			Clinical stage I-IIA – with chest CT positive and Clinical stage IIB -IIIC: • Good Performance Status (PS) (0 -2) : systemic therapy + concurrent or sequential RT Extensive stage with localized symptomatic sites: • SVC syndrome OR lobar obstruction OR bone metastasis :systemic therapy + RT; • If high risk of fracture due to osseous structural impairment, consider orthopedic stabilization and palliative external beam RT; • Spinal Cord compression: RT to symptomatic sites before systemic therapy -Extensive stage with brain metastases: • Asymptomatic patients: systemic therapy before brain RT (WBRT), • Symptomatic patients: Brain RT (WBRT) before systemic therapy Note - Systemic therapy: Extensive stage (carboplatin, etoposide)
Follow-up	• History and Physical Examination • Laboratory : Full Blood Count, Liver and renal function tests	• Imaging: Brain MRI, Chest CT scan, Abdomen CT scan, Pelvis CT scan	

Lung cancer (Non-Small Cell Lung cancer)

	Basic	Core	Enhanced
Workup	• History and Physical Examination • Imaging: Chest X/ray • Laboratory: FBC, Chemistry profile	• Organ function tests(spirometry) • Imaging: CT Chest, Abdomen CT scan, • Pathology: bronchoscopy+biopsy, Sputum Cytology	• PET scan • Molecular genetic : (EML4/ALK, EGFR, KRAS)
Management	• Supportive treatment(recommended by experts) :oxygen	Stage IA (peripheral T1abc, N0), Stage IB (peripheral T2a, N0), Stage I (Central T1abc-T2a, N0), Stage II (T1abc-2ab, N1; T2b, N0), Stage IIB (T3, N0) and Stage IIIA (T3, N1) : - If negative or unknown mediastinal nodes: • Operable patients: surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling • If margins are negative : Observe or Chemotherapy for high -risk patients (IB, IIA, IIB and IIIA) • If margins are positive: Re-resection (if possible) OR RT • If medically inoperable : definitive RT, consider adjuvant chemotherapy for high -risk stages IB-IIB.	Stage IIB (T3 invasion, N0), Stage IIIA (T4 extension, N0 -1; T3, N1; T4, N0-1): • Superior Sulcus tumor (T3 invasion, N0 -1): Preoperative chemo-radiation • Superior Sulcus tumor (T4 extension, N0 -1): -Possibly resectable: Preoperative chemo-radiation then surgery + chemotherapy. -Unresectable disease: Definitive concurrent chemo -radiation • Chest wall, proximal airway, or mediastinum (T3 invasion, N0 -1 and resectable T4 extension, N0 -1): -Chemotherapy OR Concurrent chemoradiation THEN surgical re -evaluation . If negative margins are present :observe; If positive margins are present : re-resection. - Surgery: Margins negative – follow with chemotherapy; Positive margins – follow with re-resection + chemotherapy OR RT or chemoradiation (concurrent or sequential) • Stage IIIA (T4, N0 -1), Unresectable : Definitive concurrent chemoradiation OR definitive sequential radiation then chemotherapy

Lung cancer (Non-Small Cell Lung cancer) continued

	Basic	Core	Enhanced
Workup			
Management			Stage IIIA (T1 -2, N2); Stage IIIB (T3, N2); Separate pulmonary nodules (Stage IIB, IIIA, IV): -Stage IIIA, IIIB - Usual workup investigations: • N2, N3 nodes negative :treat as T1 -3, N0-1 • N2 positive, M0 :Definitive chemoradiation OR induction chemotherapy • N3 positive, M0 :Definitive concurrent chemoradiation OR definitive sequential chemo-radiation Multiple lung cancers (N0 -1) -Asymptomatic: • Multiple lesions – Observe OR definitive local therapy – with RT; • Solitary lesions – Definitive local therapy with RT if not possible palliative RT/chemo -Symptomatic: Definitive local therapy with RT; if definitive local therapy is not possible – Palliative chemotherapy +/- local palliative therapy OR observe Note: • Concurrent chemoradiation: Carboplatin + Docetaxel, Cisplatin + Etoposide • Adjuvant chemo: Carboplatin + Paclitaxel, Cisplatin + Vinorelbine • Advanced /metastatic: Carboplatin and Paclitaxel (Carboplatin + Paclitaxel; Doses are: IV Carboplatin AUC 5-6 and Paclitaxel 200 mg/m2)
Follow-up	• History and Physical Examination • Imaging: Chest X/ray	• Imaging : CT-chest	

Renal cell carcinoma

	Basic	Core	Enhanced
Workup	• History and Physical Examination • Laboratory: Complete Blood Count, LFT,RFT, Comprehensive metabolic panel, Urinalysis • Imaging: abdominal Pelvic CT scan, Chest CT scan, • Imaging: chest X -ray ,Abdominal ultrasound(recommended by experts), • Pathology: ureteroscopy or percutaneous biopsy, with core needle biopsy, If urothelial carcinoma is suspected : consider urine cytology,		• Bone scan • Lab: genetic molecular testing: VHL, MET, Gemline mutation, TLC
Management	Stage I-III: Surgery: Partial nephrectomy or radical nephrectomy		Previously untreated patients Low to intermediate risk: • chemotherapy: Sunitinib or Sorafenib: • Supportive care: Palliative radiation therapy, metastasectomy , and bisphosphonates for bone metastasis Previously untreated patients with high risk: • chemotherapy: Temsirolimus or Sunitinib or Sorafenib Stage IV, relapsed, or recurrent: Chemotherapy: • Temsirolimus or Sorafenib or Sunitinib or Axitinib or Everolimus • Gemcitabine and doxorubicin Or Supportive care: palliative radiation therapy, metastasectomy , and bisphosphonates for bone metastasis.
Follow -up	• History and Physical Examination • Laboratory: Complete Blood Count, LFT,RFT, Comprehensive metabolic panel, Urinalysis • Imaging: Chest X -ray , Abdominal ultrasound(recommended by experts), Chest CT , abdominal pelvis CT		

Renal pelvic carcinoma

	Basic	Core	Enhanced
Workup	• History and Physical examination • Laboratory: Renal function tests, CBC, LFTs, • Imaging: Chest X -ray, Ultrasound(recommended by experts)	• Pathology: Cystoscopy + Cytology, Ureteroscopy and biopsy +/ - selective washings • Imaging: Chest CT scan, Abdomen CT scan(recommended by experts)	
Management		Non-metastatic: - Low grade: • Nephro-ureterectomy with cuff of bladder +/ - perioperative intravesical chemotherapy - High Grade, large or parenchymal invasion: • Nephro-ureterectomy with cuff of bladder + regional lymphadenectomy +/- perioperative intravesical chemotherapy • neoadjuvant chemotherapy in selected patients (cisplatin)	Metastatic: • Systemic therapy (cisplatin + gemcitabine)
Follow -up	• History and Physical Examination • Laboratory: Renal function tests, CBC, LFTs • Imaging: Ultrasound(recommended by experts)	• Imaging: Chest/abdomen CT scan(recommend by experts)	

Penile Cancer

	Basic	Core	Enhanced
Workup	• History and Physical Examination • Laboratory: CBC, RFTs, LFTs, with alkaline phosphatase, HIV testing, HPV16 Pathology: biopsy and bimanual exam under anesthesia if lesion is deep	Pathology: cystourethroscopy with biopsy • Imaging: Ultrasound, MRI (penis), inguinal ultrasound, abdomen and pelvis CT scan. • Laboratory:HPV(recommended by experts)	
Management	Treatment T1s/Ta Wide local excision Treatment of T1, grade 1-2 • Wide local excision • Partial penectomy Treatment of T1, grade 3-4 • Wide local excision • Total penectomy	Treatment T1s/Ta • Topical therapy (5-FU) or Imiquimod or ~~• Circumcision~~ • Complete Glansectomy Treatment of T1, grade 1-2 • Glansectomy, in select cases • Radiation therapy, in select cases Note: Consider – penis preservation (preferred): Circumcise first, then EBRT. Treatment of T1, grade 3-4 • Radiation therapy • Chemoradiotherapy (Cisplatin + 5FU), if not eligible for surgery	Treatment T1s/Ta Moh's surgery

Penile Cancer (continued)

