

DISCRETE EVENT SIMULATION OF WHOLE CARE PATHWAYS TO ESTIMATE COST-EFFECTIVENESS IN CLINICAL GUIDELINES

Julie Eatock

Department of Computer Science
Brunel University London
Kingston Lane
Uxbridge, UB8 3PH, UK

Joanne Lord

Health Economics Research Group
Brunel University London
Kingston Lane
Uxbridge, UB8 3PH, UK

Marta Trapero-Bertran

Economics and Business Department; CRES
(Health Economics Research Centre)
University Pompeu Fabra
c/Ramon Trias Fargas 25-27
Barcelona, 08005, SPAIN

Anastasia Anagnostou

Department of Computer Science
Brunel University London
Kingston Lane
Uxbridge, UB8 3PH, UK

ABSTRACT

For pragmatic reasons, cost-effectiveness analyses performed for NICE Clinical Guidelines use a piecemeal approach, evaluating only selected aspects of diagnosis, treatment or care. A Whole Pathway approach, considering diagnosis-to-death, may provide more realistic estimates of costs and health outcomes, taking account of the healthcare context and individual risk factors, history and choices for patients with long-term conditions. A patient-level DES model using the characteristics of 12,766 real patients was created to reflect the NICE guideline for Atrial Fibrillation. Of eight topics suggested for inclusion in an update of the guideline, the model was capable of fully answering four topics, and partially answering two topics. The remaining topics were beyond the scope of the model. The model was used by NICE in their recent update of the Atrial Fibrillation Clinical Guidelines.

1 INTRODUCTION

In England, the National Institute for Health and Care Excellence (NICE) is responsible for assessing the cost-effectiveness of drugs and other healthcare to be made available through the National Health Service (NHS). NICE produce clinical guidelines recommending care pathways for certain medical conditions, and defining criteria for access to services. This guidance is not binding and clinicians are expected to use their judgment to provide the best care for their patients, but it does influence local decisions about how much of which services to commission. The guidelines can be very large and complex, and need to be updated at regular intervals to reflect changes in knowledge and technology.

Initial development and updates are led by a Guideline Development Group (GDG), which includes clinicians and patient representatives, alongside a methodological team who are responsible for identifying and analyzing evidence of effectiveness and cost-effectiveness. Due to time constraints, the process starts with a scoping exercise, in which a limited number of review questions is selected. Cost-effectiveness modeling is also restricted to selected aspects of the pathway, and therefore runs the risk of neglecting systemic effects and interactions (Lord et al. 2013).

The MAPGuide (Modeling Algorithm Pathways in Guidelines) project was set up to test the feasibility and usefulness of modeling the entire pathway, from diagnosis to death at an individual patient level, within the context of clinical guidelines. Two exemplars, Prostate Cancer and Atrial Fibrillation, were chosen to illustrate the approach. These topics were selected as they already had relatively well-articulated care pathways defined in published NICE guidelines, and were due to be updated within the timescales of the project. This provided an opportunity to develop models to reflect the existing pathways, and then to test the models' ability to address selected cost-effectiveness questions within the context of guideline updates.

This paper describes the design of the MAPGuide Atrial Fibrillation model, based on the original NICE guideline (National Collaborating Centre for Chronic Conditions 2006). The ability of this model to assess the cost-effectiveness of potential changes to the 2006 pathway that were included in the scope for 2014 guideline update is assessed, and subsequent use of the model in the 'live' update process is discussed. Finally some conclusions are drawn about the appropriateness of this type of modeling for assessing cost-effectiveness in clinical guidelines, and areas for further research are identified.

2 ATRIAL FIBRILLATION

Atrial Fibrillation (AF) is a condition characterized by an irregular or rapid heartbeat (Camm et al. 2010). Incidence of AF increases with age, and is correlated with comorbidities such as hypertension and diabetes (National Collaborating Centre for Chronic Conditions 2006).

AF is often asymptomatic and intermittent, but progressive (Kirchhof et al. 2007). In paroxysmal AF the fibrillation occurs for a short time, usually minutes or hours, but stops spontaneously within 7 days. The frequency of episodes of paroxysmal AF can vary greatly, from several episodes per day, to months in between (Shehadeh, Liebovitch and Wood 2002). However, the frequency generally increases as the condition progresses, due to electrical remodeling in the heart tissue (Nattel 2002). Persistent AF is defined by the need for medical intervention (pharmacological or electrical cardioversion) to terminate the fibrillation within 7 days. AF is said to be permanent when it lasts for more than a year or when cardioversion attempts have failed.

