

# Improving efficiency in HTA: The role of open source models and more advanced software choice

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## Agenda

- **R. Brett McQueen**

- Overview of HTA goals in the context of openness

- **Raquel Aguiar-Ibáñez**

- Openness and use of efficient software to increase automation from an industry perspective

- **Dawn Lee**

- Model development in more advanced software such as R-Shiny

- **Gianluca Baio**

- Barriers to adoption and potential solutions

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# Why are we here today?

- ▶ Uptake of HTA findings has increased with rising global healthcare costs and the costs of innovation
- ▶ With more uptake comes requests for greater transparency and sharing
  - However, openness produces concerns about intellectual property and scholarly credit
- ▶ At same time, shifting regulatory and HTA timelines require more complex analyses in shorter timeframes, stretching the limits of Excel to breaking point

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## *Live Content Slide*

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**Poll: What software are you currently using for your economic model builds?**

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### *Live Content Slide*

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**Poll: Of those still using Excel, why are you still using Excel?**

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## Definition of model transparency and openness

- ▶ Documentation on a model's structure, equations, parameter values, and assumptions<sup>\*</sup>
  - Non-technical description of the model for non-modelers interested in the topic
  - Technical information including code in R, Excel, etc. for modelers who may want to replicate the model and findings

<sup>\*</sup>Eddy et al. Model Transparency and Validation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force – 7. Medical Decision Making/Sep-OCT 2012

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# Perspective matters

- ▶ Open source modeling depends on entities, incentives, and implications of model findings
  - Universities and commercial entities may not allow sharing of models due to intellectual property concerns/risk
  - *Health technology assessment models may require more transparency given impact of findings on resource allocation decisions*

## Statement of ICER's Commitment to Economic Model Transparency

### INTRODUCTION

The Institute for Clinical and Economic Review (ICER) is committed to open and transparent engagement with all stakeholders that have an interest in each of its evidence reviews. This commitment to transparency extends to the development and/or modification of economic models. Such transparency helps to increase the public's confidence in model results. Without detailed descriptions of model structure and processes as well as estimates used, economic models run the risk of being considered "black boxes," with no way to evaluate the validity of model processes or accuracy of model inputs. Explicit delineation of model structure and flow gives stakeholders the ability to evaluate the model's face validity. Details on the point estimates and ranges used in sensitivity analyses allow for the explicit testing of alternative assumptions and model inputs, provide insight into the drivers of specific results, and allow other interested parties to replicate or extend analyses conducted by ICER and its collaborators.

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# Recent U.S. transparency efforts

- ▶ Confidential model access through the Institute for Clinical and Economic Review (ICER)\*
  - ICER collaborators build models and with submission to manufacturers for review whereas other global HTA bodies review manufacturer submitted models
    - Built by multiple collaborators in Excel, R, and hero3
- ▶ Open-source initiatives in the U.S.
  - Innovation and Value Initiative (IVI) develops open source models in R<sup>†</sup>
  - Global Health CEA registry by Tufts Medical Center compiles cost-per-DALY-averted studies and asks modelers to share<sup>‡</sup>

\*Institute for Clinical and Economic Review Announces New Program to Make Available Draft Executable Economic Models During Drug Assessment Review Process. Accessed at: <https://icer-review.org/announcements/model-transparency-program/>

<sup>†</sup><https://www.thevalueinitiative.org/open-source-value-project/>

<sup>‡</sup><https://cevr.tuftsmedicalcenter.org/databases/gh-cea-registry>

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# Colorado Team Collaborations with ICER

## ◆ 3 Faculty

- Jon Campbell
- Brett McQueen
- Mel Whittington

## ◆ Cost-effectiveness evidence for:

- asthma biologics (2 reviews)
- rheumatoid arthritis targeted immune modulators;
- ovarian cancer PARP inhibitors
- B-cell malignancy chimeric antigen receptor t-cell (CAR-T) therapies
- **Endometriosis (elagolix)**
- **Secondary prevention of cardiovascular disease**

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# Colorado model transparency efforts with ICER

## ◆ Endometriosis (elagolix)

- Offer to view and validate model, including in-person presentation of model structure and assumptions (\$10,000 charge with licensing agreement through University) was rejected by manufacturer

## ◆ Secondary prevention of cardiovascular disease (Icosapent Ethyl and Rivaroxaban)

- Offer to view and validate model with no question and answer session was accepted by both manufacturers (\$0 charge with licensing agreement through University)
- No direct comments on the model but overall was welcomed by manufacturers
- One manufacturer expressed concerns about technical ability outside of Excel