	Basic	Core	Enhanced
Workup			
Management	Treatment of T2 or greater • Partial or total penectomy	Treatment of T2 or greater • Radiation therapy • Chemoradiotherapy (Cisplatin + 5FU), if not eligible for surgery Treatment of T4 with invasion of other adjacent structures: • Neoadjuvant chemotherapy (paclitaxel + cisplatin) followed by surgery in patients with complete/partial response;	Treatment of T4 with invasion of other adjacent structures • Palliative EBRT Treatment of metastatic disease • Systemic chemotherapy (paclitaxel + cisplatin) • Radiation therapy • Chemoradiotherapy • Best supportive care Treatment of local recurrence after conservative treatment • Salvage surgery
Follow-up	• History and Physical Examination		

Anal Cancer (squamous cell carcinoma)

	Basic	Core	Enhanced
Workup	• History and Physical Examination: digital rectal exam and palpation of inguinal lymph nodes, Pelvic exam for all women with cervical Pap smear positive • Laboratory: Basic Laboratory(FBC,LFT,RFT), HIV Test Pathology :Biopsy	Laboratory: HPV testing, other IHC: P63, pancytokinerase (2 max) Routine: Pap smear screening (HIV & MSM) • Imaging: Pelvic MRI, CT chest, Abdomen CT, Pelvis CT, Anoscopy	
Management	Localized and locally advanced • Stage 0 – I: Surgery: Wide local excision	Localized and locally advanced • Stage II-III: chemoradiation (Mitomycin ,5FU)	Recurrent/Metastatic: • APR for locally recurrent disease • Resection for oligometastatic disease • Chemotherapy (Cisplatin + Paclitaxel)
Follow-up	• History and Physical Examination: DRE & inguinal node palpation , Pelvic exam for all women with cervical Pap smear positive • Laboratory: Basic Laboratory, HPV testing, HIV Test	• Imaging :Anoscopy, Chest CT, Abdomen, CT, Pelvic CT	

Pediatric cancer (Germ cell tumor)

	Basic	Core	Enhanced
Workup	• History and Physical Examination • Laboratory: FBC, RFTs, LFTs, Serum electrolytes, LDH, • Pathology: Biopsy, IHC: Ca -125, CD30, CD45, CD10, SOX2, OCT4 (3-4 costing) • Tumor marker: AFP, β-HCG • CT scan (Chest, Abdomen), Abdominal Ultrasound		
Management	• Surgery: stageI-IV:tumor resection • Chemotherapy:Stage II -IV(IV Bleomycin 15 mg/m2,Etoposide 100mg/m2 ,Cisplatin 20 mg/m2)	Recurrence • Radiotherapy	
Follow -up	• History and Physical Examination • Laboratory: FBC, RFTs, LFTs, AFP	• Laboratory: Serum electrolytes, LDH, Ca -125, β-HCG, • Imaging :CT scan (Chest, Abdomen), Abdominal Ultrasound	

Thoracic cancer (Thymoma and thymic carcinoma)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Chest X-Ray CT Scan with Contrast -Laboratory: Basic lab tests (CBC, LFT, RFT) biopsy (Excision, core needle biopsy)	MRI (Recommended by experts) Acetecholamine	PET Scan (Recommended by experts)
Management	Stage I&II; Surgery -total thymectomy. Supportive Treatment.	-Stage III,IV(localized): Surgery , postoperative RT Plus Chemotherapy; (Cisplatin, Doxorubicin, Cyclophosphamide, Carboplatin, Paclitaxel, Vincristine, Etoposide) if tissue study concludes in thymic carcinoma.	-Metastatic disease (Stage IV) Palliative RT, Palliative Chemotherapy, Palliative surgery -Recurrence; -Locally advanced – unresectable disease – concurrent chemo-radiation/ extra-thoracic metastases – chemotherapy (capecitabine, Gemcitabine)
Follow-up	History and Physical Examination Lab exams - LFT, RFT, CBC Imaging : CT with contrast		

Thyroid Carcinoma

	Basic	Core	Enhanced
Workup	History and Physical Examination Basic Lab test(CBC, LFT,RFT) Imaging: Chest X -Ray, Neck Ultrasound Cytology FNA , Thyroid function tests: (TSH, T3, T4)	Lab tests: Calcitonin ,thyroglobulin, thyroxin Imaging: Neck & Chest CT scan/ MRI	Imaging : Bone scan, PET Scan
Management	-Localized disease (Stage I-II); SURGERY :Lobectomy ,thyroidotomy levothyroxine therapy. -Supportive Treatment.	-Localized disease (Stage III -IV); Total thyroidectomy, lobectomy, levothyroxine therapy, EBRT, systemic therapy (Lenvatinib only) -Localized recurrence – Surgery.	Radioactive Iodine Therapy -For non-resectable or incompletely respected DTC. -External beam radiation for Brain metastases -Stereotactic radiosurgery (for CNS metastases; if available) -Palliative chemotherapy (Adriamycin) - metastatic disease not responding to 131 -Iodine -Radiotherapy- Macroscopic residual disease Microscopic/unresectable
Follow-up	History and Physical Examination Basic Lab test (CBC, LFT, RFT) Thyroid function tests: (TSH, T3, T4) Imaging: Chest X -Ray, Neck Ultrasound.	Lab exams: Thyroid function tests: (TSH, T3, T4) Imaging: Head & Neck and chest CT Scan with contrast/ MRI Calcitonin ,thyroglobulin, thyroxin	-Imaging: PET Scan

Pancreatic Cancer (Adeno Carcinoma/ Neuroendocrine)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Imaging: Abdomen ultrasound (Recommended by Experts) Chest, Abdomen and pelvic CT Scan -Laboratory: Basic lab tests (CBC, LFT,RFT) Tumor markers; CA19 -9 Biopsy	-Imaging: MRI -Consider endoscopic retrograde cholangiopancreatography (ERCP),MRCP (Recommended), Stent placement	-KRAS mutation , CDKN2A,inactivation of TP53 and SMAD4) Imaging: -Octreotide Scan (for neuroendocrine) -PET/CT in high -risk patients
Management	Supportive treatment Specifically:	RESECTABLE: (T1 -3, N0-1, M0): -Surgery (Whipple or distal pancreatectomy) -Adjuvant Chemo : Gemcitabine or Leucovorin followed by 5FU -Board line Respectable /UNRESECTABLE: Neoadjuvant therapy(Gemcitabine or Leucovorin followed by 5FU),surgery.	METASTATIC : -Palliative chemo: Gemcitabine or FOLFIRINOX (5FU, Irinotecan and Oxaliplatin) -RECURRENT : (CAPECITABIN TAB, CAPECITABIN 150 AC plus Etoposide) (not in NCTG)
Follow-up	-History and Physical Examination - lab tests (CBC, LFT,RFT)	Imaging: -Chest, Abdomen and pelvic CT Scan/MRI -Tumor markers;CA19 -9	

Esophageal cancer

	Basic	Core	Enhanced
Workup	-History and Physical Examination - Laboratory: basic labs (CBC, LFT,RFT) Imaging: Chest x -ray(recommended) tests (CBC, LFT,RFT) Barium swallow Upper GI endoscopy and biopsy -Consultation for nutritional assessment.	-Imaging: • CT: Head& Neck, Chest, abdomen with contrast. • Bronchoscopy if tumor is at or above the carina with no evidence of M1 disease. • IMMUNOHISTOCHEMISTRY	-Imaging: PET -Tumor marker (HER2)
Management	Supportive treatment.	-Feeding gastrostomy -Stage I-II, Surgery -Esophagectomy for middle and lower esophagus/ Postoperative chemotherapy: (Leucovorin, Oxaliplatin, 5 FU) -Stage I-III, for Upper esophagus -Concurrent chemoradiotherapy (Capecitabine, Carboplatin, Paclitaxel) -Locally advanced, middle and lower esophagus -Neoadjuvant Concurrent Chemoradiotherapy (Capecitabine, Carboplatin, Paclitaxel),surgery	-Stage IV, Palliation RT, Palliative Chemotherapy (Capecitabine), Best Supportive care
Follow-up	-H&P -Nutritional assessment -basic labs (CBC, LFT,RFT)	-Imaging: CT: Head& Neck, Chest, abdomen with contrast.	-Imaging: PET scan