Due to the non-symptomatic nature of many AF cases, it is difficult to diagnose and to classify. Typically, diagnosis is done through a 12 lead ECG, which is often performed for some other purpose and for relatively short periods of time. Hence the AF may be missed if the heart is in normal sinus rhythm during this time and, even once diagnosed, without longer monitoring it is difficult to determine the duration of fibrillation and whether it will spontaneously terminate. Diagnosis is improved by using Holter recorders for up to 7 days (Stahrenberg et al. 2010), but still many episodes may be missed.

There is evidence to suggest that the presence of AF increases the incidence of ischemic strokes five-fold (Camm et al. 2010) and that AF may be the cause of up to 5% of all strokes of unknown origin (Christensen et al. 2014). Ischemic strokes are caused when a thromboembolism (blood clot) moves and blocks blood from reaching the brain cells. In order to reduce this risk, oral anti-coagulants are administered. This in turn, however, increases the risk of a hemorrhagic stroke – where blood vessels in the brain burst and damage cells. Strokes, of either type, can be catastrophic for the patient and very expensive for the health and social care system. The risks of recurrence, mortality and disability after stroke are also related to the type of AF (Ntaios et al. 2013). Algorithms to predict the occurrence of thromboembolic events in AF patients have had limited success (see Lip et al. 2010 for a review).

Treatment for AF falls under the broad categories of rhythm control or rate control. Rhythm control drugs aim to maintain sinus rhythm and therefore act to slow the progressive nature of the condition. In the Clinical Guidelines issued in 2006 (CG36), these drugs were recommended for all patients with paroxysmal AF, and for some with persistent AF (National Collaborating Centre for Chronic Conditions 2006). For persistent AF patients who met certain criteria and those with permanent AF, ventricular rate control drugs were recommended. Rate control drugs do not attempt to put the heart in sinus rhythm, but try to maintain a regular heartbeat of 60-80 beats per minute at rest. There are many classes of rhythm

control drugs available that work by blocking one or more different ion channels (Savelieva and Camm 2008). The cost-effectiveness of rhythm control drugs has been called into question (Camm, Savelieva and Lip 2007).

3 INDIVIDUAL LEVEL VS COHORT LEVEL IN CONTEXT OF ECONOMIC MODELING

3.1 Economic Modeling

The remit set for NICE by the UK government states that cost-effectiveness as well as clinical effectiveness should be considered when developing guidance. NICE recommends a standardized set of methods (a ‘reference case’) to be used in cost-effectiveness analysis (NICE 2013). This includes the core concept of the quality-adjusted-life-year (QALY) as the method to value health outcomes. QALYs are defined as value-weighted time i.e. life years weighted by their quality (Weinstein, Torrance and McGuire 2009). A QALY is the product of a patient’s current health state (health utility) and the time spent in that state. Health utility is measure on a sliding scale, where 0 represents a state of health equivalent to death and 1 represents perfect health. So, one year in perfect health yields one QALY, as would 2 years with a health utility of 0.5. It is further assumed that QALYs are additive across people, so 6 months in perfect health for each of two people also yields one QALY. NICE recommends that QALYs, like costs, should be discounted to adjust for societal preferences over timing; thus a particular health state is ‘worth’ more in the near future than the distant future.

The health economists who conduct cost-effectiveness analyses for NICE use decision models to estimate the long-term costs and health outcomes (QALYs) associated with alternative treatment options for defined patient groups (Briggs, Sculpher and Claxton 2006). Most usually these take the form of aggregate (cohort) models, such as decision trees or state-transition Markov models. In Markov models, distinct health states have utilities and costs attached to them. Time advances in discrete time-steps, and at each time-step patients move to the next appropriate state, based on transition probabilities. As all patients move in unison, costs and QALYs can be easily calculated for each time step, and accumulated over the time horizon. This type of model is generally far quicker to run than a discrete-event simulation (DES) model, but it has limited ability to reflect complex patterns of disease progression related to individual characteristics and history (Karnon 2003).

3.2 Advantages of Individual Level Modeling

Clinical guidelines are intended to assist clinicians in making appropriate and cost-effective treatment decisions given the health status, history and other relevant characteristics of individual patients. Modeling a whole treatment pathway where decisions can be based on individuals’ characteristics provides greater flexibility to reflect reality than a cohort-based approach, where movement through the pathway is based only on average probabilities across a group of patients. Cohort models can be elaborated to tailor decisions for patient characteristics – for example, by increasing the number of branches in a decision tree, or by increasing the number of health states or introducing tunnel states in a Markov model. However, these approaches can quickly become unwieldy if there are many characteristics to consider. In such cases, the ability to record and update an individual’s characteristics and to make progress through the pathway conditional on those characteristics can give a more efficient and compact model structure, and DES is an appropriate tool to achieve this.

