

A Data-driven Agent Based Simulation platform for Early Health Economics Device Evaluation

David Bell

Dept. of Computer Science
Brunel University London
david.bell@brunel.ac.uk

Armin Kashefi

Dept. of Computer Science
Brunel University London
armin.kashefi@brunel.ac.uk

Nurul Saleh

Dept. of Computer Science
Brunel University London
nurul.saleh@brunel.ac.uk

Tommaso Turchi

Dept. of Computer Science
Brunel University London
tommaso.turchi@brunel.ac.uk

Terry Young

Dept. of Computer Science
Brunel University London
terry.young@brunel.ac.uk

ABSTRACT

Health economics is a relatively new but growing field within the discipline of economics and is concerned with making the best use of scarce resources. Early health economic estimates of new medical devices, in particular, can assist producers of health technology in making appropriate product design and investment decisions. One problem facing decision makers at the moment is a poor understanding of the potential value gained from new or alternative product or service offerings. Understanding medical device features in the wider healthcare environment is addressed using agent based modelling and simulation (ABMS). In this paper we examine the use of ABMS underpinned by a novel data-driven approach to model generation. A Sepsis use case is presented where pathway and device characteristics are defined using the 'headroom' method and semantic evidence capture features. Types and sub-types are automatically extracted into agent models and subsequently executed in our own data-driven agent based simulation platform (TEASIM). Initial evaluation of a data-driven approach (and the TEASIM platform) is positive. The approach offers an accessible approach to product development modelling and simulation, especially in the earlier stages when deciding between potential product configurations or features.

Author Keywords

Health economic assessment, agent based modelling and simulation (ABMS), headroom method, cost effectiveness analysis

ACM Classification Keywords

I.6.1 SIMULATION AND MODELING (Model Development), SOCIAL AND BEHAVIORAL SCIENCES (Economics).

1. INTRODUCTION

Health technologies continue to make a substantial contribution to improving the health status of populations

[1]. Nonetheless, OECD countries over a period of 10 years have witnessed an annual average health expenditure growth per capita of 4%, outpacing economic growth of 2.2% during the same period [2]. A consequence of this is that health systems are faced with economic constraints and are continually looking to achieve more for less economic cost. The medical device industry and device developers have an important part to play in ensuring that efficiencies are achieved through increased efficiency of spending, and not at the expense of the quality of care received by patients [3]. One solution would be to enhance the decision maker understanding of the medical device decision domain and subsequent quality of go/no-go product development choices by incorporating health economic assessments in such decision-making processes [3,4,5]. The economic evaluation of public health interventions, in essence, provides a capability to maximize population health subject to scarce resources [6,7]. This makes it especially important and relevant to diagnostic services and Point-of-Care (PoC) technologies [8].

The PoC diagnostic sector, which is a growing market, creates a challenging evaluative scenario because, on the one hand, the unit cost-per-test is larger through the loss of the economy of scale offered by automation, whilst it offers the potential of substantial savings through enabling rapid delivery of results, and reduction of facility costs [9]. In this context, allowing PoC builders to quickly design increasingly 'realistic' representations of what the product should do with a reasonable reimbursement price is not only a critical area of research but also a challenging one due to the fact that the properties of PoC devices closely interrelate with varied technical and non-technical healthcare information needs. Knowledge platforms are able to support the collection and synthesis of healthcare information supporting economic evaluation - typically using aggregate measures and population data. Coupling knowledge platforms with agent modelling provide decision makers with a novel combination of device re-imbursement and health system impact analysis.

Adopting a design-science paradigm, a problem-solving paradigm, we introduce a number of innovative artefacts in order to design novel data-driven decision-making processes that are aimed at improving the early health economic evaluations of PoC devices and their subsequent usage. Artefacts are built as part of a design-build-evaluate cycle as an effective solution is constructed and knowledge is accumulated. The paper presents two design-build-evaluation cycles that result in knowledge (Tea-PoCT) and agent modelling (Tea-Sim) platforms for early health economic evaluations by PoC device manufacturers. Importantly, the transition from knowledge platform to agent model is a primary focus in this paper. The structure of the paper is as follows: Section 2 presents work related to our efforts in economic evaluation and agent based modelling. In Section 3 our knowledge capture and annotation approach is detailed. Section 4 presents agent modeling driven by the knowledge platform. Section 5 presents an evaluation of the resulting design artefacts, conclusions and opportunities for future work.