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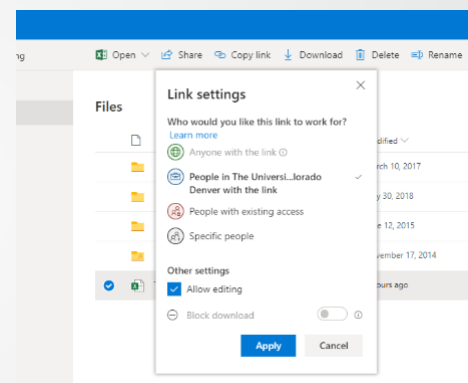
# Licensing details

- Main legal points of licensing agreement
  - Cannot install the model on more than 2 devices; no more than 2 employees may access or utilize the model*
  - No modifications or “derivatives” of model can be created*
  - Do not reverse assemble all or any portion of the model*
  - University not obligated to provide technical support*
- License can be used to create broader “open source” license with restrictions on commercial use of the model

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# How did we share the model?

- Shared model through Microsoft OneDrive
- Options for editing both within Excel and specific to OneDrive
- Tracks who has downloaded the software and allows model builder to delete/remove model after specified date
- Flexible to include other modeling software including R files
- Provides a bridge to fully capable cloud environment



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# Key Considerations for sharing and open source agreements

- ▶ Set-up infrastructure for model sharing
- ▶ Create a model license that is flexible\*:
  - Allow or deny commercial use of the model
  - Allow or deny outside users to update the model for new applications
- ▶ Copyright definitions differ between countries
  - In U.S. raw facts not copyrightable, only “selection and arrangement”
  - In Europe raw facts are copyrightable
- ▶ Develop detailed “user guide” to reduce question and answer

\*<https://creativecommons.org/licenses/>

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## Future Directions

- ▶ ICER plans cloud-based tool that allows interactive models in addition to transparency and validation step
- ▶ Provides accessibility (i.e., user-friendly aspect) in addition to transparency and validation

### ICER Plans Cloud-Based Tools to Accelerate the Use Assessments in the US Health System

*–With a late 2019 launch target, ICER’s Evidence Compendium and Interactive Modeler will enable decision-makers within payers, pharmaceutical companies, and other stakeholders to easily integrate ICER-generated analyses and curated content into their formulary, benefit design, and pricing strategy–*

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# IMPROVING EFFICIENCY IN HTAS: THE ROLE OF OPEN SOURCE MODELS AND MORE ADVANCED SOFTWARE CHOICE

Openness and Use of Efficient Software to Increase Automation

Pharmaceutical Industry Perspective



Raquel Aguiar-Ibáñez, Principal Scientist – Oncology

Center for Observation and Real World Evidence (CORE),  
Economic and Data Sciences (EDS), MSD

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## Openness in HTAs

- HTA-related economic models shared with agencies
  - Secure platform, confidential
- Agencies request further clarification and analyses
- Redacted models available to relevant stakeholders (NICE)
  - Temporary, confidential, only for review

- ✓ Transparency
- ✓ Credibility

## Open-source models - Challenges

- Intellectual property & scholarly credit
- Scope
- Involvement & responsibilities

Dunlop et al. *Pharmacoeconomics* 2017; 35:125-128; Incerti et al. *Pharmacoeconomics* 2019; 37:829-843; Jansen et al. *Pharmacoeconomics* 2019; Aug 7. doi: 10.1007/s40273-019-00827-z

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## Software Requirements for Models in HTAs

Country	Agency	Excel	Data	R	WinBUGS	TreeAge	Arena
Australia <sup>a</sup>	PBAC	✓				✓	
Canada <sup>a</sup>	CADTH	✓				✓	✓
Lithuania	VASPV	✓ <sup>b</sup>					
New Zealand <sup>a</sup>	PHARMAC	✓				✓	
Poland <sup>a</sup>	AOTMiT	✓				✓	
UK-England <sup>a</sup>	NICE STAs	✓	✓	✓	✓		
UK-England <sup>a</sup>	NICE HSTs	✓		✓	✓	✓	
UK-Scotland	SMC	✓					

<sup>a</sup>Other softwares may be allowed but need to be agreed on in advance.