The ability to remember patients’ characteristics also allows cost and QALY estimates to be individualized, which enables assessment of whether particular sub-groups of patients would benefit from different treatment strategies, while still providing population level results from a single batch of model runs. The conventional approach in economic decision analysis is to run a series of separate subgroup analyses, by adjusting the model to reflect different transition probabilities or outcomes for people with different sets of characteristics (Briggs, Sculpher and Claxton 2006). But again this can become unwieldy, particularly when there are multiple correlated characteristics that are related to event rates or outcomes,

for example key risk factors for stroke, such as high blood pressure, age and BMI (body mass index) are highly correlated. Using a DES approach, the correlations between initial characteristics can be automatically captured by using a real patient dataset.

3.3 Disadvantages of Individual Level Modeling

One of the most obvious disadvantages of modeling at an individual level is the data requirements. A key input to economic modeling is clinical trial data, which is usually reported as aggregated results with limited subgroup analysis. So for example, the effectiveness of a particular medication for patients with paroxysmal AF may be reported, but with no indication of whether it is more or less effective for patients with particular characteristics such as high blood pressure or BMI. It is also difficult to obtain more basic data to characterize the incidence, progression and risks of AF over time. As outlined above, diagnosis and monitoring of AF is problematic due to its intermittent and often asymptomatic nature. While implanted pacemakers can record data on AF episodes over a long period of time, these are generally only used for patients with recurrent and symptomatic disease, or who have other heart conditions. Follow up data for patients diagnosed with AF have been used to estimate how the risk of strokes and other adverse events are associated with patient characteristics in the short to medium term. There are also population survey data providing a snapshot of patient characteristics at a point in time. However, to predict long term outcomes we need to consider how these characteristics change over the patient's lifetime. So for example, we would need to model how blood pressure, BMI and smoking change with age, and in response to lifestyle choices or other health issues.

Another obvious disadvantage of individual level modeling is the time it takes to develop and run the model. While model run time is becoming less of an issue with the power of computing and the option of using a distributed system, it takes longer to run than the decision tree and Markov models generally used by health economists. This problem can be a significant barrier if probabilistic sensitivity analysis is to be used to characterize uncertainty over population-level parameters, as this requires an outer loop of iterations, multiplying the time needed to run a model by many times. Another important barrier may be development time, as when a model becomes more complex the time to de-bug, and validate it increases exponentially.

Patients may live with AF for many years, so the model needs to run over a long simulated time span to capture the, possibly lifelong, costs and effects of changes to the pathway. This makes it difficult to validate that the model is producing realistic results, as outcomes seen in reality in 20 years' time will differ from the results in the model in 20 simulated years, not due to model inaccuracies, but due to technological advance and change in the population and healthcare environment.

4 DESIGN OF MODEL: THE CASE OF AF

The first stage of the project was to build a model based on the 2006 clinical guidelines for AF (CG36) (National Collaborating Centre for Chronic Conditions 2006). The model development team started by turning the recommendations in the guideline into a series of flowcharts, to represent the sequence of treatment decisions and events. The modeling team consulted with clinical experts to resolve ambiguities and uncertainties over the guideline recommendations. The flowcharts were coded for easy referral to the specific item in guideline, and formed the basis of the discrete-event simulation model.

The model was designed for evaluating the cost-effectiveness of treatment options rather than as a planning tool, so while costs were assigned to tests, visits and medications, resource constraints were not included in the model. For similar reasons, the model was run as a cohort model, with all simulated patients arriving together at the start of the run and the model terminating when the last patient died.

The sample of patients was drawn from the THIN (The Health Improvement Network) database, and included 12,766 patients who had been diagnosed with AF. For each patient, 24 characteristics were recorded that would be used within the model to evaluate risks, and decide treatment options. The correlations between characteristics was therefore implicit in the data. Some characteristics, such as

hypertension and history of diabetes and stroke were allowed to increase as the patients aged in the model. However, for simplicity other characteristics such as smoking and BMI remained static.