2. BACKGROUND

Health Economics is a relatively new but growing field within the discipline of economics and is concerned with making the best use of scarce resources [10-12]. It has been an established feature of research, policymaking, practice and management in the delivery of healthcare [[9] and its role is increasing as the cost of healthcare begins to drive changes in most major healthcare systems. Economic modelling, simulation and scenario analysis are tools that help decision makers carry out choices in a rational fashion [13]. This emerging area has consequently become the focus of both public policy and private sector transactions with associated input and output, input being healthcare spending and output being improved outcomes for patients [14,15]. A relevant case for health economics is the National Health Service (NHS) in the UK as it has been acknowledged that increases in NHS spending were not being accompanied by markedly improved outcomes [16]. Taking the budget of NHS into account, ‘Health Economic’ evaluation offers decision-makers a set of tools to maximize output relative to a fixed budget input.

Value assessment for medical products is a complex task and developing products or investing in this sector can be a daunting process [17,18]. If the ultimate goal of health-economic evaluation of medical interventions is to support evidence-based policy decisions, then it is essential to place new products in terms of cost and effectiveness, relative to the current gold standard treatment [3]. The ‘Headroom method’ is used to assess the cost-effectiveness of a new technology in comparison to some existing gold standard technology, by defining a maximum cost (the Headroom) that the adopter of the technology would be willing to incur [19]. Technologies or projects whose cost exceeds the maximum Headroom can be deemed cost-ineffective and abandoned. On the other hand, technologies whose costs

fall below the Headroom are not necessarily going to be cost-effective, but they show potential for adoption, which can be decided at later stages of the cost-effectiveness assessment. Therefore, the method can be used as a barrier to unsustainable projects at early stages, or even before their commencement [20]. The Headroom method offers a simple way for manufacturers to investigate the commercial viability of a new medical device, by applying the principles of health economic evaluation early on, ideally at the concept stage [20]. Clinical data verifying effectiveness is apparently absent at this stage, but the innovator’s ideas around what the device could mean for patients (impact on health) and the NHS (cost impact for services) can be used to estimate its reimbursement prospects. Thus, the method uses early predictions of potential impact (which should be optimistic but plausible) to estimate what the healthcare system should be willing to pay for the device if it works as hoped. In short, the Headroom method explores the potential value of new technologies [20].

ABM is often a process comprising analysis, design, implementation, execution and validation [21]. State charts often underpin the ABM approach and more specifically an understanding of environmental and agent state [22] – often investigating the costs associated with a healthcare system. State machine inputs, outputs and probabilistic state transition drive the executing simulation [23]. ABM in healthcare has traditionally been driven by the analysis and construction of models [22] that rely heavily on domain experts for their construction. Alternatively, relying more on the data generated by a real-world health system is more ambitious. However, the growth in open data is providing a means to uncover insights from this type of approach. Emergency department have been a popular area to investigate, better understanding the modelling required [21] and subsequent optimization [23]. Synthesizing the economic modelling with agent approaches (especially for medical device manufacturers) has had less coverage in the literature.

3. EVIDENCE CAPTURE

The design problem being addressed is accessibility to data and decision making tools for medical device manufacturers. Our data-driven simulation design response combines a knowledge capture platform with agent based simulation environment. Traditional gold standard and economic modelling subsequently feeds an agent based approach. The remainder of this section describes the first three steps before critically focusing on the transition to agent modelling in the later section.

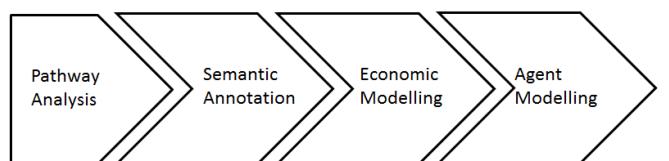


Figure 1. Data-driven Simulation Framework.



Figure 2. Snapshots of the Tea-PoCT MediaWiki.

