



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/195690/>

Version: Accepted Version

---

**Article:**

Thokala, P., Srivastava, T., Smith, R. et al. (2023) Living health technology assessment: issues, challenges and opportunities. *PharmacoEconomics*, 41 (3). pp. 227-237. ISSN: 1170-7690

<https://doi.org/10.1007/s40273-022-01229-4>

---

This version of the article has been accepted for publication, after peer review (when applicable) and is subject to Springer Nature's AM terms of use, but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: <http://dx.doi.org/10.1007/s40273-022-01229-4>

**Reuse**

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.

**Title:** Living Health Technology Assessment – Issues, Challenges and Opportunities

**Authors:** Praveen Thokala PhD<sup>1</sup>, Tushar Srivastava<sup>1,2</sup>, Robert Smith<sup>1,3</sup>, Shijie Ren PhD<sup>1</sup>, Melanie D. Whittington PhD<sup>4</sup>, Jamie Elvidge<sup>5</sup>, Ruth Wong<sup>1</sup>, Lesley Uttley PhD<sup>1</sup>

<sup>1</sup>School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom

<sup>2</sup>ConnectHEOR Ltd, London

<sup>3</sup>Dark Peak Analytics Ltd, Sheffield

<sup>4</sup>Institute for Clinical and Economic Review, Boston, MA, USA

<sup>5</sup>National Institute for Health and Care Excellence, Manchester, UK

### **Corresponding Author**

Praveen Thokala

School of Health and Related Research,

Regent Court, 30 Regent Street,

The University of Sheffield,

Sheffield, S1 4DA, UK

E-mail: [p.thokala@sheffield.ac.uk](mailto:p.thokala@sheffield.ac.uk)

**Data availability statement:** No datasets were generated or analysed during the current study.

**Author contributions:** PT conceived the initial idea and developed a draft outline in collaboration with the authors. All authors contributed to the writing, editing and finalising of the manuscript.

**Funding:** No funding was received for this manuscript.

**Conflicts of Interest:** Melanie Whittington is an employee of the Institute for Clinical and Economic Review (ICER), a non-profit organization that receives funding from a variety of sources, all of which are publicly reported at [icer.org](http://icer.org). Jamie Elvidge is an employee of NICE and has no financial conflicts. The views expressed in the manuscript are not necessarily shared by NICE or ICER. The rest of the authors have no conflicts of interest.

## Abstract

Health technology assessments (HTAs) are typically performed as one-off evaluations and can potentially become out-of-date due to the availability of new data, new comparators, or other factors. Recently, living approaches have been applied to systematic reviews and network-meta-analyses to enable evidence syntheses to be updated more easily. In this paper, we provide a definition for “Living HTA” where such a living approach could be applied to the entire HTA process. Living HTA could involve performing regular or scheduled updates using a traditional manual approach, or indeed in a semi-automated manner leveraging recent technological innovations that automate parts of the HTA process. The practical implementation of living HTA using both approaches (i.e. manual approach and using semi-automation) is described along with the likely issues and challenges with planning and implementing a living HTA process. The time, resources and additional considerations outlined may prohibit living HTA from becoming the norm for every evaluation; however, scenarios where living HTA would be particularly beneficial are discussed.

### Key Points for Decision Makers

- Health technology assessments (HTAs) are typically performed as one-off evaluations and can quickly become out-of-date
- Living HTA approaches can ensure that the HTAs are up to date, and potentially living HTAs could be updated manually or (semi-)automatically using innovative software platforms
- However, living HTA involves substantial time, planning and resource commitments, and as such should only be used in situations where it is important to ensure the HTA is up to date

## 1. Introduction

Health technology assessment (HTA) agencies perform evaluation of clinical and cost-effectiveness evidence of new interventions to decide whether they should be reimbursed. These are typically performed as one-off evaluations and can potentially become out-of-date due to various reasons (e.g., availability of new data, new comparators, new methods, etc.). Whilst some HTA agencies perform updates of HTAs periodically if certain criteria are met, these updates are typically a few years apart and the results of updates may be already out of date by the time of the publication.

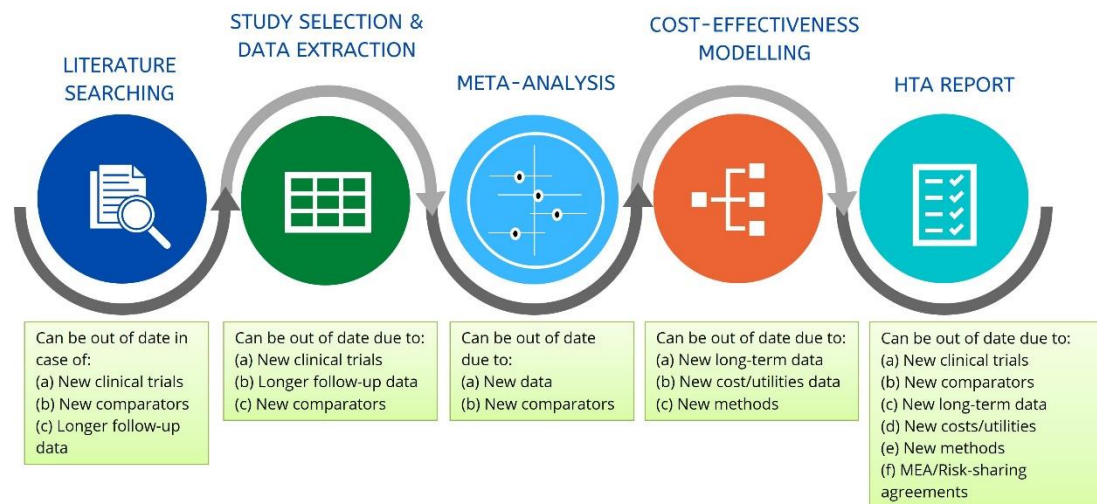
There is growing recognition of the need for the HTA process to respond to an evolving evidence base, particularly in reimbursement decisions with high uncertainty. A recent paper on “Life-cycle HTA” suggests that HTA must explore the value of health technologies from inception through maturity, and proposes a model for integrating changes arising from new evidence to feed into adoption, no adoption and disinvestment decisions [1]. However, as far as we know, there is no literature on the practicalities of performing a responsive, dynamic HTA (which we call “Living HTA”).