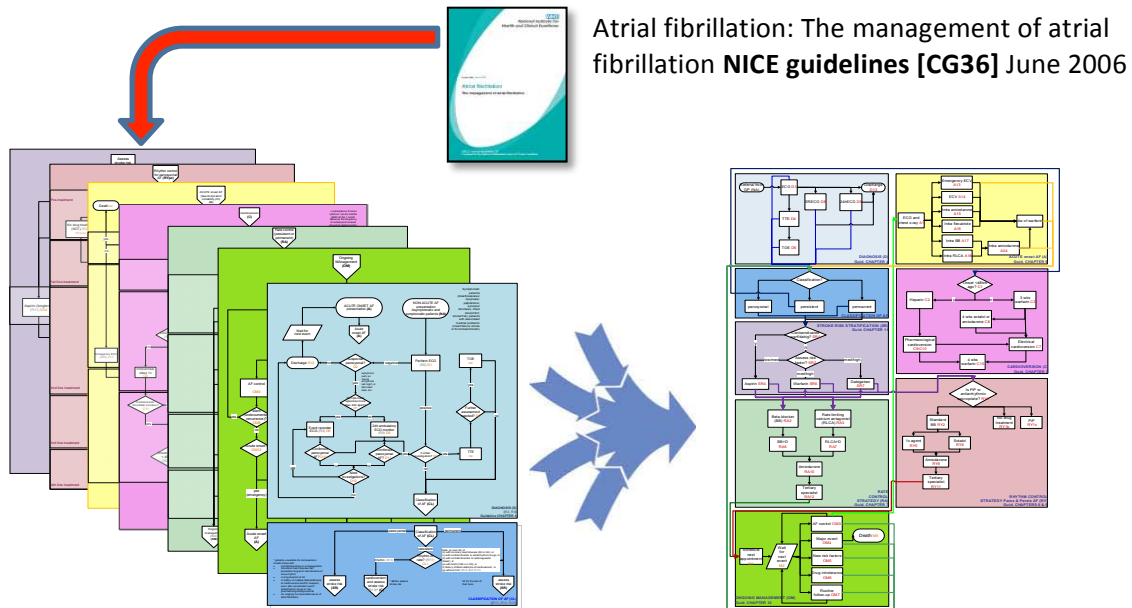


Figure 1. The current guidelines were converted to a series of flowcharts which combined to provide a comprehensive view of the management of AF which formed the basis of the DES model.

Table 1. Main competing event types in the model.

| Main event types | Event sub-types |
|------------------------------|--|
| Thromboembolic (TE) | ischemic stroke (IS) transient ischemic attack (TIA) other thromboembolic event (OTE) |
| Hemorrhagic (HE) | hemorrhagic stroke (HS) major bleed |
| AF progression | undocumented events, self-terminating events non-terminating events requiring cardioversion acute arrhythmic events requiring emergency cardioversion |
| coronary heart disease (CHD) | |
| diabetes | |
| hypertension | |
| age threshold | |
| death | |

Progression of AF is difficult to characterize, and to some extent the terms paroxysmal, persistent and permanent are simply ‘labels’ that help determine the appropriate treatment option. A flowchart of progression and control of AF, incorporating documented and undocumented instances of AF, and cardioversion events was designed to provide a definitive framework to capture progression. A risk model was also developed to quantify the risks of key outcomes (as shown in Table 1) conditional on individual characteristics and treatment effects.

The model used a time to next event design, as illustrated in Figure 2. After initial diagnosis, the model calculates the time to all the competing events (described in more detail in section 4.1), and identifies the event that is due to occur first. The patient then waits, accumulating costs and QALYs associated with their current health condition and treatment, until the event occurs. If this is a non-AF related event, such as reaching an age threshold or developing diabetes, the patient’s characteristics are updated and the risks and time to competing events re-calculated. However following an AF-related event, such as disease progression or stroke, the patient receives short-term treatment if appropriate, their costs and QALYs are updated, and their subsequent AF treatment is reviewed and possibly changed. This cycle is repeated until the next event scheduled is death, when the patient exits the model.

4.1 Calculating Time to Event

Published epidemiological sources were used to estimate individuals’ risks of the included outcomes in the absence of treatment. Rates of AF progression were based on longitudinal studies of patients with AF in Canada and Europe (Kerr et al. 2005; Nieuwlaat et al. 2005; Nieuwlaat et al. 2008; Camm et al. 2011). Rates of hemorrhagic and thromboembolic events were estimated from a large AF cohort in Sweden (Friberg, Rosenqvist and Lip 2012), with rates varying according to individual risk factors as quantified by the HAS-BLED and CHA2DS2-VASc algorithms (Lip et al. 2010; Pisters et al. 2010). Rates of coronary heart disease, diabetes and hypertension were all based on equations from the Framingham Heart Study (Anderson et al. 1991; Wilson et al. 2007; Parikh et al. 2008). A proportion of patients who experienced AF-related hemorrhagic and thromboembolic events died within 30 days. Non-AF related mortality rates came from national life table data (www.ons.gov.uk). These background risks were modified to account for the effectiveness of the treatments where appropriate. So, for instance, an anticoagulant decreased the risk of thromboembolic events but increased the risk of hemorrhagic events. The relative effects of treatments were estimated from the clinical trial literature.