Gastrointestinal stromal tumours

	Basic	Core	Enhanced
Workup	History and Physical Examination basic labs (CBC, LFT,RFT) Imaging: Abdominal ultrasound Imaging: Abdomen CT with contrast or MRI Biopsy (excision, core)	Imaging: -Chest CT With contrast &. Upper or -lower endoscopy - -IHC: CD117, CD34	Imaging: PET scan
Management	-Respectable disease: upfront surgery Resectable disease: (HBP Committee recommended) - Adjuvent imatinib -Non-metastatic unresectable disease:HBP Committee recommended): Neoadjuvant Imatinib plus Surgery. Palliative surgery for resectable metastatic lesion	Resectable disease: - upfront surgery	Metastatic Disease (stage IV): -Palliative imatinib. -Chemotherapy (2nd line Sunitinib,3rd line Regorafenib)
Follow-up	History and Physical Examination Basic labs (CBC, LFT,RFT)	Imaging: -Chest &Abdomen CT with contrast or MRI.	Imaging: PET

Leukemias (Acute Myeloid Leukemia)

	Basic	Core	Enhanced
Workup	-History and Physical Examination -Basic Lab : (CBC,LFT, RFT) -Other labs: Clotting Time, partial thromboplastin time, Fibrinogen, Blood group and human leukocyte antigen -in transplant eligible patients. -Pathology: Bone marrow aspiration and biopsy Lumbar puncture (LP) for CSF Analysis Immunohistochemistry. Imaging: Abdominal ultrasound in case of suspicion of splenomegaly.	-Flow cytometry - Imaging: Chest, Abdomen and Pelvic CT Scan with contrast.	(ASXL1, c-KIT, FLT3 [ITD (and TKD (tyrosine kinase domain)], NPM1, CEBPA [biallelic], IDH1, IDH2, RUNX1, TP53, and other mutations -cytogenetic analyses (Karyotype) -immunophenotyping, cytogenetic and molecular evaluation.
Management	Supportive treatment.		For all stages: • Induction chemo: (Cytarabine, daunorubicin) • Post-remission (Consolidation)Chemo: (Cytarabine) • Maintenance Chemo: (Daunorubicin, azacitidine decitabine) Bone marrow transplantation CNS Metastatic:-CNS prophylaxis methotrexate/ Cytarabine. Relapse/ Recurrence Chemo; (Fludarabine, Cytarabine, Idarubicin, and G -CSF) -Palliative single-dose regimen-Low-dose cytarabine (LD-AraC)
Follow-up	-History and Physical Examination -Basic labs: (CBC, LFT, RFT)		-Pathology: Bone marrow aspiration and biopsy Imaging: Chest, Abdomen and Pelvic CT Scan with contrast.

Leukemias (Chronic Myelogenous Leukemia_CML)

	Basic	Core	Enhanced
Workup	History and Physical Examination. Basic Labs (CBC, LFT,RFT) Peripheral blood smear Bones marrow aspiration and biopsy GeneXpert BCR -ABL for detecting Philadelphia chromosome.		Genetic Test Fluorescence in situ hybridization (FISH): BCR -ABL1 fusion gene in peripheral blood.
Management	Supportive treatment. • Long -term disease control without cure - use Tyrosine kinase inhibitors (TKIs) : imatinib (Gleevec) • Chronic phase : (imatinib (Gleevec), Allopurinol) • For accelerated and blast phase: (Imatinib, Hydroxyurea, Allopurinol) • Symptomatic splenomegaly -imatinib plus TKI in accelerated or blast phase		Potential cure - use allogeneic hematopoietic cell transplantation -Palliative therapy for metastatic disease: hydroxyurea -Cytoreduction with Hydroxyurea to reduce the WBC below 200,000 for GeneXpert testing -
Follow -up	History and Physical Examination Basic labs (CBC, LFT, RFT)	GeneXpert BCR -ABL Assay	Genetic Test Fluorescence in situ hybridization (FISH): BCR -ABL1 fusion gene in peripheral blood.

Leukemias (Acute Lymphoblastic Leukemia _ALL)

	Basic	Core	Enhanced
Workup	• History and Physical Examination • Basic Lab (CBC, LFT , RFT) • Other labs: Urinalysis ,Hepatitis B/C, HIV, Pregnancy testing, fertility counseling. • Tumor lysis syndrome (TLS) panel: Lactate dehydrogenase (LDH), uric acid, potassium, calcium, phosphorus, Testicular exam, Peripheral blood smear .Echocardiogram , ECG • Bones marrow aspiration and biopsy • Imaging: Abdominal/pelvic ultrasound	.	Imaging MRI cardiac angiography • Immunophenotyping, cytogenetic +/ - FISH and molecular evaluation. (For B -cell ALL) • Genetic Testing • Patients with failed cytogenetics for B -cell ALL -molecular/FISH testing for BCR -ABL . • HLA For eligible of Transplant Imaging • MUGA scan/ MRI cardiac / Echocardiogram for the Patients whom anthracycline based treatment is contemplated. CMV Ab testing,
Management	Induction Chemo: (Imatinib ,doxorubicin, cyclophosphamide, Vincristine) plus dexamethasone Consolidation Chemo: (Imatinib, Vincristine, Daunorubicin, Cyclophosphamide) plus Prednisone. Maintenance Chemo (Vincristine) and prednisone /Imatinib/Methotrexate) Supportive treatment		Recurrence Chemo: (Vincristine, imatinib, Mesna, methotrexate) plus Dexamethasone Stem-cell transplantation
Follow -up	Consultations :H&P Lab(CBC,LFT,RFT)	Imaging: CT of neck with contrast Pathology: (Bone marrow core biopsy, Bone marrow aspiration)	Other lab exams Genetic testing Imaging: CT of neck with contrast

Appendix 4: Criteria

The following table summarizes how all nine criteria were assessed in Rwanda, based on a draft version of Standard Operating Procedures for prioritizing the HBP.

Table 19: Methods for assessment of all criteria

#	Criteria	Definition	Measure	Assessment description
1	Cost-effectiveness	The relative measure of the extent to which an intervention improves population health for the resources used.	Disability-adjust life years averted	Quantitative. Review of existing literature in the Tufts registry + expert opinion for gaps
2	Burden of disease	The extent to which the disease contributes to mortality, morbidity or disability in a population.	DALYs per capita Presenting incidence Projected incidence	Quantitative. Obtain estimates of DALYs per capita where feasible. For gaps, document reported (presenting) incident cases and estimated current (projected incident cases)
3	Cost	The full value of resources used to provide a service.	Full economic cost for the population	Quantitative. Estimated using local costing data combined with international sources.
4	Financial risk protection	Assesses whether paying for the service out of pocket would result in impoverishment.	Out-of-pocket expenditure as a proportion of average annual household consumption expenditure in Rwanda.	Quantitative, based on cost. Calculated as cost of intervention divided by annual household expenditure.
5	Budget impact	Estimates how affordable the service is to the CBHI.	Total cost of providing selected services at estimated coverage rates	Quantitative, based on cost. Calculated by multiplying unit cost per case by expected coverage rates.
6	Feasibility	The extent to which an intervention can be delivered through the existing health system.	Classified as highly feasible, moderately feasible, or infeasible.	Qualitative. Expert judgment.
7	Vulnerable groups	The extent to which services benefit vulnerable groups	Classified if a vulnerable group identified for that intervention.	Qualitative. Expert judgment.
8	Individual effectiveness	The health gains of the service at patient level.	Classified as low, medium, or high.	Qualitative. Expert judgment.
9	Life threatening	The immediate need for a service, also known as the 'rule of rescue' – if the service is not provided, the patient will die.	Classified as low, medium, or high.	Qualitative. Expert judgment.

Source: Adapted from the draft Rwanda Standard Operating Procedures for Prioritizing HBPs

The following tables summarize the unit costs per case; cost-effectiveness ratios; and burden of disease for the 49 cancers assessed.