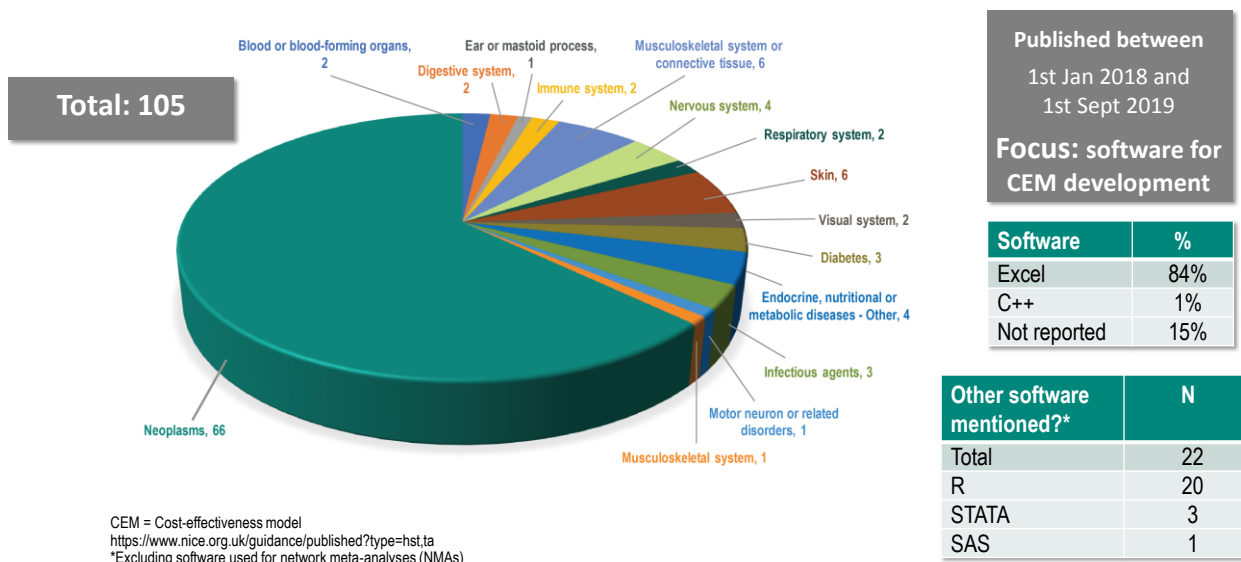
<sup>b</sup>Specified as part of legislation.

Other HTA agencies do not have specific, published requirements. In some cases, implicit understanding that Excel is the software of preference

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## Case Study: Software used to develop CEMs submitted to NICE 2018-2019



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### Microsoft® Excel Spreadsheet-Based

- **Pros**
  - Familiarity
  - Widely available
  - Simple to use
  - Easy to share
- **Cons**
  - Statistical limitations
  - Hard to keep track of:
    - Calculations
    - Modifications
  - Hard to test:
    - Prone to accidental errors
  - No fit-for-purpose for complex models

### R Script-Based

- **Pros**
  - Open source
  - CE-specific, free packages
  - Statistical advantages
    - Integrated steps & analyses
    - More complex analyses and models
  - Computational efficiency
  - Automation of results into reports
  - ✓ Transparency & reproducibility
  - ✓ Efficient implementation, running and reporting
- **Cons**
  - Steep learning curve
  - Statistical skills

Jalal et al. *Med Decis Making* 2017;37:735-746; Holman et al. *Pharmacoeconomics* 2017; Krijkamp et al. *Med Decis Making* 2018;38(3):400-422; Williams et al. *Med Decis Making* 2017;37:340-352; Wright et al. *Value in Health* 2018:S380; heemod package for R (<https://arxiv.org/abs/1702.03252> and <https://cran.r-project.org/web/packages/heemod/heemod.pdf>)

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## Looking at the Future...

- **Increased use of more efficient software over time**
- **But:**
  - Excel still predominant in the shorter term
  - Some HTA agencies will still rely on less sophisticated software
- **How to move toward more efficient, higher-quality software?**
  - Upskill of HTA agencies and HE/modelling teams within pharma companies
  - Graduate training
  - Hybrid solutions

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- Imre Veres, Sr. Specialist Market Access, Hungary

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## Live Content Slide

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**Poll: I think a CE model in a software like R would be more complicated than:**

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### *Live Content Slide*

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**Poll: If a major HTA body asked for live integrated statistical analyses (e.g. survival regressions, mixed-effects models) to be a feature of a CE model – would you currently be able to provide that?**

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## Improving Efficiency in HTA: The Role of Open-Source Models and More Advanced Software Choice

Dawn Lee  
Chief Scientific Officer  
04 November 2019

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## Case study: model development in R