Whilst examples of living systematic reviews and living meta-analyses are already well established, living HTA is not yet fully defined or understood. In this paper, we outline the ways in which the different parts of HTA can go out of date, and provide a definition for living HTA and the situations in which it could be useful. While there are similarities between living HTA and the updates that HTA groups make, we outline how the living HTA process could potentially be operationalised from the outset, provide recommendations regarding when its implementation may be necessary, and describe potential triggers for an update. We also outline the practical implementation of living HTA, using a manual approach to operationalise living HTA or leveraging recent innovations to operationalise living HTA using semi-automation. Finally, issues and challenges with planning and implementing living HTA are considered.

## 2. Static HTAs and how they can become out-of-date

An illustration of how the current (static) HTA process can quickly become out of date is presented in Figure 1 and described in more detail below.

**Figure 1: Steps involved in HTA and how HTA can become out-of-date\***



\*Note that this figure presents some common reasons for the HTA process to be 'out-of-date' but it is not an exhaustive list. In addition, the latter stages could be out of date for all the reasons in the earlier stages (as the reasons for being out of date are cumulative i.e. they 'build up' from left to right).

## 2.1 Clinical effectiveness (Evidence synthesis and meta-analysis)

### 2.1.1 Current process for evidence synthesis and meta-analysis

Systematic review and meta-analysis are essential tools for synthesising evidence to inform clinical decision-making. Systematic reviews summarise available evidence based on a thorough review of the literature followed by rigorous critical appraisal to synthesise the findings on a specific topic [2; 3; 4]. Meta-analysis uses statistical techniques for combining quantitative data from several independent studies identified in the systematic review to produce a single clinical effectiveness estimate [2].

### 2.1.2 How clinical effectiveness evidence can become out-of-date

Systematic reviews frequently take between 1-3 years to complete [5] and the searches are often out-of-date at the time of publication [6; 7; 8]. Conclusions from clinical effectiveness assessments can become out of date if there is new evidence since the publication of systematic review and/or new comparators. New relevant evidence could be in the form of availability of data with longer follow-up for the previously included studies or publication of new studies after the literature searches, which occurs at the onset of the systematic review process. If the systematic review is out of date, then the pooled result from the corresponding meta-analysis would also be out of date.

## 2.2 Cost-effectiveness (Health economic modelling)

### 2.2.1 Current process for cost-effectiveness modelling

Health economic models are used to compare the costs and consequences of alternative options to estimate the cost-effectiveness of a health technology of interest [9]. The structure of these models is based on the clinical condition, and the models use synthesised evidence on natural history/disease

progression, clinical effectiveness, costs, and utilities as inputs to inform cost-effectiveness for reimbursement decisions [9]. It should be noted that long-term data and real-world evidence often do not exist when the health economic model for HTA is developed.

### 2.2.2 How cost-effectiveness evidence can become out-of-date

The model structural assumptions and the model inputs can become out of date over time, as well as the methods used to estimate the cost-effectiveness [10]. Examples of changes related to the model structure include a new technology becoming standard of care, or additional knowledge around the clinical condition that would influence either the model health states or structural assumptions. Model input changes include longer-follow up trial evidence on treatment effectiveness and safety events, or real-world evidence on discontinuation, safety or other outcomes. Additionally, methods for cost-effectiveness modelling can change over time, such as changes in the threshold, discount rate, or perspective.

## 2.3 HTA report

### 2.3.1 Current process for developing HTA reports

A HTA report is typically released around, or soon after, the time of regulatory approval of an intervention to inform the reimbursement decisions. The report includes clinical effectiveness evidence (from the evidence synthesis) and cost-effectiveness evidence (from the health economic modelling) along with a summary of key results and recommendations.

### 2.3.2 How HTA reports can become out-of-date

As discussed above, once either the clinical effectiveness evidence or health economic modelling are out of date, the conclusions of the entire HTA can be compromised. The report can be out of date if the set of potentially relevant interventions and comparators change since time of publication. For example, new interventions can enter the marketplace, and the comparator can be replaced by a new standard of care. Similarly, the report can be out of date if there is better data to inform the inputs to the cost-effectiveness model e.g., if there is long-term data to inform the survival beyond the trial period or if there is new data on the costs or utilities.

## 3. Living HTA

Most people understand 'living' research to be a process that is updated periodically [11;12;13], but there is no consensus on definition and the methods involved. Furthermore, living systematic reviews, living meta-analyses or living health economic models are sometimes erroneously referred to as living HTAs, despite not covering the full HTA process (which includes literature searching, systematic reviewing, meta-analysis, health economic modelling and HTA reporting).

We define living HTA as a full HTA that is planned from the outset to be updated at regular intervals or at specific trigger points (e.g., in light of new evidence and/or feedback from stakeholders). Table 1 provides a brief overview of key characteristics of living HTA.