Table 20: Cost per case per cancer US$

Cancer	Health Sector Cost per Case - US$			CBHI Cost per Case - US$		
	Basic	Core	Enhanced	Basic	Core	Enhanced
Brain Tumours	1,124	5,428	1,029	1,026	2,278	792
Glioma	1,678	4,078	5,392	1,745	1,889	1,836
Head and Neck	2,070	3,046	1,378	886	2,459	882
Ovary	1,434	1,460	3,141	477	353	1,532
Vulva/ Vagina	806	1,885	224	303	1,491	137
Melanoma	350	289	17,292	82	108	1,034
Non Melanoma	355	293	555	109	113	397
Bone Cancers	1,277	1,346	3,019	85	413	2,379
Non Small Cell Lung Cancer	161	2,831	27,436	83	1,798	2,067
Endometrial (uterine)	846	2,935	1,963	403	1,721	1,472
Gestational	717	948	-	302	381	-
Renal Cell Carcinoma	1,596	549	5,490	809	304	1,597
Penile	513	1,079	-	124	713	-
Esophageal	444	2,437	7,634	412	1,379	1,587
ALL	23,281	764	161,671	556	579	120,252
Kaposi Sarcoma	675	858	226	193	463	103
AML	606	258	160,323	432	179	120,899
CML	37,226	461	156,163	765	161	119,772
Hodgkin Lymphoma	2,395	2,385	40,827	595	1,477	25,343
Thyroid	887	860	6,975	491	430	5,354
Pancreas	416	771	3,776	178	304	1,940
Anus	201	4,994	476	102	2,831	9
SCLC	395	3,868	2,428	192	2,532	1,445
Non-Hodgkins	2,132	5,758	33,998	867	2,056	25,806
T-cell	459	-	42,536	220	-	28,056
Neuroblastoma	670	3,305	29,948	457	2,784	22,814
Multiple Myeloma	6,873	2,132	27,194	435	1,112	17,696
Mesothelioma	161	2,831	27,436	83	1,798	2,067
Thymoma/ Thymic	6,873	2,132	27,194	435	1,112	17,696
Renal Pelvis	1,596	549	5,490	809	304	1,597
Neuroendocrine	416	771	3,776	178	304	1,940
Germ Cell Tumour	2,224	1,161	-	437	1,361	-
GIST	6,873	2,132	27,194	435	1,112	17,696
Soft tissue Sarcoma	1,277	1,346	3,019	85	413	2,379
Adrenal	6,873	2,132	27,194	435	1,112	17,696

Table 21: Cost-effectiveness ratios

Round	Cancer and Level	Cost-effectiveness ratio (2021 USD/DALY)
1	Cervical - Prevention	212
1	Gastric - Basic	381
1	ALL - Basic	432
1	Wilm's Tumour - Basic	445
1	Retinoblastoma - Basic	459
1	Colon - Core	495
1	Rectal - Core	495
1	Cervical - Basic	644
1	Breast - Core	645
1	Colon - Enhanced	650
1	Rectal - Enhanced	650
1	Cervical - Enhanced	655
1	Gastric - Core	672
1	Cervical - Core	811
1	Gastric - Enhanced	916
1	Prostate - Basic	1,006
1	Prostate - Core	1,403
1	Breast - Enhanced	1,445
1	Breast - Basic	1,600
1	Prostate - Enhanced	2,881
2	Lymphoma - NHL - DLBCL - Basic	23
2	Thyroid - Basic	50
2	Lymphoma - NHL - DLBCL - Core	450
2	Esophageal - Core	473
2	H & N - Core	814
2	Lymphoma - HL - Enhanced	893
2	Lung - NSCLC - Enhanced	999
2	Lung - SCLC - Enhanced	3,065
2	Pancreatic - Enhanced	3,609
2	Lung - Mesothelioma - Core	3,808
2	Leukemia - CML - Core	4,265
2	Renal cell carcinoma - Enhanced	4,537
2	Brain - glioma - Core	4,584
2	Brain - glioma - Enhanced	4,584
2	Skin - Melanoma - Enhanced	6,431
2	Multiple myeloma - Enhanced	10,714
2	Lung - Mesothelioma - Enhanced	16,523
2	Esophageal - Enhanced	17,922
2	Ovarian - Enhanced	43,708

Source: Nemzoff et al, forthcoming(24)

Table 22: Expert-elicited cost-effectiveness ratios

Cancer and Level	CER		
Esophageal - Basic	417	Lymphoma - NHL - DLBCL - Enhanced	1,668
Skin - Melanoma - Basic	417	Ovarian - Core	1,668
Adrenal tumors - Basic	417	Adrenal tumors - Core	1,668
Anus - Enhanced	417	Brain - brain tumors - Core	1,668
Uterine – Enhanced*	417	Uterine – Core*	1,668
Kaposi sarcoma - Basic	417	Kaposi sarcoma - Enhanced	1,668
Neuroblastoma - Core	417	Leukemia - ALL - Basic	1,668
Penile - Basic	417	Leukemia - AML - Core	1,668
Penile - Enhanced	417	Leukemia - AML - Enhanced	1,668
Skin - Non-melanoma - Basic	417	Leukemia - CLL - Basic	1,668
Vulva/Vagina - Basic	417	Neuroblastoma – Enhanced	1,668
Lung - NSCLC - Core	834	Renal pelvis carcinoma – Basic*	1,668
Lymphoma - HL - Basic	834	Renal pelvis carcinoma – Enhanced*	1,668
Lymphoma - HL - Core	834	Vulva/Vagina - Core	1,668
Multiple myeloma - Basic	834	H & N - Enhanced	2,502
Ovarian - Basic	834	Leukemia - CML - Enhanced	2,502
Renal cell carcinoma - Basic	834	Pancreatic - Basic	2,502
Skin - Melanoma - Core	834	Pancreatic - Core	2,502
Thyroid - Core	834	Thyroid - Enhanced	2,502
Anus - Basic	834	Adrenal tumors - Enhanced	2,502
Anus - Core	834	Bone - Enhanced	2,502
Bone - Basic	834	Brain - brain tumors - Enhanced	2,502
Bone - Core	834	Leukemia - ALL - Core	2,502
Brain - brain tumors - Basic	834	Leukemia - ALL - Enhanced	2,502
Uterine – Basic*	834	Leukemia - AML - Basic	2,502
Germ cell tumors - Basic	834	Leukemia - CLL - Core	2,502
Germ cell tumors - Core	834	Leukemia - CLL - Enhanced	2,502
Gestational/Placenta - Basic	834	Skin - Non-melanoma - Enhanced	2,502
Gestational/Placenta - Core	834	Vulva/Vagina - Enhanced	2,502
Kaposi sarcoma - Core	834	Neuroendocrine tumors - Basic	2,502
Lymphoma - NHL - T-cell - Basic	834	Neuroendocrine tumors - Core	2,502
Neuroblastoma - Basic	834	Neuroendocrine tumors - Enhanced	2,502
Penile - Core	834	Soft tissue sarcoma – Enhanced	2,502
Renal pelvis carcinoma – Core*	834	Multiple myeloma – Core	-
Skin - Non-melanoma - Core	834	Renal cell carcinoma - Core	-
Soft tissue sarcoma - Basic	834	Germ cell tumors - Enhanced	-
Soft tissue sarcoma - Core	834	Gestational/Placenta - Enhanced	-
Brain - glioma - Basic	1,668	GIST – Basic	-
H & N - Basic	1,668	GIST – Core	-
Leukemia - CML - Basic	1,668	GIST – Enhanced	-
Lung - Mesothelioma - Basic	1,668	Lymphoma - NHL - T-cell - Core	-
Lung - NSCLC - Basic	1,668	Lymphoma - NHL - T-cell - Enhanced	-
Lung - SCLC - Basic	1,668	Thymoma/thymic carcinoma* – Basic	-
Lung - SCLC - Core	1,668	Thymoma/thymic carcinoma* – Core	-
		Thymoma/thymic carcinoma* - Enhanced	-

"-" : either no incident cases were reported, or no treatment was included in this package

*Note: each of the following includes two cancers for which CERs were sought: thymoma/thymic carcinoma (n=2), uterine (corpus uteri + endometrial) (n=2), renal pelvis (renal pelvis carcinoma + urothelial (n=2)

Source: Nemzoff et al, forthcoming(24)

Appendix 5: Coverage

Coverage refers to the number of patients being treated relative to the total number of patients with a given cancer in Rwanda. Table 23 below summarizes the coverage estimates. Column A is the number of new cancer cases across the country ("predicted incidence"), estimated by the Institute for Health Metrics and Evaluation(22).

Column B is the current coverage rate. This is estimated using incidence from the Rwanda cancer registry. For the basic package, current coverage is calculated by taking the number of new patients in the Rwanda cancer registry ("presenting incidence") (C) and dividing it by predicted incidence (A).

Column C is the number of patients treated now, using the presenting incidence. For basic, this is the number of patients in the registry for each cancer. For core, it is a percentage of the patients getting basic, as estimated by the cancer experts. For enhanced, it is a percentage of the patients getting core, as estimated by the cancer experts.