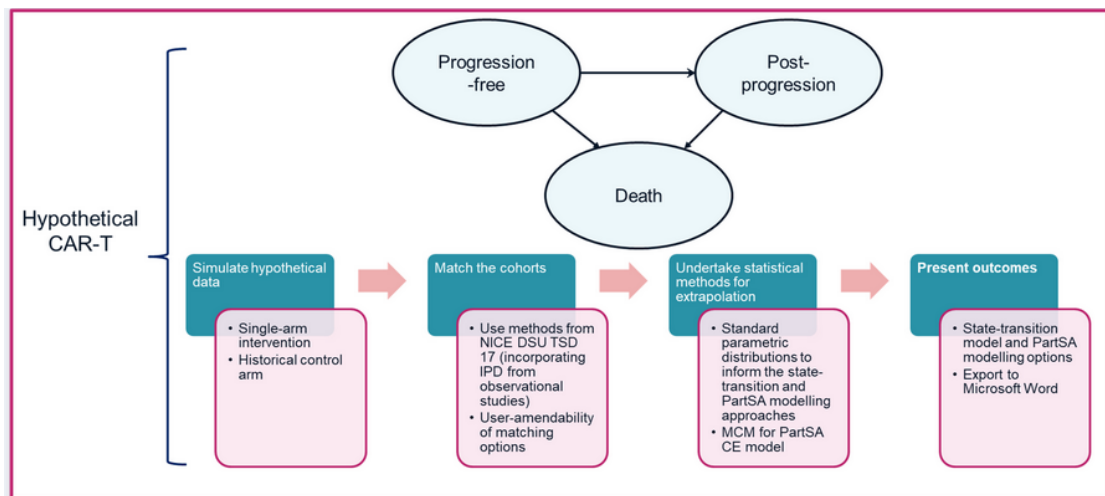
- Model set-up to address a hypothetical decision problem for a CAR-T problem
- Why was Excel less than ideal?
  - Complex analyses to consider
    - Propensity score matching – single-arm trial
    - Complex extrapolation – potentially curative
  - Not long with the data before submission
  - Potential for a large number of requests for tweaks to submitted analyses at clarification
- Considered R / R-Shiny
- What is Shiny?
  - A user-interface designed to be *user-friendly*
  - Server: the engine

**Key:** CAR-T, chimeric antigen receptor T-cell therapy.

**Reference:** Sullivan et al. *Eur J Health Econ*. 2016; 17:755–77; Hart et al. *PharmacoEconomics*. 2019; in process; Alarid-Escudero et al. *PharmacoEconomics*. 2019; <https://doi.org/10.1007/s40273-019-00837-x>; Jansen et al. *PharmacoEconomics*. 2019. <https://doi.org/10.1007/s40273-019-00827-z>; <https://heroapps.io/>

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## What does the model do?



**Key:** CE, cost-effectiveness; MCM, mixture cure model; NICE DSU TSD, National Institute for Health and Care Excellence Decision Support Unit Technical Support Document; PartSA, partitioned survival model.

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## Excel-like menu system and user interactive tables

Investigating CAR T-cell Therapy in B-cell Acute Lymphoblastic Leukaemia

**Resource use**

**Monitoring costs**

Below are the monitoring costs for patients in the Progression-free and Post-progression health states. The columns for costs and percentage of patients (in blue) are user amendable. If any of the cells are amended, please select 'update costs' to immediately view cost updates; any cost changes are automatically included when the model is run.

All frequency and use data presented below are per week.

Resource name	PF 5+ years - Use per week	PF 5+ years - % patients	Post- progression - Use per week	Post- progression - % patients	Cost of resource per use (GBP)	Reference
Chemistry profile	0.05	100%	0.50	50%	1.13	NHS ref 16/17: DAPS04 - Clinical Biochemistry
Blood tests	0.05	100%	0.50	50%	3.06	NHS ref 16/17: DAPS05 - Haematology
Haematologist/consultant	0.05	100%	0.50	50%	167.83	NHS ref 16/17: WF01A Consultant Led, Non-admitted face to face follow-up. Service code: 303
Biopsy (bone marrow)	0.00	25%	0.13	50%	283.33	NHS ref 16/17: Outpatient - Clinical Haematology - SA33Z
Nurse	0.05	100%	0.50	100%	36.93	NHS ref 16/17: Face-to-face - N02AF
CT scan	0.02	50%	0.25	40%	120.34	NHS ref 16/17: RD027Z
MRI scan	0.02	50%	0.25	30%	139.30	NHS ref 16/17: RD01A

Key: CT, computer tomography; MRI, magnetic resonance imaging; NHS, National Health Service; PF, progression-free.