**Table 1: Brief overview of key characteristics of Living HTA**

	Description
<b>Definition</b>	Full HTA that is planned from the outset to be updated at regular intervals or at specific trigger points (e.g., in light of new evidence and/or feedback from stakeholders).
<b>When is living HTA useful?</b>	As living HTA requires substantial time and resource commitments, it is posited that a living HTA is not necessary or useful in all cases. Living HTA might be most appropriate in cases of very new technologies or emerging treatment pathways, for example in the UK National Institute for Health and Care Excellence (NICE)'s "only in research" recommendations; in very populated clinical areas with many interventions (e.g., rheumatoid arthritis); or in areas where healthcare and resource allocation decisions are based on early stopping rules or interim analyses. It may also be useful in situations of medical patent expiry, where there are significant changes in clinical practice guidelines or scientific understanding, and areas of strong public interest. These scenarios are not exhaustive and there may be other situations where a living HTA approach could be useful.
<b>When/how often living HTA should be updated?</b>	The frequency of update to a potentially living HTA is likely to depend on the context of the decision problem. For example, in the case of global pandemics such as seen recently with COVID-19, this could be performed in an almost real-time manner (see the section on the 'potential for semi-automation of living HTA'). However, in most cases, updates may be performed at specific time intervals (e.g., every 12 months) or at time points when certain criteria are 'triggered' (e.g., new intervention entering the treatment pathway, major new evidence to inform the treatment pathway, regulatory updates such as a population expansion, companies exiting the market ) based on feedback from the stakeholders. In these cases, it may be advisable to schedule a check-in/assessment step to decide if an update is needed. It is important to ensure that the updates are not overly frequent, as this would be a burden to researchers and

	the stakeholders as well as being potentially confusing (for example, if treatments frequently change from being favourable and unfavourable as new living analyses emerge).
<b>Scope/scale of the update</b>	If the overall model structure stays the same, then the model can be updated with new data/parameter inputs (e.g., new clinical effectiveness data, new costs/utilities, etc.). However, in some circumstances the clinical pathway or understanding of disease may have changed sufficiently to warrant a change in model structure in which case the model may need to be adapted. Also, the model may need to include additional comparators or a different standard of care in case of new treatments. Updates should be limited to only those key areas (e.g., where new evidence has become available) and these updates should be made transparent.
<b>How long to maintain the living HTA?</b>	Living HTA does not necessarily mean that such a project should remain living indefinitely. In emerging clinical areas where few treatments exist but new treatments are expected, or where regulatory approval has been granted on early-phase trial evidence, it may be wise to structure a HTA as living from the outset so that new data, treatments and model parameters can be easily factored in for a number of years. In other situations, it may be appropriate to conclude the living HTA more quickly (e.g., after a couple of years) if it seems that there will be no substantial changes in the evidence base or new treatments in the future.

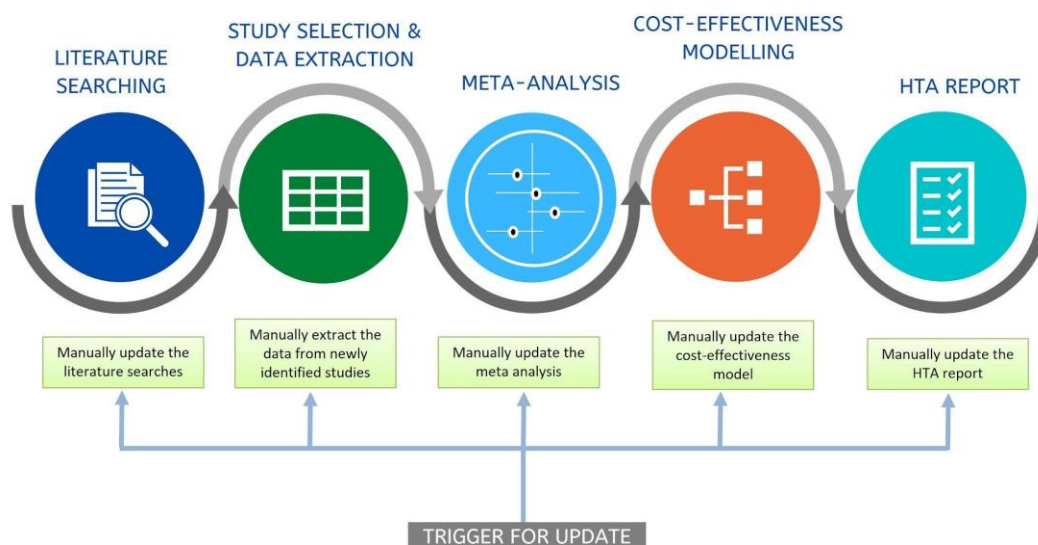
#### 4. Operationalising Living HTA

To our knowledge, there is no published example of living HTA so we present an idealised version of living HTA by combining parts of the HTA process that have been made ‘living’. We outline two approaches for the practical implementation of living HTA: a) using a manual approach to operationalise living HTA, and b) leveraging recent innovations to operationalise living HTA using (semi-)automation. In the manual living HTA, each of the HTA parts are made “living” using manual updates and the different HTA parts are also combined manually. In the (semi-)automated living HTA, each of the HTA parts are automatically updated and they can be combined using automation (i.e., fully automated living HTA) or manually (i.e., semi-automated living HTA).

## 4.1 Manual Living HTA

To operationalise manual living HTA, we suggest combining “manually” the different parts of the HTA process that have been made ‘living’. We present examples of living systematic reviews and meta-analysis [14], and living health economic models that are updated manually [15]. Then, we present the need for standard templates to transfer the data between the different steps to ensure the smooth running of the “manual living HTA”. Figure 2 presents a brief overview of manual living HTA.

**Figure 2: Manual Living HTA**



### 4.1.1 Living Systematic Reviews

There are now several examples of ongoing living systematic reviews in which the literature searches are updated periodically and new evidence incorporated accordingly [16; 17]. Updating electronic searches can involve the use of manual searching and/or auto alerts [18; 19]. Performing updates to grey literature searches such as registries and websites are likely to be challenging and time-consuming compared to electronic searches. In some cases, it may be necessary to revise the original search by looking at the yield of potentially relevant records and the appropriateness of the sources searched. Once all the citations are collated, they are screened manually by reviewers to select the relevant studies for data extraction and quality assessment.