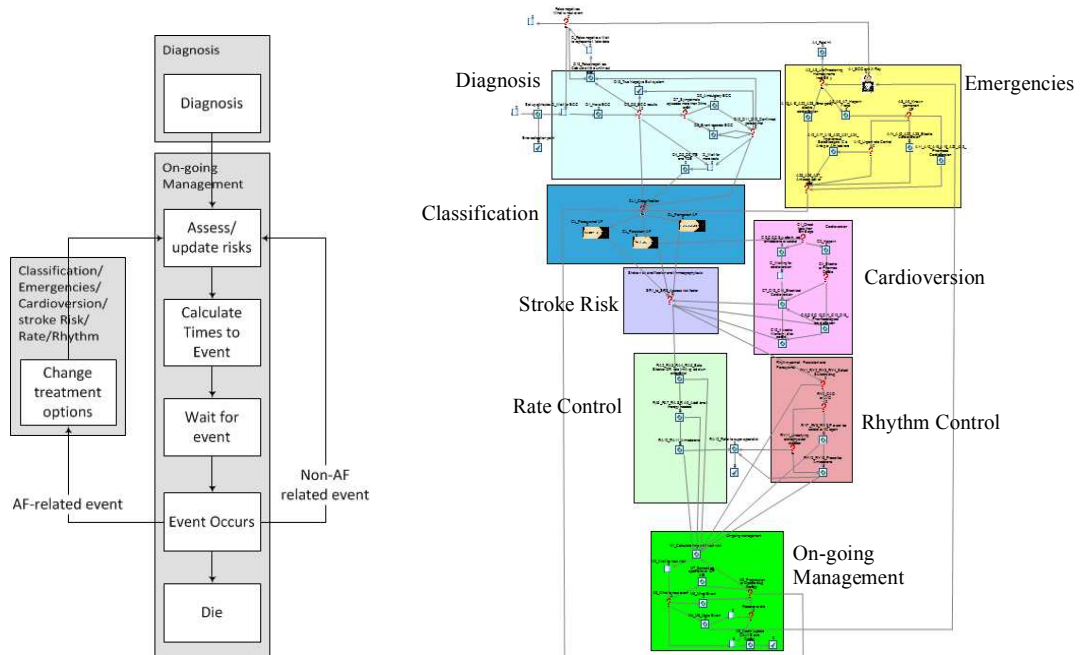


Figure 2. Overview of model structure (left) and final DES model built using Simul8 (right).

The chance of not having a particular event until a time t , given an adjusted hazard rate of λ is modelled by an exponential survival function (i.e. $1 - e^{-\lambda t}$). This assumes that the hazard remains constant

over the period of time modelled. However, as patients move through the model, their risk of a particular type of event may change in response to other associated risks, or as they age. We modelled this using a piecemeal exponential distribution, in which the hazard is constant except for changes at defined points in time (when an event has occurred or an age-threshold has been crossed).

At model entry, each patient is assigned a random number for each of the main types of event (see Table 1). This could be considered as a proxy for unknown factors that influence a patient’s propensity for that particular type of event. For each of the three composite events in Table 1 (i.e. thromboembolic, hemorrhagic, or progression), patients are assigned second random number, which determines which sub-type of event will occur next (i.e. IS, TIA or OTE in the case of a thromboembolic event). This approach ensures that related groups of events are not treated as independent.

Once an event has occurred, care is needed in adjusting the times for competing events. For example, it would be counterintuitive if the predicted time to a TE event were to increase following a bleed. To avoid this, the random numbers used to determine the time to the next events are only resampled when that specific type of event has occurred. This approach produced a piecemeal increasing function for each of the competing risks (as illustrated in Figure 3).