Column D is the expert recommended coverage rate, meaning the percentage of patients that the experts estimated that they could reasonably increase to. Column E is the expert recommended patients treated, calculated by multiplying A*D. For the top ten cancers, experts estimated that all patients could receive the basic package at 70% coverage. For core, they estimated a percentage for each cancer separately. For the remaining cancers, experts estimated increases in basic and core packages specifically for each cancer, which is illustrated below.

Table 23: Coverage summary

		A Incidence	B Current coverage (C/A)	C Patients treated now (A*B)	D Expert recommended coverage	E Expert recommended patients treated (A*D)
ALL	Basic	87	45%	39	70%	61
ALL	Core	87	11%	10	60%	52
ALL	Enhanced	87	0%	-	0%	-
Breast	Basic	1112	50%	552	70%	778
Breast	Core	1112	12%	138	60%	667
Breast	Enhanced	1112	0%	-	0%	-
Cervical	Prevention	150049	80%	120,039	70%	105,034
Cervical	Basic	1495	36%	535	70%	1,047
Cervical	Core	1495	9%	134	60%	897
Cervical	Enhanced	1495	0%	-	0%	-
Colon	Basic	273	33%	91	70%	191
Colon	Core	273	8%	23	60%	164
Colon	Enhanced	273	0%	-	0%	-
Gastric	Basic	432	84%	362	70%	302
Gastric	Core	432	21%	91	50%	216
Gastric	Enhanced	432	0%	-	0%	-
Liver	Basic	294	88%	258	70%	206
Liver	Core	294	22%	65	0%	-
Liver	Enhanced	294	0%	-	0%	-
Prostate	Basic	699	57%	401	70%	489
Prostate	Core	699	14%	100	60%	419
Prostate	Enhanced	699	0%	-	0%	-
Rectal	Basic	306	30%	91	70%	214
Rectal	Core	306	7%	23	50%	153
Rectal	Enhanced	306	0%	-	0%	-
Retinoblastoma	Basic	48	81%	39	70%	34
Retinoblastoma	Core	48	20%	10	60%	29

Retinoblastoma	Enhanced	48	0%	-	0%	-
Wilm's Tumour	Basic	84	48%	40	70%	59
Wilm's Tumour	Core	84	12%	10	80%	67
Wilm's Tumour	Enhanced	84	0%	-	0%	-
Adrenal tumours	Basic	1	90%	1	100%	1
Adrenal tumours	Core	1	63%	1	79%	1
Adrenal tumours	Enhanced	1	13%	0	0%	-
Anus	Basic	42	45%	19	70%	29
Anus	Core	42	32%	13	49%	21
Anus	Enhanced	42	6%	3	0%	-
Bone	Basic	308	45%	139	56%	172
Bone	Core	308	32%	97	39%	120
Bone	Enhanced	308	6%	19	0%	-
Brain - brain tumours	Basic	85	78%	66	98%	83
Brain - brain tumours	Core	85	54%	46	78%	66
Brain - brain tumours	Enhanced	85	11%	9	0%	-
Brain - glioma	Basic	85	78%	66	97%	83
Brain - glioma	Core	85	54%	46	78%	66
Brain - glioma	Enhanced	85	11%	9	0%	-
Uterine (corpus uteri + endometrial)	Basic	146	22%	32	50%	73
Uterine (corpus uteri + endometrial)	Core	146	15%	22	19%	28
Uterine (corpus uteri + endometrial)	Enhanced	146	3%	4	0%	-
Esophageal	Basic	650	12%	77	16%	104
Esophageal	Core	650	8%	54	15%	98
Esophageal	Enhanced	650	2%	11	0%	-
Germ cell tumours	Basic	1	90%	1	100%	1
Germ cell tumours	Core	1	63%	1	79%	1
Germ cell tumours	Enhanced	1	13%	0	0%	-
Gestational/Placenta	Basic	180	45%	81	70%	126

Gestational/Placenta	Core	180	32%	57	35%	63
Gestational/Placenta	Enhanced	180	6%	11	0%	-
GIST	Basic	19	90%	17	100%	19
GIST	Core	19	63%	12	0%	-
GIST	Enhanced	19	13%	2	0%	-
H & N	Basic	378	53%	202	67%	253
H & N	Core	378	37%	141	47%	178
H & N	Enhanced	378	7%	28	0%	-
Kaposi sarcoma	Basic	84	45%	38	56%	47
Kaposi sarcoma	Core	84	32%	26	39%	33
Kaposi sarcoma	Enhanced	84	6%	5	0%	-
Leukaemia - ALL	Basic	75	51%	38	64%	48
Leukaemia - ALL	Core	75	36%	27	0%	-
Leukaemia - ALL	Enhanced	75	7%	5	0%	-
Leukaemia - AML	Basic	63	51%	32	64%	40
Leukaemia - AML/CLL	Core	63	36%	22	0%	-
Leukaemia - AML/CLL	Enhanced	63	7%	4	0%	-
Leukaemia - CML	Basic	62	51%	32	63%	39
Leukaemia - CML	Core	62	36%	22	0%	-
Leukaemia - CML	Enhanced	62	7%	4	0%	-
Lung - Mesothelioma	Basic	19	21%	4	26%	5
Lung - Mesothelioma	Core	19	15%	3	18%	3
Lung - Mesothelioma	Enhanced	19	3%	1	0%	-
Lung - NSCLC	Basic	401	23%	94	29%	116
Lung - NSCLC	Core	401	16%	66	20%	80
Lung - NSCLC	Enhanced	401	3%	13	0%	-
Lung - SCLC	Basic	71	23%	17	30%	21
Lung - SCLC	Core	71	16%	12	0%	-
Lung - SCLC	Enhanced	71	3%	2	0%	-
Lymphoma - HL	Basic	82	36%	30	81%	66
Lymphoma - HL	Core	82	25%	21	40%	33

Lymphoma - HL	Enhanced	82	5%	4	0%	-
Lymphoma - NHL - DLBCL	Basic	188	73%	137	90%	169
Lymphoma - NHL - DLBCL	Core	188	51%	96	63%	119
Lymphoma - NHL - DLBCL	Enhanced	188	10%	19	0%	-
Lymphoma - NHL - T-cell	Basic	21	73%	15	90%	19
Lymphoma - NHL - T-cell	Core	21	51%	11	0%	-
Lymphoma - NHL - T-cell	Enhanced	21	10%	2	0%	-
Multiple myeloma	Basic	86	17%	14	40%	34
Multiple myeloma	Core	86	12%	10	0%	-
Multiple myeloma	Enhanced	86	2%	2	0%	-
Neuroblastoma	Basic	10	45%	5	60%	6
Neuroblastoma	Core	10	32%	3	40%	4
Neuroblastoma	Enhanced	10	6%	1	0%	-
Neuroendocrine tumours	Basic	1	90%	1	100%	1
Neuroendocrine tumours	Core	1	63%	1	79%	1
Neuroendocrine tumours	Enhanced	1	13%	0	0%	-
Ovarian	Basic	325	19%	61	24%	78
Ovarian	Core	325	13%	43	16%	52
Ovarian	Enhanced	325	3%	9	0%	-
Pancreatic	Basic	194	14%	27	18%	35
Pancreatic	Core	194	10%	19	0%	-
Pancreatic	Enhanced	194	2%	4	0%	-
Penile	Basic	112	45%	50	56%	63
Penile	Core	112	32%	35	39%	44
Penile	Enhanced	112	6%	7	0%	-
Renal cell carcinoma	Basic	118	53%	62	66%	78
Renal cell carcinoma	Core	118	37%	43	0%	-
Renal cell carcinoma	Enhanced	118	7%	9	0%	-
Renal pelvis carcinoma + urothelial	Basic	1	90%	1	70%	1
Renal pelvis carcinoma + urothelial	Core	1	63%	1	30%	0

Renal pelvis carcinoma + urothelial	Enhanced	1	13%	0	0%	-
Skin - Melanoma	Basic	79	41%	33	52%	41
Skin - Melanoma	Core	79	29%	23	36%	28
Skin - Melanoma	Enhanced	79	6%	5	0%	-
Skin - Non-melanoma	Basic	276	42%	116	52%	143
Skin - Non-melanoma	Core	276	29%	81	37%	102
Skin - Non-melanoma	Enhanced	276	6%	16	0%	-
Soft tissue sarcoma	Basic	240	45%	108	56%	134
Soft tissue sarcoma	Core	240	32%	76	39%	94
Soft tissue sarcoma	Enhanced	240	6%	15	0%	-
Thymoma + thymic carcinoma	Basic	1	90%	1	70%	1
Thymoma + thymic carcinoma	Core	1	63%	1	0%	-
Thymoma + thymic carcinoma	Enhanced	1	13%	0	0%	-
Thyroid	Basic	158	18%	28	70%	111
Thyroid	Core	158	12%	20	50%	79
Thyroid	Enhanced	158	2%	4	0%	-
Vulva/Vagina	Basic	86	45%	39	56%	48
Vulva/Vagina	Core	86	32%	27	39%	34
Vulva/Vagina	Enhanced	86	6%	5	0%	-
Total number of patients treated			Current	4,100	Recommended	5,700

Appendix 6: Summary of final package

Overall, the final recommended package combines the basic and core packages of services, depending on the specific cancers, with expanded screening.