### 4.1.2 Living Meta-analysis

The living meta-analysis presents a pooled result of the most recent available evidence, repeating the same statistical method/model after adding the newly identified studies. Simmonds et al [20] summarises the methods that could be used to avoid type I error inflation, but cautions some issues relating to the use of these adjustment methods remain uncertain and further research is required.

#### 4.1.3 Living Health Economic Models

There has been substantial conversation about model transparency and open source modelling in the field of health economics [15; 21], but progress has been lacking as to how an economic model can be made “living”. A living health economic model is one that is updated over time as new evidence emerges. Early living health economic models have varied from fully open source models to models which are not made publicly accessible but updated solely by the model developer and from which only the final updated outputs are presented.

#### 4.1.4 Operationalising manual living HTA

It is important to note that in manual living HTA, all the different steps and the combination of the steps are all performed physically by researchers. To operationalise living HTA, it would be helpful to develop and share standard templates for data extraction, meta-analysis outputs, model inputs and model results. In particular, an economic model that has a standard template (and process) for entering model inputs/settings, and to output the results would be useful [22]. The HTA report then needs to be updated with the latest clinical and cost-effectiveness evidence results, as well as an updated executive summary and discussion/conclusions based on the new findings.

### 4.2 Potential for (semi-)automation of living HTA

Recently, there have been technological innovations to (semi-)automate parts of the HTA process which indicate potential to achieve real-time living HTA by building on and combining these technologies. It should be noted that these tools have not been formally evaluated, or currently accepted, by HTA agencies.

Figure 3 presents an example for potentially operationalising a living HTA using (semi-)automation. There are many tools available for automating elements of HTA, however, we present examples of open-source technologies to automate literature searching (e.g., RobotSearch), systematic reviews (e.g., RobotReviewer), meta-analyses, and health economic modelling (e.g. using R software). Then, we present the need for secure web-based user-interfaces (e.g., R-Shiny [23]) to transfer the data between the different steps to ensure the smooth automatic updating to achieve real-time living HTA. It may not be feasible to automate completely as it is important to have manual input from HTA researchers to sense check the updates and to ensure that the outputs of each stage are appropriate.

#### 4.2.1 Automated Literature Searching

Custom tools can be used to mechanise parts of the literature searching process such as sifting. For example, RobotSearch [24] is an open source machine-learning tool that identifies randomized controlled articles (RCTs) from PubMed search results. To identify the RCT studies without the requirement of manual screening, RobotSearch uses a high recall and validated machine learning classifier which is capable of ordering retrieved papers by study sample size and quality (i.e. risk of

bias). Similar tools offer efficiency in the searching and study selection stages, where algorithms built in programmes such as Python can narrow down potentially relevant articles in fields where many thousands of articles are published (e.g., HIV [25]).

#### 4.2.2 Automated Systematic Reviews

Custom tools can also be used to mechanise parts of the systematic review process to produce semi-automated systematic reviews. Collaborative initiatives have developed open source software to support researchers in evidence synthesis by using machine learning for data extraction (such as RobotReviewer [26]). This is a rapidly developing field that could potentially reduce the time and resource burden that living systematic reviews inevitably require to sustain on a long-term basis.

#### 4.2.3 Automated Processes for Combined Literature Searching and Systematic Review

Trialstreamer [27] combines both trial identification (using RobotSearch [24]) and data extraction (using RobotReviewer [26]) to maintain a new and publicly available living database of all healthcare RCTs in humans from PubMed and WHO International Clinical Trials Registry Platform. The tool utilises population, intervention, control and outcomes (PICO) search strategies for identifying and classifying RCTs, as well as extracting and summarising the key information from the RCTs retrieved.

#### 4.2.4 Automated Meta-analysis

Software environments such as R could be used to facilitate the automation of the meta-analysis process. Given the updated input data is arranged in a consistent way which allows an R script to load the data and perform the required analysis, the same R script could be employed to analyse the updated data. For example, the COVID-NMA initiative [28] launched in March 2020, is a living systematic review of COVID-19 trials where the review is updated weekly and the meta-analysis is updated every two weeks using the “metaCovid” [29], which is freely available as an R-shiny application allowing users to explore the data and conduct the analysis tailored to their needs.

Automating complex evidence syntheses such as network meta-analysis (NMA) and population-adjusted indirect treatment comparisons require more careful consideration than a pairwise meta-analysis. For NMA, the application should allow users to add/remove interventions, perform inconsistency checking, and conduct subgroup analysis/meta-regression to explain heterogeneity. In the case of population-adjusted indirect comparisons, it should allow for the flexibility of choosing specific baseline covariates to match.

#### 4.2.5 Automated Health Economic Models

Automatic model updates can be scheduled to run at a set time or when triggered by an event using script based programming languages (such as R or Python) or web-based interfaces [30], where the model will run using parameter inputs and data located in the paths provided. These web-enabled

platforms are separate to the health economic models (e.g., Excel files or R code) which could help address potential intellectual property concerns. There have been many examples of health economic models with web-based user-interfaces where the users can amend model inputs and view the subsequent impact on the model findings and conclusions in real-time. Examples of these include models hosted online using the R Shiny platform interfaces [30; 31] and the ICER interactive modeller platform hosting dozens of models [32].

Automated updates are most likely to be undertaken for input parameters only as it is relatively simple to automate to reflect changes in input parameter values (e.g. a new cut of trial data). However, it is much harder to automate changes in structural assumptions since this typically requires adaptation of the model source code.