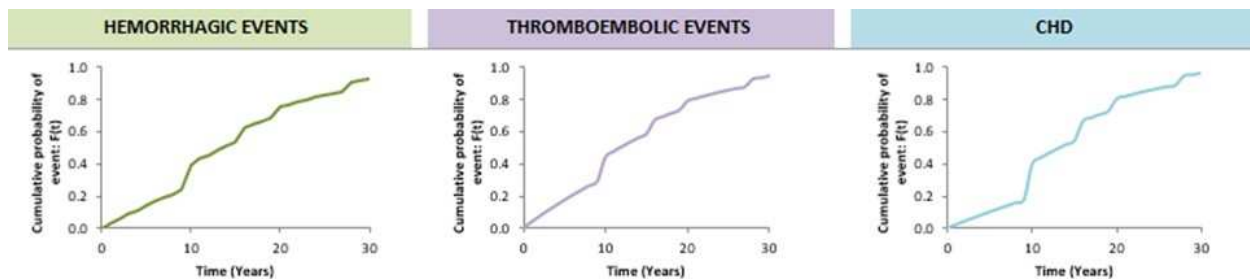


Figure 3. Cumulative probability of three competing events over 30 years for an individual patient.

5 MODEL OUTPUTS

The model was designed to produce results at two levels, individual diaries of patients’ experiences and interactions with the healthcare system, and aggregated cohort-level outputs for use in cost-effectiveness analysis. The individual level diaries (see Figure 4) provided a simple but effective way for clinicians to verify and assess the model. The diary recorded the individual’s medical history and their associated risks when they entered the process, and their subsequent treatment and events as the patient progressed through the model. Costs and QALYs were also recorded at each stage of the process (see Figure 4) to enable reviewing of calculations.

The cohort-level outputs were designed for use in cost-effectiveness analyses. These recorded the numbers of events, costs and QALYs across the patient sample. For each version of the pathway model, results were summarized using a net benefit statistic. This is calculated by multiplying the total QALYs by a monetary value – the cost-effectiveness threshold λ – and then subtracting total costs. We used a threshold of £20,000 per QALY in our analyses, the lower limit of the range recommended by NICE. Probabilistic Sensitivity Analysis (PSA) was used to account for uncertainty over the input parameters. In PSA, the model is repeatedly run, each time drawing a set of input parameters from defined probability distributions (using random, Monte Carlo simulation). There were therefore two nested sets of iterations: an outer layer of PSA sampling and an inner layer of individual simulation. The output from the model was presented as the mean and variance of the net benefits across the PSA iterations. Different versions of the care pathway can be compared in terms of net benefit: the most cost-effective pathway (at a defined level of λ) being that which produces the maximum net benefit.