3.1 Knowledge Capture Platform

We use a Sepsis scenario to demonstrate our approach. Initially, a first data model is created, recording Sepsis facts on our Tea-PoCT platform. MediaWiki software was extended to support visual and semantic tagging and hosted at www.Tea-PoCT.com.

MediaWiki (or Wiki technology) was chosen at it offers functionality to store several revisions of the same file, made by different users, and provides a place to store and validate emerging evidence. Secondly, it provides a basis by which an analyst can turn validated information residing in the wiki into structured information for later use. MediaWiki is also a full-fledged development framework (PHP), with available extensions (i.e. semantic MediaWiki, html tags) that can turn a wiki into a flexible knowledge management system. All data created within Tea-PoCT can then be accessible on the Semantic Web, allowing other applications to use this data seamlessly (due in part to the self-describing nature of the platform). Figure 2 shows two snapshots of the Tea-PoCT wiki, one from the main page and one from the Sepsis page.

To provide accessible and consumable data for platform services and PoC device manufacturers, an extractor was developed for accessing wiki stored clinical and device data. The aim of the extractor is to harvest the ‘semantically annotated data’ ready for the agent platform. Semantically annotated data is able to be read and understood not only by human but also by machines. The main point in creating semantically annotated data is enabling applications to search, retrieve and process the content in a more intelligent way. Authorized clients can then download this data into the Agent platform, Excel spreadsheet or Web based economic modelling for device specific analysis.

Once the Tea-PoCT system was available, an extensive literature review was undertaken (typical of an economic evaluation) to collect data about the clinical area under investigation.

3.2 Knowledge Gathering

Currently, the key problem facing PoC decision makers is lack of access to good evidence and clear cases concerning product or service data. A comprehensive literature review is therefore needed to identify product data sources and to summarize the existing evidence for the clinical area being explored (Sepsis). Sepsis is one of the most expensive conditions that can affect patients. In the UK alone, the Sepsis Trust puts NHS spending linked to the condition at £2.5 billion (NCEPOD, 2014). The diagnosis of this condition is complicated as it appears similar to a range of other medical conditions in its early stages. For clinicians that have seen Sepsis develop before, they may be able to diagnose it with successful treatment during the early stages. Nevertheless, for clinicians without prior direct experience with Sepsis, the diagnosis is more problematic. Although Health Economic basics are relatively easy to grasp, accessing quality data quickly, is however problematic. Data will often not exist – especially if the product is novel and therefore appropriate data must be inferred from the literature, elicited from experts or even estimated. Once identified, product and service data is semantically annotated and compiled into Tea-PoCT using ‘PicTags’ (or picture tags). PicTags are small icons that have a unique name, associated value (e.g. cost, price and charge), Web links and semantic annotation. With the help of PicTags the key names and values can be differentiated from the surrounding text ready for re-use through semantic search and extraction. Figure 3 illustrates the semantically annotated data in our MediaWiki system. Importantly, MediaWiki was extended to provide a secure means of safeguarding the data from unauthorized access. Accordingly, unauthenticated users (i.e. public view) cannot read or understand the semantically annotated data that is crucial for cost-effectiveness analysis. Once data is captured and semantically annotated, economic and scenario modelling can be carried out using JSON extracted evidence.

3.3 Economic Modelling

At this stage an economic model was constructed within the knowledge platform Tea-PoCT, based on the Headroom method, in order to explore various Sepsis cost-effectiveness scenarios. The economic model was developed in such a way as to evaluate and predict the cost-effectiveness of PoC devices with specific functionalities, quality-adjusted life years (QALYs) and the Headroom over time periods up to 6 years, which can be extended as required. The rationale is to allow decision maker to interact with the data directly and to explore different development consequences. The same PicTags are used to describe the economic model with the Tea-PoCT system – in an Excel like format for ease of use.