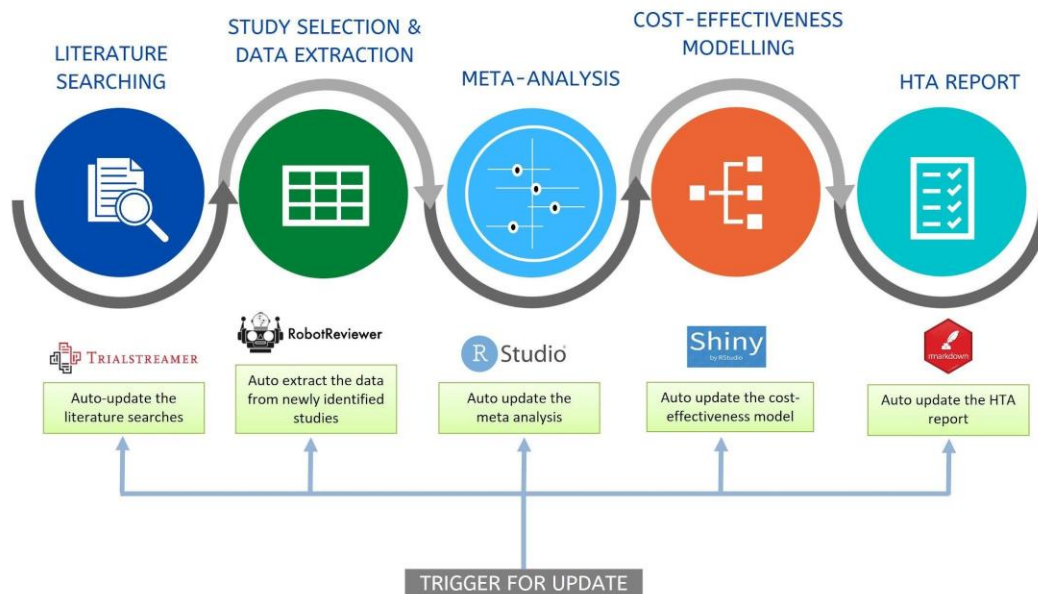
#### 4.2.6 Automated HTA reporting

Packages such as – R Documentation and RMarkdown [33] (under R framework) could be utilised for automating the HTA documentation. These packages allow the results (i.e. text, figures, and tables) for systematic review, meta-analysis and health economic modelling to be automatically updated in the report when the data underlying the analysis is updated. In addition, RMarkdown consolidates code and documents into a single file (negating the need for copy-pasting results from one place to another), allowing for automated, transparent and completely reproducible archives of work. RMarkdown documents can be ‘parsed’ to produce reports in a variety of different formats, including, HTML, PDF, MS Word, Open document type etc. Recently developed R package ‘bookdown’ further enhances the reporting and allows for the development of long reports/books with features such as cross-referencing to different sections, tables, and figures [34].

#### 4.2.7 Operationalising (semi-) automated living HTA

Automated HTA can loosely be defined as a system by which HTA updates are scheduled to run automatically at a set time or when triggered by an event. Script based programming languages (such as R or Python) could be used to link the different steps in the HTA process and scheduled as any other program (e.g. an update to your computer). This would be relatively straightforward to set up, but has not yet been implemented on a live HTA project. It is important to note that semi-automation raises issues such as ethical considerations and potential for errors in automated processes [35]. Furthermore, none of the HTA agencies currently accept automated processes (e.g. automated systematic reviews) in HTA submissions.

### **Figure 3: Potential example living HTA using (semi-)automation**



## 5. Issues and Challenges

We have outlined two different approaches for living HTA: a) manual living HTA, and b) living HTA using (semi-)automation, each of which has specific issues and challenges compared to the traditional one-off static HTAs performed currently. Table 2 presents a brief comparison of the static HTA approach, manual living HTA approach and (semi-)automated living HTA approach. The pragmatic limitations and implications of implementation are discussed below.

**Table 2: Comparison of static HTA, manual living HTA and (semi-)automated living HTA**

	Static HTA process	Manual living HTA	(Semi-)automated living HTA
Incorporates updates	No	Yes	Yes
Update frequency	None	At specific points	Potentially real-time
How updates are performed	N/A	Requires researcher time	Requires researcher time and software
Is the HTA up-to-date	Unlikely	Yes (until next update)	Potentially always

Ongoing stakeholder input	No	Yes	Yes
Researcher skills required	HTA	HTA	HTA and advanced software skills
Additional software/infrastructure	No	No	Yes, to set up the automation process
Additional set up costs/considerations	No	Moderate (to develop standard templates for regular updates)	High (to set up standard templates for data transfer and the software infrastructure)
Requirements for researcher time	Standard	High (to perform the updates)	Moderate (initial set up time is offset by efficiency gained by automation)
Extra funding required	No	Yes, for researcher time for the updates	Yes, for researcher time, software and IT expertise required for the updates
Version control for HTA report	N/A	Yes, updated at specific time points and each version stored in archive	Yes, updated in real-time and older versions can be extracted using software if needed
Aligned with current HTA procedure	Yes	Yes	No, automated software are not currently accepted by HTA agencies

### 5.1 Standardisation/interoperability

For living HTA to be successfully realised, it is crucial that the analysts involved have a common understanding of how the various components of a dataset connect to one another and to the components of other datasets. For example, modellers should build models which can be run using an

agreed meta-analysis output structure, and statisticians should ensure that their meta-analysis outputs remain consistent to this agreed structure. If the output nomenclature of meta-analysis is standardised, the analysts can easily input the data manually into the health economic model (for manual living HTA) or the model can directly read the results from meta-analysis using software (for semi-automated living HTA). Standardisation of inputs and outputs across sub-disciplines, also known as data interoperability, has a huge potential for living HTA.