These are summarized in text here, and in Table 24 below.

A. The basic package of services was recommended for all cancer patients.

B. The core package of services was recommended for most cancers, except for gastrointestinal stromal tumor, acute lymphomblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, small-cell lung cancer, non-Hodgkins' lymphoma (T-cell), multiple myeloma, pancreatic cancer, renal cell carcinoma, and thymoma/thymic carcinoma, where only the basic package was recommended. Specifications were made regarding the recommended core package. Target coverage rates were suggested by experts depending on the feasibility of expanding services to new patients, and these rates were endorsed by the committee (Table 23).

C. To improve diagnosis at earlier stages, it was recommended that mass screening programs be expanded for four cancers: breast, cervical, colon and rectal. For the nine highest incidence cancers (breast, cervical, prostate, gastric, colon, rectal, acute lymphoblastic leukaemia, retinoblastoma, and Wilms tumour), the core package was limited to treatment for stages I-III; stage IV cancer was excluded.

D. Finally, the integration of palliative care within overall cancer therapy was recommended.

E. The committee did not recommend the enhanced package for any cancers. This is because the cost of treatment is proportionately much higher and offers little health gain compared with the basic and core packages.

Table 24: Summary of the cancer package

Cancer	Recommended coverage	Stage exclusion for core
Breast	Core	Stages I-III only
Cervical	Core	Stages I-III only
Prostate	Core	Stages I-III only
Gastric	Core	Stages I-III only
Colon	Core	Stages I-III only
Wilm's Tumour	Core	Stages I-III only
ALL	Core	Stages I-III only
Rectal	Core	Stages I-III only
Liver	Basic	N/A
Retinoblastoma	Core	Stages I-III only
Adrenal tumors	Core	No exclusion
Anus	Core	No exclusion
Bone	Core	No exclusion
Brain - brain tumors	Core	No exclusion
Brain - glioma	Core	No exclusion
Uterine (corpus uteri + endometrial)	Core	No exclusion
Esophageal	Core	No exclusion
Germ cell tumors	Core	No exclusion
Gestational/Placenta	Core	No exclusion
GIST	Basic	N/A
H & N	Core	No exclusion
Kaposi sarcoma	Core	No exclusion
Leukemia - ALL	Basic	N/A
Leukemia - AML/CLL	Basic	N/A
Leukemia - CML	Basic	N/A
Lung - Mesothelioma	Core	No exclusion
Lung - NSCLC	Core	No exclusion
Lung - SCLC	Basic	N/A
Lymphoma - HL	Core	No exclusion
Lymphoma - NHL - DLBCL	Core	No exclusion
Lymphoma - NHL - T-cell	Basic	N/A
Multiple myeloma	Basic	N/A
Neuroblastoma	Core	No exclusion
Neuroendocrine tumors	Core	No exclusion
Ovarian	Core	No exclusion
Pancreatic	Basic	No exclusion
Penile	Core	No exclusion

Renal cell carcinoma	Basic	N/A
Renal pelvis carcinoma + urothelial	Core	No exclusion
Skin - Melanoma	Core	No exclusion
Skin - Non-melanoma	Core	No exclusion
Soft tissue sarcoma	Core	No exclusion
Thymoma/thymic carcinoma	Basic	N/A
Thyroid	Core	No exclusion
Vulva/Vagina	Core	No exclusion

In the event that not all cancers can be covered at once, the recommendation was supplemented by a hierarchy of cancers, developed by the cancer experts. Table 25 summarizes which cancers are considered high, medium, and low priority.

Table 25: Expert ranking of cancers

Cancer	**Priority level**
Top 10 cancers	
Breast	High
Cervical	High
Prostate	Medium
Gastric	Low
Colon	High
Wilm's Tumour	High
ALL	Medium
Rectal	Medium
Liver	Low
Retinoblastoma	Low
Remaining cancers	
Anus	High
Uterine	High
Gestational/Placenta	High

GIST	High
Leukaemia - CML	High
Ovarian	High
Skin - non-melanoma	High
Thymoma/thymic carcinoma	High
Thyroid	High
Adrenal tumours	Medium
Bone	Medium
Brain - brain tumours	Medium
Brain - glioma	Medium
Esophageal	Medium
Germ cell tumours	Medium
H & N	Medium
Kaposi sarcoma	Medium
leukaemia - ALL	Medium
leukaemia - AML	Medium
Lymphoma - HL	Medium
Lymphoma - NHL - DLBCL	Medium
Lymphoma - NHL - T-cell	Medium
Multiple myeloma	Medium
Neuroblastoma	Medium
Neuroendocrine tumours	Medium
Penile	Medium
Renal cell carcinoma	Medium
Vulva/Vagina	Medium
Lung - Mesothelioma	Low
Lung - NSCLC	Low
Lung - SCLC	Low
Pancreatic	Low

Renal pelvis carcinoma	Low
Skin - Melanoma	Low

In addition to the specific cancer recommendations, the committee made several procedural recommendations for future consideration.

A. First, it assigned the rapporteur, who is from RSSB, to follow up the application of the committee's recommendations.

B. Second, it proposed the set-up of a sub-committee to re-examine the co-payment structure for cancer, given the cumulative high cost of treatment and associated high out-of-pocket expenditure for patients.

C. Third, it emphasized the role of the Tumour Board in determining suitable treatment for specific cases and recommending it be extended to the national level.