Key facts about sepsis

Some key facts about sepsis according to the UK Sepsis Trust (UK Sepsis Trust⁶) are as follows:

- Sepsis can affect anyone.
- Common causes among all age groups, such as a cut in the hand and a chest infection can give rise to sepsis.
- The most common cause of sepsis is pneumonia/chest infection.
- Sepsis is more common cause of death than breast cancer, bowel cancer, HIV/AIDS and road traffic accidents combined.
- The chances of survival of severe sepsis, when diagnosed and treated properly, are [PercentSurvival 70] .
- Better response to sepsis will save around [TotCostSave 150000000] per year.
- Following basic procedures, could save [PerEpisodeSave 4000] per episode.
- After diagnosis, doctor should give basic treatment to a person with severe sepsis as soon as possible and always within the first hour.
- For every hour of delay giving antibiotics to a patient with septic shock, death risk increases by [DeathRiskUpPerHour 8] .
- In 2011, only [PercentAntibio1Hour 27] of patients who were admitted to hospital with sepsis received antibiotics within 1 hour.
- If a patient with sepsis receives the basic care quickly, their chances of survival double.
- Sepsis costs the NHS [TotCostNHS 250000000] per year.

Figure 3. Semantically annotated data with PicTags.

We believed that this approach would further help PoC developers to attain a better understanding of the early health economic evaluations and the challenges they might face. It can be clearly seen in Figure 3 how disease or device data is annotated with PicTags, providing a repository of variables for later use. Unsurprisingly, much of this same data can be easily utilized for uncovering agents and their behaviors. Furthermore, interested parties are able to join the Tea-PoCT project and provide further input into the modelling and to make the prediction and economic assessments more fine-grained. Firstly, in our economic model the Headroom is formulated as follows:

$$MRP = P2 = WTP \text{ threshold} \times \Delta QALY - \Delta SC + P1$$

Where:

- MRP = Maximum reimbursable price
- P2 = The maximum price the manufacturer can charge for the new device (= MRP)
- WTP threshold = Pre-determined QALY tariff between £20,000 and £30,000 per patient
- $\Delta QALY$ = Increments in effectiveness between the new device and the gold standard, measured in QALYs. $\Delta QALY$ = (utility score of treatment B x duration (years) of that health state) - (utility score of treatment A x duration (years) of that health state)
- ΔSC = Decrements or savings in service costs due to the new more effective device. ΔSC = Cost of Treatment B (New tech) – Cost of Treatment A (Old/Gold standard)
- P1 = The price of the old device (if it exists)

A challenge is often found when trying to gather all elements of change in service cost (ΔSC). The pathway must be analyzed in detail in order to uncover accurate cost figures. The quality-adjusted life-year (QALY) is a measure of disease outcome, combining quality and the quantity of life¹.

Scenario 3: PoCT with Ability to Detect Haematology, Biochemistry and Clinical Factors	
QALY (Standard)	[StCareQALY] 0.4
Total Service Cost (Standard)	[StTotalCost 25000]
Sensitivity of PoCT	[PoCTSensitivity] 75%
Organ Injury Detection Feature	[PoCTOrgInjDetect]
Clinical Factors Measurement Feature	[PoCTClinFactDetect]
PoCT Response Time	[PoCTRespTime] 2.5
PoCT QALY and cost	
QALY (PoC)	0.45
Total Service Cost (PoC)	24250

Figure 4. Scenario Analysis Input Variables.

Percentage QALY increase per year (0.05 = 5%)						
	-	0.05	0.10	0.15	0.20	0.25
Mean QALY	0.45	0.473	0.495	0.518	0.54	0.563
$\Delta QALY$	0.05	0.073	0.095	0.118	0.14	0.163
Headroom (WTP £20000)	1750	2200	2650	3100	3550	4000
Headroom (WTP £30000)	2250	2925	3600	4275	4950	5625

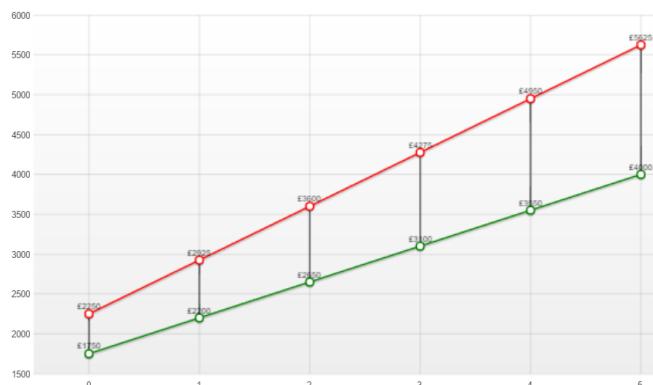


Figure 5. Scenario Analysis Outputs.