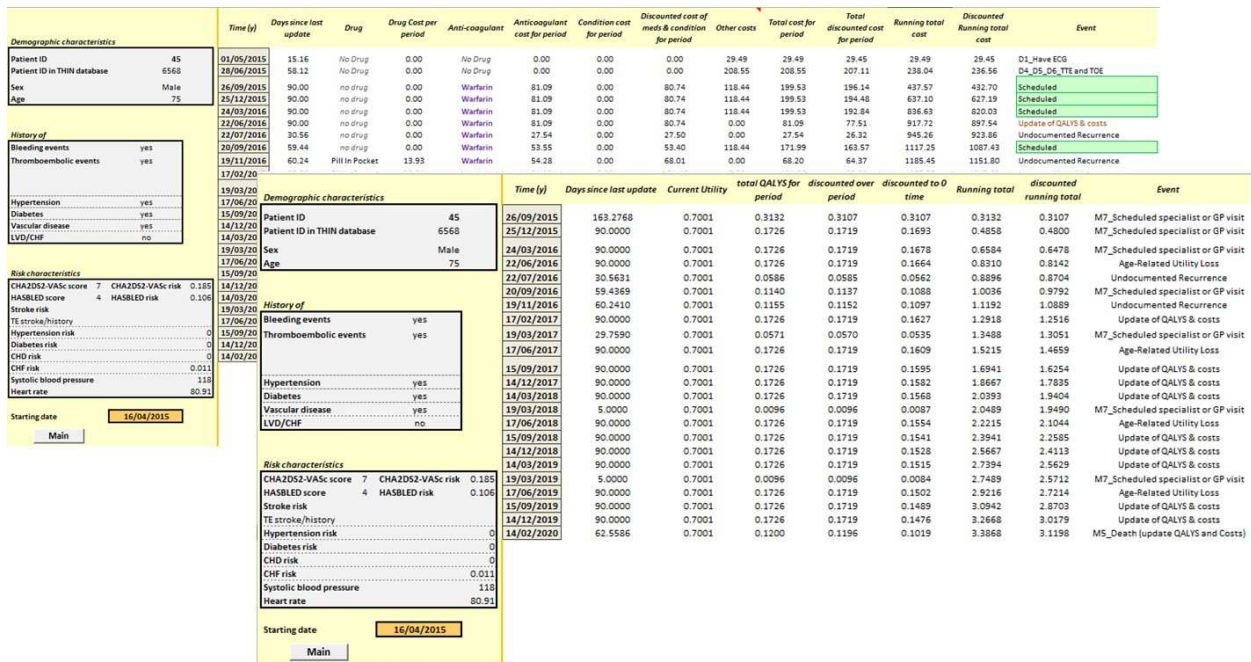
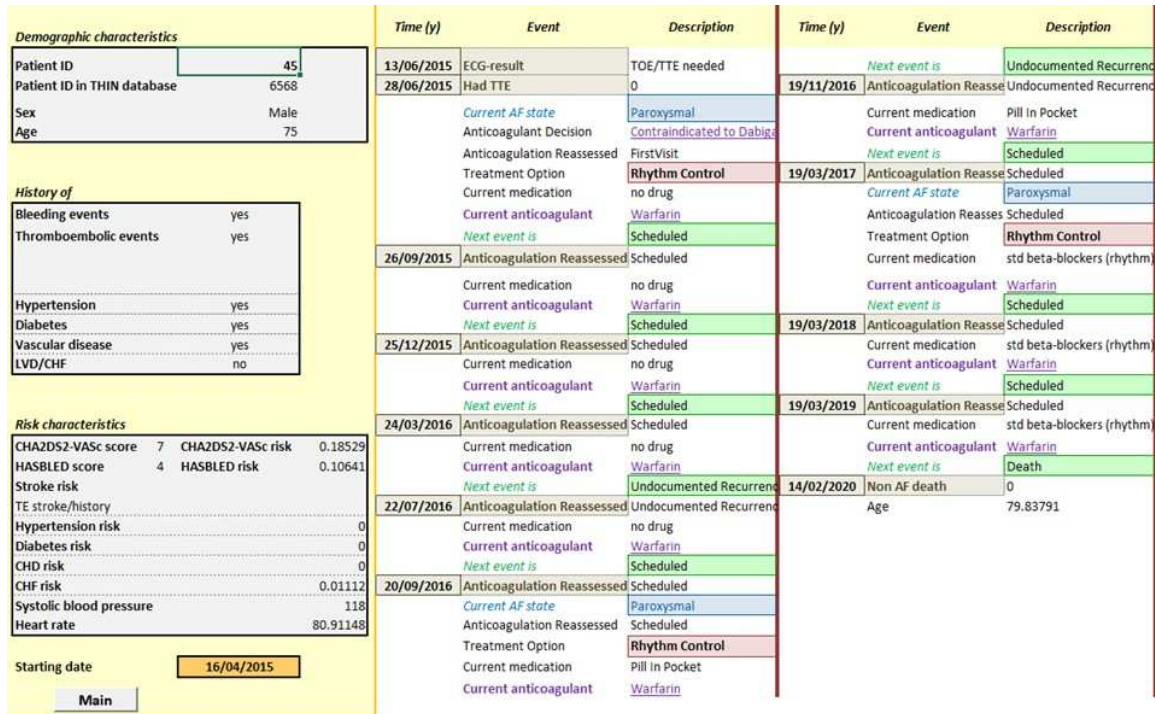


Figure 4. Model Outputs: Patient Diary (top) and Cost and QALY reports (bottom).

6 USE OF MODEL DURING GUIDELINE UPDATE PROCESS

The model was designed to reflect the current guideline and answer questions on cost effectiveness on potential guideline updates. During the building of the model, the model developers were unaware of the specific questions that would be asked as part of the update process. This ensured that the model was not designed specifically to answer the update questions, but to determine whether a whole pathway DES model could be utilized and adapted as part of the update process. There were 8 topics identified by the GDG that would be considered in the update process (see Table 2).

Table 2. Update topics.

| Topic Description |
|---|
| A Prophylaxis for the prevention of post-operative AF |
| B Anti-arrhythmic drugs as pharmacological cardioversion (PCV) for people with atrial fibrillation |
| C Rhythm versus rate control for persistent AF; subgroups including those with hypertension, previous MI and congestive heart failure |
| D Treatment for maintaining Sinus Rhythm in people with AF after cardioversion. |
| E Alternative risk factor based scoring systems to estimate stroke and embolism risk |
| F Stratification tools to assess bleeding risk before prescription of antithrombotic medication |
| G Apixaban, rivaroxaban or Dabigatran etexilate versus warfarin as for patients at moderate or high risk of stroke or systemic embolism |
| H Cather ablation for paroxysmal and persistent AF patient |

The model was therefore able to answer some of the update questions but as the nature of the questions were unknown to the modeling team during development, other update questions were unanswerable in the time given. The GDG were unfamiliar with the simulation software, so *Topics C, E* and *F* were included by the model development team as menu driven options from the start screen of the model, while *Topics B* and *G* were addressed by making changes in the spreadsheet containing input data to the model, which the GDG were able to do themselves.