## 5.2 Responsibility, ownership and publication

Management of an ongoing update process, such as in living HTA, is likely to involve continued ownership of the research topic. It is likely that each living HTA would require a designated webpage or website, however, most institutions do not currently have web templates to support the research software to underpin semi-automated living HTAs. If a designated webpage/website for the living HTA is maintained, previous versions of the living HTA should be archived as supplementary appendices. Also, some academic publishers have already embraced the living systematic review model and it is possible that this could be extended to living HTAs.

## 5.3 Resource/time commitments and Skills

The resource commitments for 'Living HTA' are likely to be considerably larger than the status-quo, especially in instances where updates cannot be semi-automated. In instances where updates can be semi-automated, high initial sunk costs in establishing a code-base for the living HTA framework could be recouped by lower ongoing costs. However, semi-automated living HTA is likely to require considerable upskilling (e.g., to build and review script based models that would be utilised in a semi-automated framework).

Whether decision makers and other stakeholders are willing to pay the additional cost to receive living HTA is uncertain. Most academic researchers are funded by fixed-term contracts and therefore living HTA cannot exceed the period for which designated researchers are salaried to work on it. However, living HTA does not have to mean that these research projects live "forever", they can be live for a finite number of years during a period of uncertainty in the evidence or until such a time that a stable conclusion to the decision problem can be reached.

The individuals responsible for the update may not have to be HTA agencies in all instances. Academic groups or consultancies could lead these efforts, or share the responsibility and effort with HTA groups. Additionally, national HTA agencies could work collaboratively to share resources and minimise duplication of similar updates being undertaken in different settings.

#### 5.4 Confidential pricing data

HTAs often involve commercially or clinically sensitive data such as patient access schemes or clinical study reports. Traditionally these are redacted in static documents which are made publicly available but the possibility of more frequent updates in a living HTA approach could lead to more frequent changes (e.g., commercial discounts for technologies and their comparators), cascading to make each reassessment more complex and less transparent than the last. A potential solution to this issue is that HTA agencies require consistent, 'clean' results to be provided during each reassessment, using all technologies' public list prices as at the time of the first assessment. Such analyses would not be suitable for decision making as the prices would not reflect the true cost to the healthcare system at the time of reassessment, however, they would ensure the magnitude of effect is made transparent, and not lost in the noise caused by any simultaneous price changes.

#### 5.5 Data security, copyright and intellectual property

The copyright or intellectual property of the work is more complex in a living HTA. Separate from cost inputs, some clinical, epidemiological, and quality of life inputs may be provided as confidential at the time of the initial assessment which can limit the transparency potentially needed to conduct the reassessment and the ability for automation. In addition, there may be issues with data management policies, especially for automated living HTA (which requires storing data in the cloud). Thus, consideration of data security, copyright and intellectual property issues need to be discussed at the outset by all stakeholders to ensure that they are aligned with all the institutional requirements.

#### 5.6 Stakeholder involvement

Agencies need to consider the extent of stakeholder involvement in their living HTA updates. Decision making panels, such as NICE's independent appraisal committees, need to be involved in the update of their previous decisions in light of new evidence, and therefore require some level of 'sign off' for any new recommendations. Clinicians and patients may be able to provide important insights into current practice since the previous HTA. Manufacturers of the technology of interest and its comparators will also likely seek to engage in any living HTA reassessment. Depending on the scale of update (e.g., using the same model structure that was accepted previously and amending only a small number of inputs that have changed in a meaningful way since the last assessment, or a "full" HTA update with entirely new clinical and economic evidence), the level and type of stakeholder involvement can be decided. Living HTA will require conversations with stakeholders to help determine the need for an update, the intervals of the update, the triggers for an update, the type of update and the level of stakeholder engagement that may be needed with each update.

### 5.7 Impact on policy/decision making

In the current static HTA approach, the agencies provide evidence-based recommendations about health technologies near the time of regulatory approval. Recently, there has been a push towards a “life-cycle” approach to HTA, where the recommendations are updated regularly in light of new evidence [1, 36, 37, 38, 39]. Living HTA can help the decision makers in this regard with a frequently updated, living approach to HTA. However, HTA recommendations that change frequently may be difficult for the healthcare system as, at a practical level, it takes time to procure and supply medical technologies that are newly considered to be cost effective, and to use up existing supply of technologies that are no longer deemed cost effective. It may also be confusing for clinicians and patients if recommended treatments change often, and HTA processes are less impactful if payers cannot act upon them and other stakeholders lose trust in them. Further, a living HTA approach necessitates a commitment to disinvest in technologies that are no longer cost effective and remove them from clinical practice. To understand the potential policy impact of living HTA, the readers are referred to a paper outlining “Life cycle HTA” which suggests a framework for constant HTA process to feed into reassessment, adoption, and no adoption decisions [1].

## 6. Conclusions and considerations for implementation

Living HTA can be defined broadly as one that is planned from the outset to be updated at regular intervals or at specific trigger points based on feedback from the stakeholders. The methods for practical implementation of living HTA and the responsibility for ownership and updating require careful consideration, as living HTA approaches are likely to involve substantial time and resource commitments. .

Those interested in piloting a living HTA, such as HTA agencies and healthcare decision makers, should ensure that the decision problem requires a living approach to justify the time and resources required. They should consider what update frequency is required and feasible, or whether the updates should be performed at specific trigger points, and ensure that the stakeholder meetings and reimbursement decision-making timelines align with the living HTA updates. The decision between a manual or semi-automated approach to living HTA should be made by the research team in consultation with stakeholders, and ongoing researcher time needs to be factored across the lifespan to ensure that the HTA can be updated appropriately at the chosen time points. Input from skilled HTA analysts is needed to ensure the rigour of updates and, in addition, semi-automated approaches require advanced software knowledge. Ownership and copyright of the final outputs should be considered in advance, and data management infrastructure (e.g. software or cloud-based services) may be necessary if the living HTA is hosted on a dedicated website.