Appendices – Chapter 7

Appendix 1: Data used to populate the ARCH

Table 26: Data for the ARCH

Cancer intervention	A ICER (US$/DALY)	B Unit cost (US$)	C Incidence	D Cost	E Score	F p(wrong)	G Risk (D* (1+F)
ICERs from the literature							
Lymphoma - NHL - DLBCL - Basic	23	2,131	188	280,671	3	1%	2,807
Thyroid - Basic	50	887	158	98,013	2	3%	2,940
Cervical - Prevention	212	6	150,049	592,393	2	3%	17,772
ALL - Basic	432	3,436	87	209,252	2	12%	25,110
ALL - Core	432	5,463	87	332,680	2	12%	39,922
ALL - Enhanced	432	5,963	87	363,127	2	12%	43,575
Wilm's Tumour - Basic	445	865	84	50,885	2	6%	3,053
Wilm's Tumour - Core	445	1,004	84	59,016	2	6%	3,541
Wilm's Tumour - Enhanced	445	2,174	84	127,858	2	6%	7,671
Lymphoma - NHL - DLBCL - Core	450	7,887	188	1,038,851	3	1%	10,389
Retinoblastoma - Basic	459	128	48	4,305	2	6%	258
Retinoblastoma - Core	459	1,417	48	47,611	2	6%	2,857
Retinoblastoma - Enhanced	459	1,897	48	63,737	2	6%	3,824
Esophageal - Core	473	2,880	650	1,311,249	2	6%	78,675
Colon - Basic	495	2,017	273	385,396	2	6%	23,124
Colon - Core	495	4,182	273	799,183	2	6%	47,951
Rectal - Basic	495	1,530	306	327,826	2	6%	19,670
Rectal - Core	495	5,930	306	1,270,268	2	6%	76,216
Cervical - Basic	644	2,442	1,495	2,555,845	2	3%	76,675
Breast - Core	645	3,962	1,112	3,084,287	2	3%	92,529
Colon - Enhanced	650	6,560	273	1,253,671	2	6%	75,220
Rectal - Enhanced	650	6,921	306	1,482,578	2	6%	88,955
Cervical - Enhanced	655	5,159	1,495	5,398,514	2	3%	161,955
Gastric - Basic	672	567	432	171,374	2	3%	5,141
Gastric - Core	672	4,165	432	1,259,587	2	3%	37,788
Cervical - Core	811	4,012	1,495	4,198,438	2	6%	251,906
H & N - Core	814	5,114	378	1,352,687	2	6%	81,161
Lymphoma - HL - Enhanced	893	45,592	82	2,614,547	2	4%	104,582
Gastric - Enhanced	916	7,793	432	2,356,733	2	3%	70,702
Lung - NSCLC - Enhanced	999	30,419	401	8,541,807	2	6%	512,508
Prostate - Basic	1,403	217	699	105,946	2	3%	3,178
Prostate - Core	1,403	6,012	699	2,941,595	2	3%	88,248
Breast - Enhanced	1,445	5,630	1,112	4,382,650	2	3%	131,479
Breast - Basic	1,600	1,322	1,112	1,028,935	2	6%	61,736
Prostate - Enhanced	2,881	7,193	699	3,519,497	2	9%	316,755
Lung - SCLC - Enhanced	3,065	6,689	71	331,447	2	6%	19,887
Pancreatic - Enhanced	3,609	4,961	194	673,321	2	6%	40,399
Lung - Mesothelioma - Core	3,808	2,992	19	39,791	2	3%	1,194
Leukemia - CML - Core	4,265	37,675	62	1,639,717	2	6%	98,383
Renal cell carcinoma - Enhanced	4,537	7,633	118	629,520	2	3%	18,886
Brain - glioma - Core	4,584	5,754	85	342,934	2	6%	20,576
Brain - glioma - Enhanced	4,584	11,144	85	664,228	2	6%	39,854
Skin - Melanoma - Enhanced	6,431	17,925	79	990,027	2	6%	59,402
Multiple myeloma - Enhanced	10,714	30,430	86	1,825,149	2	6%	109,509
Lung - Mesothelioma - Enhanced	16,523	30,419	19	404,574	2	3%	12,137
Esophageal - Enhanced	17,922	10,512	650	4,786,074	2	3%	143,582
Ovarian - Enhanced	43,708	6,032	325	1,370,723	2	6%	82,243
Elicited ICERs							
Adrenal tumors - Basic	416	3,263	1	2,284	1	27%	617
Anus - Enhanced	416	5,669	42	166,675	1	27%	45,002

Uterine - Enhanced	416	5,742	146	587,699	1	27%	158,679
Esophageal - Basic	416	444	650	202,183	1	27%	54,589
Kaposi sarcoma - Basic	416	675	84	39,691	1	27%	10,717
Neuroblastoma - Core	416	3,974	10	27,818	1	27%	7,511
Penile - Basic	416	513	112	40,192	1	27%	10,852
Penile - Enhanced	416	1,591	112	124,738	1	27%	33,679
Skin - Melanoma - Basic	416	350	79	19,319	1	27%	5,216
Skin - Non-melanoma - Basic	416	355	276	68,607	1	27%	18,524
Vulva/Vagina - Basic	416	806	86	48,493	1	27%	13,093
Anus - Basic	834	201	42	5,898	1	27%	1,593
Anus - Core	834	5,194	42	152,689	1	27%	41,226
Bone - Basic	834	1,277	308	275,324	1	27%	74,337
Bone - Core	834	2,622	308	565,336	1	27%	152,641
Brain - brain tumors - Basic	834	1,123	85	66,945	1	27%	18,075
Uterine - Basic	834	846	146	86,578	1	27%	23,376
Germ cell tumors - Basic	834	2,223	1	1,556	1	27%	420
Germ cell tumors - Core	834	3,384	1	2,369	1	27%	640
Gestational/Placenta - Basic	834	717	180	90,357	1	27%	24,396
Gestational/Placenta - Core	834	1,665	180	209,776	1	27%	56,640
Kaposi sarcoma - Core	834	1,533	84	90,145	1	27%	24,339
Lung - NSCLC - Core	834	2,992	401	840,100	1	27%	226,827
Lymphoma - HL - Basic	834	2,394	82	137,281	1	27%	37,066
Lymphoma - HL - Core	834	4,778	82	274,015	1	27%	73,984
Lymphoma - NHL - T-cell - Basic	834	459	21	6,722	1	27%	1,815
Multiple myeloma - Basic	834	3,263	86	195,741	1	27%	52,850
Neuroblastoma - Basic	834	670	10	4,689	1	27%	1,266
Ovarian - Basic	834	1,434	325	325,756	1	27%	87,954
Penile - Core	834	1,591	112	124,738	1	27%	33,679
Renal cell carcinoma - Basic	834	1,595	118	131,578	1	27%	35,526
Renal pelvis carcinoma - Core	834	2,145	1	1,501	1	27%	405
Skin - Melanoma - Core	834	639	79	35,275	1	27%	9,524
Skin - Non-melanoma - Core	834	648	276	125,164	1	27%	33,794
Thyroid - Core	834	1,747	158	193,100	1	27%	52,137
Adrenal tumors - Core	1,668	5,220	1	3,654	1	27%	987
Brain - brain tumors - Core	1,668	6,549	85	390,364	1	27%	105,398
Brain - glioma - Basic	1,668	1,677	85	99,968	1	27%	26,991
Uterine - Core	1,668	3,780	146	386,875	1	27%	104,456
H & N - Basic	1,668	2,069	378	547,272	1	27%	147,763
Kaposi sarcoma - Enhanced	1,668	1,759	84	103,453	1	27%	27,932
Leukemia - ALL - Basic	1,668	23,274	75	1,229,894	1	27%	332,071
Leukemia - AML - Core	1,668	864	63	37,948	1	27%	10,246
Leukemia - AML - Enhanced	1,668	161,137	63	7,074,531	1	27%	1,910,123
Leukemia - CML - Basic	1,668	37,214	62	1,619,680	1	27%	437,314
Lung - Mesothelioma - Basic	1,668	161	19	2,144	1	27%	579
Lung - NSCLC - Basic	1,668	161	401	45,260	1	27%	12,220
Lung - SCLC - Basic	1,668	394	71	19,544	1	27%	5,277
Lung - SCLC - Core	1,668	4,261	71	211,153	1	27%	57,011
Lymphoma - NHL - DLBCL - Enhanced	1,668	41,874	188	5,515,249	1	27%	1,489,117
Neuroblastoma - Enhanced	1,668	33,913	10	237,388	1	27%	64,095
Ovarian - Core	1,668	2,893	325	657,304	1	27%	177,472
Renal pelvis carcinoma - Basic	1,668	1,595	1	1,117	1	27%	302
Renal pelvis carcinoma - Enhanced	1,668	7,633	1	5,343	1	27%	1,443
Vulva/Vagina - Core	1,668	2,690	86	161,928	1	27%	43,721
Germ cell tumors - Enhanced	2,502	28,593	1	20,015	1	27%	5,404
Liver - Basic	2,502	3,071	294	631,956	1	27%	170,628
Liver - Core	2,502	7,065	294	1,453,893	1	27%	392,551
Liver - Enhanced	2,502	10,324	294	2,124,655	1	27%	573,657
Adrenal tumors - Enhanced	2,502	30,430	1	21,301	1	27%	5,751
Bone - Enhanced	2,502	5,640	308	1,215,925	1	27%	328,300
Brain - brain tumors - Enhanced	2,502	7,578	85	451,692	1	27%	121,957
Gestational/Placenta - Enhanced	2,502	26,875	180	3,386,188	1	27%	914,271
GIST - Basic	2,502	3,263	19	43,405	1	27%	11,719
GIST - Core	2,502	5,220	19	69,430	1	27%	18,746
GIST - Enhanced	2,502	30,430	19	404,718	1	27%	109,274
H & N - Enhanced	2,502	6,492	378	1,717,043	1	27%	463,602
Leukemia - ALL - Core	2,502	24,038	75	1,270,276	1	27%	342,974