An additional benefit of the process of building the model was that during development we were able to highlight to the GDG any existing inconsistencies and ambiguities within the current guideline which could be corrected in the update.

7 DISCUSSION

The model accurately captured the AF care pathway as described by the clinical guideline, and was able to produce estimates of costs and health outcomes from diagnosis-to-death for the simulated patient cohort. Using a patient level DES model allowed realistic modeling of the treatment pathway, with decisions based on individual characteristics and history. The model used the characteristics of real patients, which provided implicit correlations between the characteristics that would be difficult to replicate with distribution-generated characteristics. Arguably, this individual-level simulation approach resulted in a much more complex model with far greater data requirements than a more conventional cost-effectiveness model.

Once the model was complete it was provided to the GDG for their clinical update of the AF guideline. Despite the modeling team being unaware of the questions that would be raised during the update process during the development of the model, it allowed some of the update questions to be answered, but other questions would have required re-modeling of certain aspects of the model. As the GDG were unfamiliar with the software, the model development team designed a user interface to enable testing of some of the topics, while others could be tested by altering the data within the input parameter spreadsheet. This highlighted the need to be familiar with both the software and the model itself, in order

to use the model to address specific cost-effectiveness questions. This suggests that access to specialist DES expertise or training for economic modelers would be necessary to implement this approach in routine guideline development. The time taken to build the model was greater than that usually available to the GDG, and therefore would be prohibitive. Now built, however, the model has the potential to be re-used, with little additional development for subsequent guidelines. The model could also be extended to include prevalent (existing) cases as well as incident (new) cases, which would help assess the budget impact of the changes across a population.

Some members of the GDG were unfamiliar with, or did not have access to, the software and therefore couldn't fully review the model. The flowcharts that were created as part of the model development process were highly accessible and understandable and linked to the existing guidelines. These together with the individual patient diaries were used by the members to review the model design and output, providing the development group with confidence in the model's results. An additional benefit of creating the flowcharts was that inconsistencies and ambiguities within the original guideline could be addressed in the update.

8 CONCLUSION

In summary, the individual level modeling adds complexity, but allows a much more realistic representation of the clinical pathway based on a patient's experiences. It must be mentioned that there is more to guideline development than cost-effectiveness analysis. The GDG are responsible for identifying areas of clinical interest, and reviewing the available evidence for relevance and quality, and consulting with stakeholders. Therefore the time available for cost-effectiveness analysis is extremely limited, and this needs to be taken into account when assessing the usefulness of different modeling techniques.

ACKNOWLEDGMENTS

The MAPGuide project was funded by the Medical Research Council and the National Institute for Health Research through the Methodology Research Programme (G0901504). Julie Eatock is currently funded by an EPSRC grant (EP/K037145/1) Forecasting personal health in an uncertain environment.

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AUTHOR BIOGRAPHIES

JULIE EATOCK is a Research Fellow at Brunel University London. Her main area of research is discrete event simulation modeling, and she has applied this in many different areas including information systems and policing. In more recent times her interests have tended towards healthcare and she has applied her skills in areas such as healthcare service provision, the impact of disruptive technology, and cost-effectiveness. Her email address is Julie.Eatock@brunel.ac.uk.

JOANNE LORD is a Reader in Health Economics at Brunel University London conducting applied and methodological research into the cost-effectiveness of health care technologies. She previously worked at NICE, Imperial College Management School and St George's Hospital Medical School. Her first job was in the Operational Research Service at the Department of Health. Joanne has a BSc in Economics and Mathematics, MSc in Operational Research and PhD in health economics. Her email address is Joanne.Lord@brunel.ac.uk.

MARTA TRAPERO-BERTRAN is a Research Fellow at Universitat Pompeu Fabra (UPF) and Universidad Castilla-La Mancha (UCLM). Her main research interests include modeling techniques for economic evaluation, transmission of lifestyle behavior, and incorporation of external effects into economic evaluation. She is the former President of the Spanish Association of Health Economics (AES). She defended her PhD in Health Economics at HERG-Brunel University. Her email address is Marta.Trapero-Bertran@upf.edu.

ANASTASIA ANAGNOSTOU is a Research Fellow at the Department of Computer Science, Brunel University London. She holds a PhD in Hybrid Distributed Simulation. Her research interests are related to the application of modeling and simulation techniques in the Healthcare sector and Industry. Her email address is Anastasia.Anagnostou@brunel.ac.uk.