Figures 4 and 5 represent the economic aspects of a PoC device capabilities, allowing the user to change the highlighted fields and explore different cost-effectiveness and development scenarios. The headroom method is implemented within the wiki page alongside these scenario specifications. The above tables and graphical results are also defined (as PicTags) and presented within the page. Now that the device manufacturer understands the economic impact of the device, the data can then be extracted and used for simulating the healthcare environment for a specific clinical area.

4. AGENT MODELLING

The next design challenge was how best to reuse the captured and validated data within a simulation environment – extracting appropriate PicTag data of value. Our first design instantiation (presented in this paper)

¹National Institute for Health and Care Excellence (NICE).

focuses on the agent modelling paradigm. A number of agent modelling environments exist, but tend to be either graphical based, where the user builds a model inside a tool, or programming language based. In contrast, with a rich data repository it was decided to explore how the agent model could more easily be driven by the data itself. Underpinning our simulation approach is a relational model with tables as agent types and rows represented agent instances. This approach enables nuanced variation of agent properties (e.g. age) without the need to define a new agent. The executing simulator user JSON files (extracted from a relational model, Tea-PoCT or hand-crafted) to specify agents and behaviors. This form of modelling enables decision makers to gain additional insight into a complex system behavior and to demonstrate the real situation of a Sepsis patient within a hospital environment. A simulation is constructed from available Tea-PoCT pathway or economic data. The simulation is designed to determine the estimated cost of Sepsis patient based on their condition and the duration of stay at the hospital. Our data-driven simulation platform is called Tea-Sim and implemented in PHP with JSON files. Both file types can be generated from Tea-PoCT (or other data sources such as relational databases). PHP configuration, agents and agent behavior can make use of Tea-PoCT data to further explore medical device effectiveness within a health context, e.g. cost impact to a hospital or practical viability. We have developed a proof of concept model in this paper, but envisage that the same approach can be extended to apply the same medical device economics in a more specific hospital, area or country.

Our hospital environment requires a number of agents to be implemented:

A critical_patient of type people,

A not_critical_patient of type people,

A dead_patient of type people,

A normal_patient of type people and

A nurse of type people.

In our Tea-Sim platform, each agent is denoted by a specific *id* and set of variables. Agent variables are listed below:

\$this->_supertype

\$this->_type

\$this->_id

\$this->_img

\$step

These variables are accessible to the step functions, including the pointer to a visual representation of the current agent's state (*_img*).

Agent behavior is implemented in a number of available functions, such as:

```
getPosition()
move($distance)
anyNeighbour($distance[$type][$select][$update]))
allNeighbour($distance[$type][$select][$update]))
morph($type)
```

In order to set up the Sepsis simulation, two configuration files are required for initialization and model execution - init.json and model.json. JSON file are easily extracted from the Tea-PoCT platform using a Web service call. The init.json file is where the initialization is carried out. Grid size, number of instances for each agent, the position of each agent and the simulation steps are defined in init.json. Agent attributes of class people are defined in model.json with behavior (step functions) in steps.php.

Agent behavior specification is described in a module called steps.php. The stepping function, step() describes how each agent of a specific type progresses from one iteration to another, including state changes. In steps.php, the health states or internal rules are being processed. Figure 6 show the rules applied to *critical_patient* of class people agent and figure 7 shows the rules applied to *not_critical_patient*. Rules are easily implemented using PHP syntax, e.g. in figure 7 the rand(0,1) defines that 50% of critical patients without medical staff nearby will have their mortality measure changed.

```
<?php
class people_critical_patient extends Agent {
    function step($step) {
        $count_cost = 0;
        if ($this->Critical && $count_cost==0 && $this->anyNeighbour(1, 5)) {
            $this->Ward_day = rand(6,10);
            $this->Critical = false;
            $this->Mortality = 8 * $step . "%";
            $this->Cost = "2340 *". $this->Ward_day . "=" . 2340*$this->Ward_day;
            $this->_img = "img/notcritical.png";
            $count_cost = 1;
        }
        elseif ($this->Critical && $count_cost==0 && !$this->anyNeighbour(1, 5) && $step>=9) {
            $this->Ward_day = rand(6,10);
            $this->Alive = false;
            $this->Mortality = 8 * $step . "%";
            $this->_img = "img/dead.png";
            $this->Cost = "2340 *". $this->Ward_day . "=" . 2340*$this->Ward_day;
            $count_cost = 1;
        }
        $this->Mortality = 8 * $step . "%";
        $this->move();
    }
}
```