Leukemia - ALL - Enhanced	2,502	185,658	75	9,810,902	1	27%	2,648,944
Leukemia - AML - Basic	2,502	606	63	26,610	1	27%	7,185
Leukemia - CML - Enhanced	2,502	193,788	62	8,434,205	1	27%	2,277,235
Lymphoma - NHL - T-cell - Core	2,502	2,416	21	35,359	1	27%	9,547
Lymphoma - NHL - T-cell - Enhanced	2,502	44,938	21	657,644	1	27%	177,564
Multiple myeloma - Core	2,502	5,220	86	313,107	1	27%	84,539
Neuroendocrine tumors - Basic	2,502	416	1	291	1	27%	79
Neuroendocrine tumors - Core	2,502	1,187	1	831	1	27%	224
Neuroendocrine tumors - Enhanced	2,502	4,961	1	3,473	1	27%	938
Pancreatic - Basic	2,502	416	194	56,430	1	27%	15,236
Pancreatic - Core	2,502	1,187	194	161,047	1	27%	43,483
Renal cell carcinoma - Core	2,502	2,145	118	176,875	1	27%	47,756
Skin - Non-melanoma - Enhanced	2,502	1,202	276	232,251	1	27%	62,708
Soft tissue sarcoma - Basic	2,502	3,263	240	548,268	1	27%	148,032
Soft tissue sarcoma - Core	2,502	5,220	240	877,009	1	27%	236,793
Soft tissue sarcoma - Enhanced	2,502	30,430	240	5,112,225	1	27%	1,380,301
Thymoma/thymic carcinoma - Basic	2,502	3,263	1	2,284	1	27%	617
Thymoma/thymic carcinoma - Core	2,502	5,220	1	3,654	1	27%	987
Thymoma/thymic carcinoma - Enhanced	2,502	30,430	1	21,301	1	27%	5,751
Thyroid - Enhanced	2,502	8,720	158	963,933	1	27%	260,262
Vulva/Vagina - Enhanced	2,502	2,914	86	175,434	1	27%	47,367

Source: Umuhoza/Nemzoff/Madriz et al., forthcoming and Nemzoff et al forthcoming

Scoring

Each intervention is assigned a score of 1, 2, or 3 based on the uncertainty factors. Scores which are assigned are presented below. This is reproduced from Nemzoff et al which reports the results of the cost-effectiveness analysis for cancer. To obtain the final score, the rounded average of the three scores is taken. In other words, if geographic relevance was 3, relevance of the intervention/comparator was 2 and quality was 2, the final score would be 2.

Table 27: Scoring

Measure	Measurement approach	3	2	1
Geographic relevance	Country/ income level	Rwanda or other African country	Lower-middle income country	Upper-middle income country
Relevance of intervention/ comparator	Reviewers' interpretation	Exact match	Partial match	No match
Quality	Tufts quality scoring framework	4-7	2-4	1 or unscored

Reproduced from Nemzoff et al, forthcoming

Appendix 2: Survey

Survey

Question 1: Which assessment method would you select?
150 interventions: model cost-effectiveness for everything. 12.5 years.
150 interventions: 50 review in literature; 100 model cost-effectiveness. 9 years

Question 2: Which assessment method would you select?
150 interventions: model cost-effectiveness for everything. 12.5 years.
150 interventions: 120 expert opinion; 30 'oranges' model cost-effectiveness. 3 years.

Question 3: Which assessment method would you select?
150 interventions: model cost-effectiveness for everything. 12.5 years.
150 interventions: 100 expert opinion; 50 green/orange/red review in literature. 18 months.

Question 4: Which assessment method would you select?
150 interventions: model cost-effectiveness for everything. 12.5 years.
150 interventions: 120 expert opinion; 30 'oranges' review in literature. 14 months.

Question 5: Which assessment method would you select?
150 interventions: model cost-effectiveness for everything. 12.5 years.
150 interventions: all expert review. 7 months.

Question 6: Which assessment method would you select?
150 interventions: 50 review in literature; 100 model cost-effectiveness. 9 years
150 interventions: 120 expert opinion; 30 'oranges' model cost-effectiveness. 3 years.

Question 7: Which assessment method would you select?
150 interventions: 50 review in literature; 100 model cost-effectiveness. 9 years
150 interventions: 100 expert opinion; 50 green/orange/red review in literature. 18 months.

Question 8: Which assessment method would you select?
150 interventions: 50 review in literature; 100 model cost-effectiveness. 9 years
150 interventions: 120 expert opinion; 30 'oranges' review in literature. 14 months.

Question 9: Which assessment method would you select?
150 interventions: 50 review in literature; 100 model cost-effectiveness. 9 years
150 interventions: all expert review. 7 months.

Question 10: Which assessment method would you select?
150 interventions: 120 expert opinion; 30 'oranges' model cost-effectiveness. 3 years.

150 interventions: 100 expert opinion; 50 green/orange/red review in literature. 18 months.

Question 11: Which assessment method would you select?
150 interventions: 120 expert opinion; 30 'oranges' model cost-effectiveness. 3 years.
150 interventions: 120 expert opinion; 30 'oranges' review in literature. 14 months.

Question 12: Which assessment method would you select?
150 interventions: 120 expert opinion; 30 'oranges' model cost-effectiveness. 3 years.
150 interventions: all expert review. 7 months.

Question 13: Which assessment method would you select?
150 interventions: 100 expert opinion; 50 green/orange/red review in literature. 18 months.
150 interventions: 120 expert opinion; 30 'oranges' review in literature. 14 months.

Question 14: Which assessment method would you select?
150 interventions: 100 expert opinion; 50 green/orange/red review in literature. 18 months.
150 interventions: all expert review. 7 months.

Question 15: Which assessment method would you select?
150 interventions: 120 expert opinion; 30 'oranges' review in literature. 14 months.
150 interventions: all expert review. 7 months.

Table 28: Time ranges

1	150 interventions: model cost-effectiveness for everything. 12.5 years.	3 months * 50 cancers = 150 months = 12.5 years
2	150 interventions: 50 review in literature; 100 model cost-effectiveness. 9 years	Model: 3 months * 30 cancers = 90 months = 7.5 years Review: 50*1 week = 50 weeks / 4 = 12.5 months Total = 9 years
3	150 interventions: 120 expert opinion; 30 'oranges' model cost-effectiveness. 3 years.	Model: 3 months * 10 cancers = 30 months Expert opinion: 120 * 1 day = 120 days / 20 days per month = 6 months Total = 3 years
4	150 interventions: 100 expert opinion; 50 green/orange/red review in literature. 18 months.	Review: 50*1 week = 50 weeks / 4 = 12.5 months Expert opinion: 100 * 1 day = 100 days/20 days per month = 5 months Total = 18 months
5	150 interventions: 120 expert opinion; 30 'oranges' review in literature. 14 months.	Review: 30 * 1 week = 30 weeks /4 = 7.5 months Expert opinion: 120 * 1 day = 120 days / 20 days per month = 6 months Total = 14 months
6	150 interventions: all expert review. 7 months.	Expert opinion: 150 * 1 day = 150 days/20 days per month = Total = 7 months

Appendix 3: Time, data, and capacity for cancer

Table 29: Cancer summary

	Scope	Time	Data	Capacity
Initial expectations	? cancers	3-4 months	Cost: MoH costing data available Cost-effectiveness: cancer studies available from the Tufts Registry Budget impact: cost from above + local incidence from Registry + IHME predicted incidence	2 senior health economists 8 research assistants Supported by LSHTM/ CGD
Final results	50 cancers	2 years	Cost: MoH costing data needed to be adapted for basic, core, and enhanced packages + validated with local experts Cost-effectiveness: data only available for ~30% of interventions, remainder had to be elicited from experts	Same as above, but reduced to 4 research assistants Training throughout the assessment

Acronyms: MoH = Ministry of Health; IHME = Institute for Health Metrics and Evaluation; LSHTM = London School of Hygiene and Tropical Medicine; CGD = Center for Global Development

Appendix 4: Cost-effectiveness

Table 30: Expert-elicited cost-effectiveness ratios

Category	Level of cost-effectiveness	Typical characteristics	ICER range
1	Not cost-effective	High costs & low effects	> $2502 (3x GDP pc)
2	Potentially not cost-effective	High costs & medium/high effects Medium costs & low/medium effects	$834 - $1668 (1-3x GDP pc)
3	Potentially cost-effective	Medium costs & high effects Low costs & low/medium effects	$417 - $834 (.5-1x GDP pc)
4	Very cost-effective	Low costs & high effects	< $417 (.5x GDP pc)

GDP pc = gross domestic product per capita

Reproduced from Nemzoff, et al. forthcoming