These additional considerations mean that extra funding will almost certainly be required and thus, living HTA should be considered at the time of research commissioning. Living HTA should only be used when there is clear need (e.g., in high-priority therapeutic areas), and HTA decision makers should consider close collaboration and shared learning on living HTA, to minimise duplication of efforts.

## **References**

- [1] Kirwin, E, Round, J, Bond, K, McCabe, C. "A conceptual framework for life-cycle health technology assessment". *Value in Health* 2022. <https://doi.org/10.1016/j.jval.2021.11.1373>
- [2] Gopalakrishnan, S, Ganeshkumar, P. "Systematic reviews and meta-analysis: understanding the best evidence in primary healthcare". *Journal of family medicine and primary care* 2013; 2(1):9. <https://doi.org/10.4103/2249-4863.109934>
- [3] Moher, D, Liberati, A, Tetzlaff, J, Altman, D, PRISMA Group\*. "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement". *Annals of internal medicine* 2009; 151(4):264–269. <https://doi.org/10.1371/journal.pmed.1000097>
- [4] Page, M, McKenzie, J, Bossuyt, P, Boutron, I, Hoffmann, T, Mulrow, C, Shamseer, L, Tetzlaff, J, Akl, E, Brennan, S, others. "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews". *Systematic reviews* 2021; 10(1):1–11. <https://doi.org/10.1186/s13643-021-01626-4>
- [5] Andersen, M, Gulen, S, Fønnes, S, Andresen, K, Rosenberg, J. "Half of Cochrane reviews were published more than 2 years after the protocol". *Journal of Clinical Epidemiology* 2020; 124:85–93. <https://doi.org/10.1016/j.jclinepi.2020.05.011>
- [6] Runjic, E, Behmen, D, Pieper, D, Mathes, T, Tricco, A, Moher, D, Puljak, L. "Following Cochrane review protocols to completion 10 years later: a retrospective cohort study and author survey". *Journal of clinical epidemiology* 2019; 111:41–48. <https://doi.org/10.1016/j.jclinepi.2019.03.006>
- [7] Shojania, K, Sampson, M, Ansari, M, Ji, J, Garritty, C, Rader, T, Moher, D. "Updating systematic reviews". *Agency for Healthcare Research and Quality* 2010. <https://doi.org/10.1371/journal.pone.0009914>
- [8] Borah, R, Brown, A, Capers, P, Kaiser, K. "Analysis of the time and workers needed to conduct systematic reviews of medical interventions using data from the PROSPERO registry". *BMJ open* 2017; 7(2):e012545. <https://doi.org/10.1136/bmjopen-2016-012545>
- [9] Petrou, S, Gray, A. "Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting". *Bmj* 2011; 342. <https://doi.org/10.1136/bmj.d1766>
- [10] Shields, G, Pennington, B, Bullement, A, Wright, S, Elvidge, J. "Out of Date or Best Before? A Commentary on the Relevance of Economic Evaluations Over Time". *PharmacoEconomics* 2022; 40(3):249–256. <https://doi.org/10.1007/s40273-021-01116-4>
- [11] CADTH. CADTH Strategic Plan 2022 [Internet]. [strategicplan.cadth.ca](https://strategicplan.cadth.ca). 2022 [cited 3 August 2022]. Available from: [https://strategicplan.cadth.ca/wp-content/uploads/2022/03/cadth\\_2022\\_2025\\_strategic\\_plan.pdf](https://strategicplan.cadth.ca/wp-content/uploads/2022/03/cadth_2022_2025_strategic_plan.pdf)
- [12] Elvidge J, Dawoud D. Assessing Technologies for COVID-19: What are the Challenges for Health Technology Assessment Agencies? Findings From a Survey and Roundtable Workshop. *PharmacoEconomics*. 2021 Dec;39(12):1455-63.

[13] Golob MM, Livingstone-Banks J. 131 Toward a living model for health technology assessments. *BMJ Evidence-Based Medicine*. 2022 Jul 1;27(Suppl 2):A9-10.

[14] Elliott, J, Synnot, A, Turner, T, Simmonds, M, Akl, E, McDonald, S, Salanti, G, Meerpohl, J, MacLehose, H, Hilton, J, others. "Living systematic review: 1. Introduction—the why, what, when, and how". *Journal of clinical epidemiology* 2017; 91:23–30.  
<https://doi.org/10.1016/j.jclinepi.2017.08.010>

[15] Jansen, J, Incerti, D, Linthicum, M. "Developing open-source models for the US health system: practical experiences and challenges to date with the open-source value project". *Pharmacoeconomics* 2019; 37(11):1313–1320. <https://doi.org/10.1007/s40273-019-00827-z>

[16] Michelen, M, Manoharan, L, Elkheir, N, Cheng, V, Dagens, A, Hastie, C, O'Hara, M, Suett, J, Dahmash, D, Bugaeva, P, others. "Characterising long COVID: a living systematic review". *BMJ Global Health* 2021; 6(9):e005427. <https://doi.org/10.1136/bmjgh-2021-005427>

[17] Owen, R, Bradbury, N, Xin, Y, Cooper, N, Sutton, A. "Metalnsight: an interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta". *Research synthesis methods* 2019; 10(4):569–581. <https://doi.org/10.1002/jrsm.1373>

[18] Dressler, C, Lambert, J, Grine, L, Galdas, P, Paul, C, Zidane, M, Nast, A. "Therapeutic patient education and self-management support for patients with psoriasis—a systematic review". *JDDG: Journal der Deutschen Dermatologischen Gesellschaft* 2019; 17(7):685–695.  
<https://doi.org/10.1111/ddg.13840>

[19] Drucker, A, Morra, D, Prieto-Merino, D, Ellis, A, Yiu, Z, Rochweg, B, Di Giorgio, S, Arents, B, Burton, T, Spuls, P, others. "Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis". *JAMA dermatology* 2022.  
<https://doi.org/10.1001/jamadermatol.2022.0455>