Figure 6. *critical_patient* of type people agent

```

class people_not_critical_patient extends Agent {
    function step($step) {
        $count_cost = 0;

        if (!$this->Critical && $count_cost == 0 && $this->anyNeighbour(1, 5)) {
            $this->Ward_day = rand(3,5);
            // $this->Critical = $this->Alive = true;
            $this->Mortality = 8 * $step . "%";
            $this->Cost = "600 " . $this->Ward_day . " = " . 600*$this->Ward_day;
            $this->_img = "img/ok.png";
            $count_cost = 1;
        }
        elseif (!$this->Critical && $count_cost == 0 && !$this->anyNeighbour(1, 5) && !$count_cost) {
            $this->status = rand(0,1);
            if ($this->status == 1)
            {
                $this->Mortality = 8 * $step . "%";
                $this->Critical = true;
                $this->_img = "img/critical.png";
            }
        }
        $this->move();
    }
}

```

Figure 7. *not_critical_patient* of type *people* agent

Processing defined in steps.php describes agent actions, such as:

- i. If (*nurse* is not near the *not_critical_patient*), then make a yes/no decision to become *critical_patient* or *not_critical_patient*,
 - i.i. If (*not_critical_patient* is still *not_critical_patient*), check if *nurse* is around,
 - i.i.i. If YES (*nurse* is around), *not_critical_patient* become *normal_patient*,
 - i.i.ii. If NO (*nurse* is not around), *not_critical_patient* become *critical_patient*,
 - i.ii. If (*not_critical_patient* is now *critical_patient*), check if *nurse* is around,
 - i.ii.i. If YES (*nurse* is around), probabilistically determine the length of stay in intensive care unit (ICU) and associated calculate cost.
 - i.ii.ii. If NO (*nurse* is not around and steps is more or equal than 9), *critical_patient* become *dead_patient* and store the total number of days and cost.
- ii. If (*nurse* is not near or near the *critical_patient*),
 - ii.i. If YES (*nurse* is around), *critical_patient* become *not_critical_patient*, probabilistically determine the length of stay in ICU ward and calculate cost.
 - ii.ii. If NO (*nurse* is not around and steps is more or equal than 9), *critical_patient* become *dead_patient* and store the total number of days and cost.

Executing simulations can be seen in figures 8-10. In this early model, we use *nurse* to depict any member of the clinical staff. The model assumed the *nurse* has a new medical device for disease identification. Agent changes and costs can be collected during real-time visualization or whilst running in batch mode.

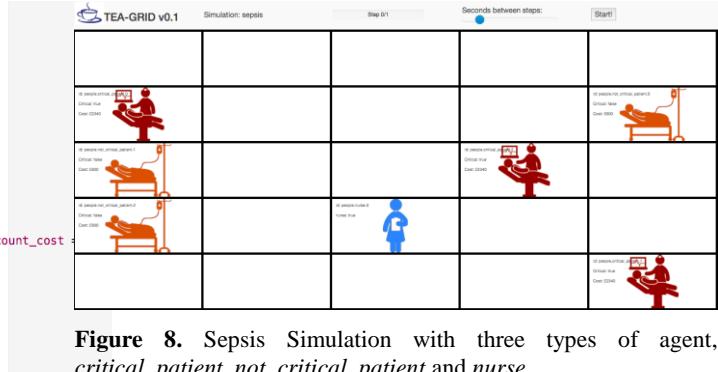


Figure 8. Sepsis Simulation with three types of agent, *critical_patient*, *not_critical_patient* and *nurse*