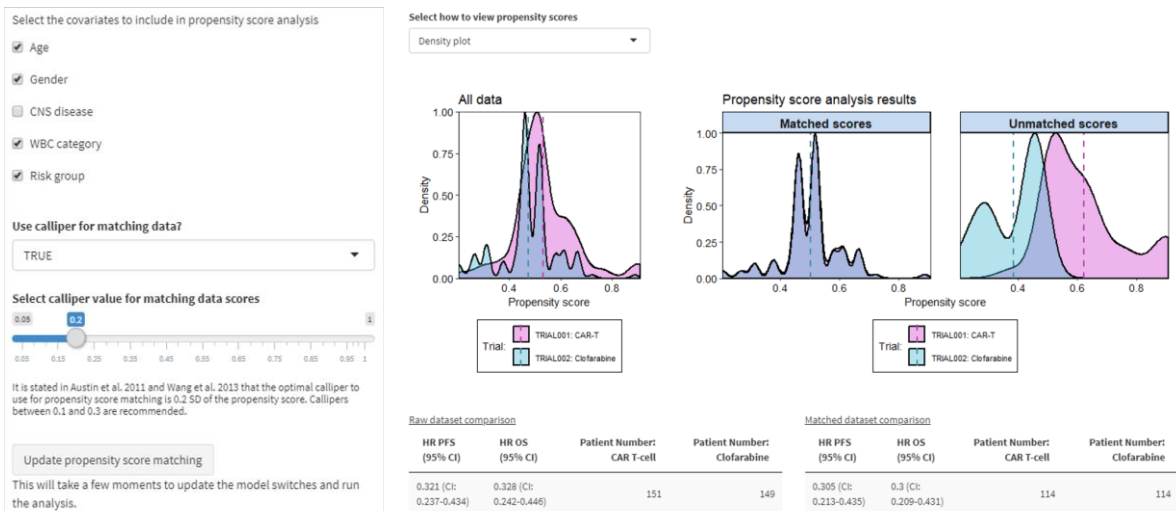
Update costs

The following table is calculated from the above inputs for cost per health state per week, which are applied in the model for the proportion of patients who are occupying the particular health state.

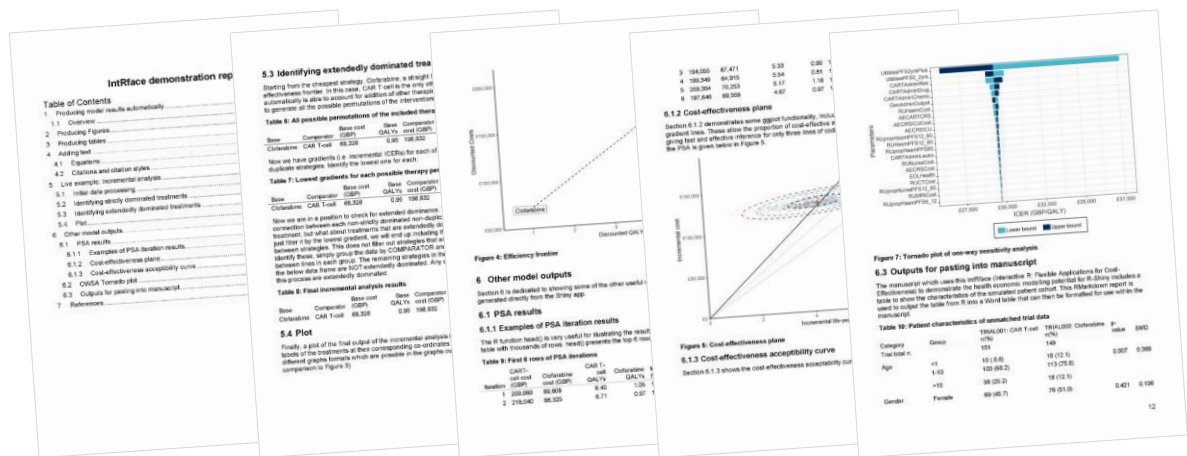
	PF: 0-6 months	PF: 6-12 months	PF: 1-5 years	PF: 5+ years	Post-progression
Cost of health state ( GBP )	163.02	121.39	45.18	12.45	101.66

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## Ability to easily set up analyses and view results



## Output straight to report



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## Our learnings during development

- Trade-offs
  - Recyclability vs speed & resource intensiveness of initial coding
  - Full exploration of uncertainty vs simplicity of the message
  - Desirability of transparency vs need to protect intellectual property
- Learning curve
- Client comfort, QC & version control
  - Different to Excel – linear read vs tracing individual inputs
  - Pressure testing equally easy with user interface
  - Ability to work simultaneously with changes only taken in when QC'd & accepted
  - Need for industry standard validation procedures
- Considerable improvement but not a silver bullet!