[20] Simmonds, M, Salanti, G, McKenzie, J, Elliott, J, Agoritsas, T, Hilton, J, Perron, C, Akl, E, Hodder, R, Pestridge, C, others. "Living systematic reviews: 3. Statistical methods for updating meta-analyses". *Journal of clinical epidemiology* 2017; 91:38–46.  
<https://doi.org/10.1016/j.jclinepi.2017.08.008>

[21] Carlson, J, Walton, S, Basu, A, Chapman, R, Campbell, J, McQueen, R, Pearson, S, Touchette, D, Veenstra, D, Whittington, M, others. "Achieving appropriate model transparency: challenges and potential solutions for making value-based decisions in the United States". *Pharmacoeconomics* 2019; 37(11):1321–1327. <https://doi.org/10.1007/s40273-019-00832-2>

[22] Whittington M, Topachevskiy O, Volovyk A. MSR9 Moving from Static to Dynamic Economic Assessments: The Process of Migrating Economic Models to a Web Environment. *Value in Health*. 2022 Jul 1;25(7):S519.

[23] Smith, R, Schneider, P. "Making health economic models Shiny: A tutorial". *Wellcome Open Research* 2020; 5. <https://doi.org/10.12688/wellcomeopenres.15807.2>

- [24] Marshall, I, Noel-Storr, A, Kuiper, J, Thomas, J, Wallace, B. "Machine learning for identifying randomized controlled trials: an evaluation and practitioner's guide". *Research synthesis methods* 2018; 9(4):602–614. <https://doi.org/10.1002/jrsm.1287>
- [25] Thiabaud, A, Triulzi, I, Orel, E, Tal, K, Keiser, O, others. "Social, behavioral, and cultural factors of HIV in Malawi: semi-automated systematic review". *Journal of medical internet research* 2020; 22(8):e18747. <https://doi.org/10.2196/18747>
- [26] Iain J. Marshall, Joël Kuiper and Byron C. Wallace. RobotReviewer: Evaluation of a System for Automatically Assessing Bias in Clinical Trials. *Journal of the American Medical Informatics Association (JAMIA)*, 23 (1): 193-201. 2016
- [27] Marshall IJ, Nye B, Kuiper J, Noel-Storr A, Marshall R, Maclean R, Soboczenski F, Nenkova A, Thomas J, Wallace BC. Trialstreamer: A living, automatically updated database of clinical trial reports. *Journal of the American Medical Informatics Association*. 2020 Dec;27(12):1903-12. Link to Trialstreamer: <https://trialstreamer.ieai.robotreviewer.net>
- [28] Boutron I, Chaimani A, Devane D, Meerpohl JJ, Rada G, Hróbjartsson A, Tovey D, Grasselli G, Ravaut P. Interventions for the prevention and treatment of COVID-19: a living mapping of research and living network meta-analysis. *Cochrane Database of Systematic Reviews*. 2020(11).
- [ 29] Evrenoglou, T, Boutron, I, Chaimani, A. "metaCOVID: An R-Shiny application for living meta-analyses of COVID-19 trials". *medRxiv* 2021. <https://doi.org/10.1101/2021.09.07.21263207>
- [ 30] Smith, R, Schneider, P, Mohammed, W. "Living HTA: Automating Health Technology Assessment with R ". *Wellcome Open Research* 2022; 7. <https://doi.org/10.12688/wellcomeopenres.17933.2>
- [ 31] Incerti, D, Thom, H, Baio, G, Jansen, J. "R you still using excel? The advantages of modern software tools for health technology assessment". *Value in Health* 2019; 22(5):575–579. <https://doi.org/10.1016/j.jval.2019.01.003>
- [32] ICER Interactive Modeler™. <https://analytics.icer.org/docs/ICER.Analytics.Overview.pdf>
- [ 33] Xie Y, Allaire JJ, Grolemond G. *R markdown: The definitive guide*. Chapman and Hall/CRC; 2018 Jul 27. <https://doi.org/10.1201/9781138359444>
- [ 34] Xie Y. *Bookdown: Authoring books and technical documents with R markdown*. Chapman and Hall/CRC; 2016 Dec 12. <https://doi.org/10.1201/9781315204963>
- [35] Sutton, S.G., Arnold, V. and Holt, M., 2018. How much automation is too much? Keeping the human relevant in knowledge work. *Journal of emerging technologies in accounting*, 15(2), pp.15-25.
- [36] Canadian Agency for Drugs and Technologies in Health. Convalescent Plasma Therapy for the Treatment of COVID-19: A Review of Clinical Effectiveness [Internet]. CADTH Covid-19 Evidence Portal. 2021 [cited 2022 Sep 14]. Available from: <https://covid.cadth.ca/treatment/convalescent-plasma-therapy-for-the-treatment-of-covid-19-a-review-of-clinical-effectiveness-2/>

[37] Canadian Agency for Drugs and Technologies in Health. Stereotactic Ablative Radiotherapy for the Treatment of Oligometastatic Cancer | CADTH [Internet]. www.cadth.ca. [cited 2022 Sep 14]. Available from: <https://www.cadth.ca/stereotactic-ablative-radiotherapy-treatment-oligometastatic-cancer>

[38] Innovate or Continuously Be Outdated: The Need for a 'Living' Approach to HTAs: Panel Session, ISPOR Vienna Nov 2022. <https://www.ispor.org/docs/default-source/euro2022/eu-ispor-issue-panelliving-htafinal.pdf>

[39] The Living Guidelines Handbook: Guidance for the production and publication of living clinical practice guidelines [Internet]. 1.0. Australian Living Evidence Consortium; 2022. Available from: <https://livingevidence.org.au/>