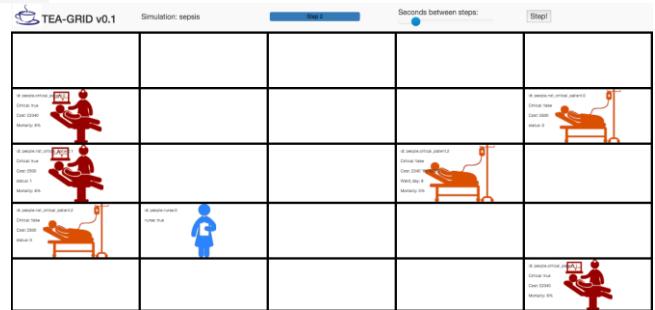


Figure 9. *critical_patient* become *not_critical_patient* and *not_critical_patient* become *normal_patient* with calculated cost and number of days in ward

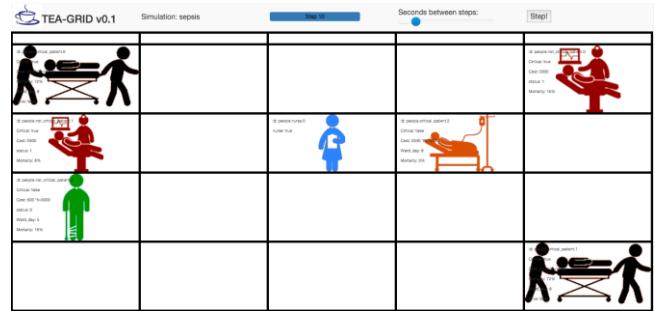


Figure 10. *critical_patient* become *dead_patient* after mortality reaches 80% or more

Figure 8 depicts when agent of *nurse* (blue image) is near agent of *critical_patient* and some way from agent of *not_critical_patient*. The simulation will change one *critical_patient* to *not_critical_patient* (orange image) and a *not_critical_patient* to *critical_patient* and the cost will be calculated (Figure 9). Although we are using simple imagery, any image can be used in the simulation with additional state annotation as an option. In a further step of the simulation, Figure 10, the agent *nurse* is not next to agent *critical_patient* after the mortality rate reaches 80% or more, *critical_patient* become *dead_patient* (black image).

5 EVALUATION AND CONCLUSION

Tea-PoCT and Tea-Sim provide users with the methods, framework and evidence, or simply the basis for making early estimates, through a set of innovative hosted digital services. Tea-PoCT is the first phase of a vision where product and service providers are better connected to patients and near patient practitioners. While the purpose of evaluation in the project's initial phase was to assess the feasibility and effectiveness of the idea of the Tea-PoCT's extended MediaWiki system and the process of data acquisition and economic modelling, the aim of the subsequent design iteration evaluates the utility of economic data to the simulation process. The instantiation of a number of simulations demonstrates the viability of the approach. Furthermore, it was clear that data can be easily re-used in a wider simulation, specifically: 1) Variations of disease, 2) Disease Burden, i.e. mortality rate of 8%/hour and 3) Economic burden and cost in terms of duration and finance.

This research also opens a number of future research avenues, stimulate improvements to the existent processes and further lead to advances. It is envisaged that the platform proposed in this paper can further evolve and support research into novel client decision-making apps, mobile apps and collaborative economic modelling. Originality in Tea-PoCT and Tea-Sim is the bringing together elements of knowledge seeking and acquisition, modelling and simulation. In addition, a further contribution for a platform of this type will be a state of the art medical data vault populated with real world product and service offerings and associated simulations and scenarios.

The paper provides a practical insight into how data can drive both the economic modelling of medical devices and their impact on a wider health environment. Two design research instantiations are presented – a knowledge acquisition tool Tea-PoCT and agent based simulator Tea-Sim. A Sepsis scenario demonstrates how economic modelling data acquisition can be re-used in an agent based simulation.

ACKNOWLEDGMENTS

We thank Innovate UK for providing the funding for the Tea-PoCT project.