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**Poll: What problems concern you most with your current economic builds (barring of course the challenge of achieving cost-effectiveness!)?**

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Improving efficiency in HTA: The role of open source models and more advanced software choice

Future perspectives

Gianluca Baio


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# Main barriers?

- There **is** wide interest!
  - In academia
  - In industry
  - In places like ISPOR combining the two areas
- ... and not just in the “usual places”
  - UK strong tradition & NICE (for how much longer??...)
  - In our experience, people get involved from all over the world!
- There **are** barriers
  - Circular argument: “NICE doesn’t require we use R, so we use Excel, because that’s what they like...”
  - Paradigm shift & learn new language

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<http://www.statistica.it/gianluca/teaching/r-hta-workshop>



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## R for trial and model-based cost-effectiveness analysis

Tue, 22 Jan, 2019



This is an annual event organised jointly by a “consortium” of academics and modellers working in health economic evaluation. Academic institutions involved include [UCL](#), the [University of Bristol](#), the [University of York](#), the [University of Oxford](#), [Bangor University](#).

Cost-effectiveness analysis (CEA) and, more generally, health technology assessment (HTA), is often performed using Excel. Despite its (perceived) ease of use, Excel incurs the disadvantages of slow computational speed and, contrary to health economics [folk theorem](#), a lack of transparency.

The objective of this workshop is to explore the use of R for CEA as an alternative to less efficient, generalisable and powerful statistical software. General topics of interest include a wide range of technical aspects, e.g. the discussion of the many available R add-on packages, as well as ways to help users get the most out of R for CEA. Presentations and public discussions are used to address the computational and transparency advantages of R over Excel for CEA and for easing collaboration. Our expert speakers have diverse experience in government (including [NICE](#)), academia, and industry. We also aim at having contributed oral presentations and poster sessions.


The first edition of the workshop has been held at UCL in 2018. The links below point to the specific pages for the various editions.

1. 11 July 2018
2. 9 July 2019






### Scientific Committee


[Howard Thom](#), University of Bristol  
[Gianluca Balo](#), University College London  
[Anthony Hatzewell](#), Delta Hat Limited and University College London  
[Nathan Green](#), Imperial College London  
[Iryna Schlackow](#), University of Oxford  
[Claire Williams](#), University of Bristol  
[Pedro Saramago Goncalves](#), University of York  
[Padraig Dixon](#), University of Bristol  
[Bobby Mihaylova](#), University of Oxford  
[Nicky Welton](#), University of Bristol

Health economics R



Gianluca Balo





### Related

- [New stuff in BCEA](#)
- [survHE new release](#)
- [WinDiskin in TeDentin](#)

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## Confounding & unconfounding...

- **PERSONAL VIEW:** much of the resistance to use of **proper** statistical software *may* (is...) a proxy for lack of statistical sophistication
  - OF COURSE not everybody who uses Excel doesn't know their stats – LOTS of people do!!
  - BUT: often over-reliance to the status-quo also due to lack of suitable skills in statistical (vs health economic!) modelling
- **SOLUTION:** Expand training at all levels
  - University – MSc programmes (eg @UCL – *selection bias alert*)
  - Specific events, eg “Using R for HTA” (eg DARTH, UCL/Bristol/Cambridge/Sheffield, ... – *selection bias alert*)
  - Industry training & uptake
  - Books/documentation/case studies/repositories

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## The problem with Open Access

- Open Access **sounds** great
  - ... and it *is* great!
  - BUT: we can't pretend there are no issues...
- “Proprietary” models/data
- Fair(-ish...) point... But:
  - Models at least should be available for scrutiny at various levels
  - We often use very similar model structures (eg oncology), so we shouldn't really hide them...
  - Just because we can't/won't share individual level data, doesn't mean we can't provide more and more relevant information... (eg correlation across covariates)
- Just because you can see what I do, doesn't mean you can do what I do...
  - Back to square 1: better training...

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*Live Content Slide*

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**Poll: What would make you more likely to use more efficient software?**

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*Live Content Slide*

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**Poll: Are you aware of any HTA agencies moving towards using more efficient software?**

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