REFERENCES

1. Grootendorst, P., Piérard, E., & Shim, M. *Life-expectancy gains from pharmaceutical drugs: a critical appraisal of the literature*, 2009.
2. Simoens, S. Health economic assessment: a methodological primer. *International journal of environmental research and public health*, 6(12), 2950-2966, 2009.
3. Chapman, A. M. *The use of early economic evaluation to inform medical device decisions: an evaluation of the Headroom method* (Doctoral dissertation, University of Birmingham), 2013.
4. Vallejo-Torres, L., Steuten, L., Parkinson, B., Girling, A.J., and Buxton, M.J. *Integrating Health Economics into the Product Development Cycle: A Case Study of Absorbable Pins for Treating Hallux Valgus*. *Medical Decision Making*, 31(4): 596-610. 2011.
5. Miller, P. *Role of pharmacoeconomic analysis in R&D decision making: when, where, how?*, *Pharmacoeconomics*, vol. 23, no. 1, pp. 1-12, 2005.
6. Williams, I., McIver, S., Moore, D., & Bryan, S. *The use of economic evaluations in NHS decision-making: a review and empirical investigation*, *Health Technology Assessment* (Winchester, England), vol. 12, no. 7, p. iii. 2008.
7. Carlsson, P. *Health technology assessment and priority setting for health policy in Sweden*. *International journal of technology assessment in health care*, 20(01), 44-54, 2004.
8. Edwards, R. T., Charles, J. M., & Lloyd-Williams, H. *Public health economics: a systematic review of guidance for the economic evaluation of public health interventions and discussion of key methodological issues*. *BMC Public Health*, 13, 1001, 2013.
9. Sanavio, B., & Krol, S. *On the Slow Diffusion of Point-of-Care Systems in Therapeutic Drug Monitoring*. *Frontiers in Bioengineering and Biotechnology*, 3, 20, 2015.
10. St John, A., & Price, C. P. *Economic Evidence and Point-of-Care Testing*. *The Clinical Biochemist Reviews*, 34(2), 61–74, 2013.
11. Mishra, D., & Nair, S. R. *Systematic literature review to evaluate and characterize the health economics and outcomes research studies*, India. *Perspectives in Clinical Research*, 6(1), 20, 2015.
12. Angevine, P. D., & Berven, S. *Health Economic Studies: An Introduction to Cost-benefit, Cost-effectiveness, and Cost-utility Analyses*. *Spine*, 39(22S), S9-S15, 2014.
13. Akeem, B. O., & Juni, M. H.. *Health economics evaluation in health planning*. *International Journal of Public Health and Clinical Sciences*, 2(2), 93-103, 2015.
14. Farag, I., Howard, K., Ferreira, M. L., & Sherrington, C. *Economic modelling of a public health programme for fall prevention*. *Age and ageing*, afu195, 2014.
15. Graves, N., & Zheng, H. *Modelling the direct health care costs of chronic wounds in Australia*, 2014.
16. Webber, L., Mytton, O. T., Briggs, A. D., Woodcock, J., Scarborough, P., McPherson, K., & Capewell, S. *The Brighton declaration: the value of non-communicable*

- disease modelling in population health sciences.*
European journal of epidemiology, 1-4, 2014.
17. Craven, M. *The MATCH Project: collaboration between academia and industry*, Focus magazine, Association of British Healthcare Industries, July 2004.
 18. Girling, A.J., Lilford, R.J., and Young, T.P., *Pricing of Medical Devices under Coverage Uncertainty - a Modelling Approach*. Health Economics, 21(12), 2012.
 19. Davey, S., Brennan, M., Meenan, B., McAdam, R., Girling, A., Chapman, A., and Lilford, R., A, *Framework to Manage the Early Value Proposition of Emerging Healthcare Technologies*. Irish Journal of Management, 31(1), pp.59-75, 2011.
 20. Van Nimwegen, K. J. *Feasibility of the Headroom Analysis in Early Economic Evaluation of Innovative Diagnostic Technologies with no Immediate Treatment Implications*. Value in Health, 17(7), A550, 2014.
 21. Stainsby H, Taboada M, Luque E. *Towards an agent-based simulation of hospital emergency departments*. Services Computing, IEEE, 2009.
 22. Borshchev A, Filippov A. *From system dynamics and discrete event to practical agent based modeling: reasons, techniques, tools*. Proceedings of the 22nd international conference of the system dynamics society 2004 Jul 25 (Vol. 22).
 23. Cabrera E, Taboada M, Iglesias ML, Epelde F, Luque E. *Optimization of healthcare emergency departments by agent-based simulation*. Procedia computer science. Dec 31;4:1880-9, 2011.