A multicentre double-masked randomised non-inferiority clinical trial comparing the clinical and cost-effectiveness of intravitreal ranibizumab (Lucentis), aflibercept (Eylea) and bevacizumab (Avastin) for Macular Oedema due to Central Retinal Vein Occlusion (LEAVO)

Health Economic and Decision Modelling Analysis Plan

Addendum: health economic model structure

Becky Pennington

School of Health and Related Research, University of Sheffield,
Regent Court,
30 Regent Street, Sheffield, S1 4DA

2nd October 2018

Investigators

Health Economic Modeller:

Name: Mrs Becky Pennington
Address: School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Email: b.pennington@sheffield.ac.uk

Lead Health Economist:

Name: Prof. John Brazier
Address: School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Email: j.e.brazier@sheffield.ac.uk

Health Economist:

Name: Mr Abualbishr Alshreef
Address: School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Email: a.o.alshreef@sheffield.ac.uk

Systematic Reviewer:

Name: Dr. Edith Poku
Address: School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Email: e.poku@sheffield.ac.uk

Chief Investigator:

Name: Mr. Philip Hykin
Address: Moorfields Eye Hospital.
162, City Road, London, EC1V 2PD.
Email: Philhykin@aol.com

Co-lead:

Name: Miss Sobha Sivaprasad
Address: Moorfields Eye Hospital & UCL Institute of Ophtalmology.
162, City Road, London, EC1V 2PD
Email: sobha.sivaprasad@nhs.net

Chair of Trial Steering Committee:

Name: Miss Susan Downes
Address: Consultant Ophthalmologist, Oxford Eye Hospital,
Oxford University Hospitals

West Wing, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU
Email: susan.downes@ouh.nhs.uk

Acknowledgements

The author wishes to thank Dr Philip Hykin, Prof Andrew Lotery, Dr Michael Williams and Dr Yang Yit for reviewing a draft of this document and providing advice and clinical input.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
BCVA	Best Corrected Visual Acuity
BNF	British National Formulary
CRVO	Central Retinal Vein Occlusion
EQ-5D	EuroQol Five Dimension
EQ-5D-3L	EuroQol Five Dimension Three Level
EQ-5D-5L	EuroQol Five Dimension Five Level
ETDRS	Early Treatment Diabetic Retinopathy Study
HEDMAP	Health Economics and Decision Modelling Analysis Plan
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention-to-treat
LEAVO	A multicentre double-masked randomised non-inferiority clinical trial comparing the clinical and cost-effectiveness of intravitreal ranibizumab (Lucentis), aflibercept (Eylea) and bevacizumab (Avastin) for Macular Oedema due to Central Retinal Vein Occlusion
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OCT CST	Optical Coherence Tomography Central Sub-field Thickness
QALY	Quality Adjusted Life Year
RVO	Retinal Vein Occlusion
TA	Technology Appraisal
VFQ	Visual Function Questionnaire
VFQ-UI	Visual Function Questionnaire-Utility Index

1. BACKGROUND

The HEDMAP outlines the planned procedure for conducting the Health Economic Evaluation sub-study of the LEAVO trial. The HEDMAP states that a health economic model will be developed and states that 'the model structure will be determined in consultation with clinical experts'. This document has been developed following consultation with the LEAVO trial team and describes the model structure and required input data.

The HEDMAP discusses potential model structures and states that it is expected that a Markov model will be used. Following further research, it is now believed that a discrete event simulation is a more appropriate approach. This document explains Markov models and discrete event simulation, discusses their application to LEAVO and considers data sources.

2. MARKOV MODELS AND DISCRETE EVENT SIMULATIONS

2.1 Introduction to Markov models

State-transition models are structured around a set of mutually exclusive and collectively exhaustive health states, and as such are useful when the problem/disease can be conceptualised into a series of homogenous states[1]. State-transition models can consider a cohort of patients (termed a Markov model), or can simulate individual patients. In a cohort model, a proportion of the whole cohort move between health states each model cycle, according to transition probabilities[2]. The transition probabilities in a Markov model do not depend on history – that is, the probability of transitioning from any given state does not depend on which states the patients were previously in (the Markov property).

2.2 Limitations of a Markov model for LEAVO

There are several challenges in developing a Markov model for LEAVO:

1. It is not clear what the health states should be - there has been discussion between ophthalmologists and optometrists whether ETDRS or ICD classification systems should be used, and what the range within each state should be. The economic models for TA229[3], TA283[4] and TA305[5] all used ETDRS, but used different score ranges within the health states.
2. Modelling both the study eye and non-study eye is known to be important for accurately modelling quality of life[6,7], but is challenging in a Markov model where there may be very small patient numbers in some states.

3. Markov models use a fixed cycle length, but the follow-up times in LEAVO vary – 4-week or 8-week follow-up may be required by the retreatment algorithm and there is further variability in arranging interim visits around milestone visits.
4. The retreatment algorithm in LEAVO asks whether patients were treated at previous visits, so to accurately model this requires a model that can track history.
5. Modelling a cohort would use average patient characteristics and not account for heterogeneity.

2.3 Alternatives to a Markov model for LEAVO

The alternative to modelling a cohort of patients is to simulate individual patients, and average their results at the end of the model. Simulations imitate real-world process, so simulating individual patients involves using data on a patient population to generate a large number of hypothetical patients to represent that population. State-transition models can be used for individual-level simulation – this would overcome some of the challenges, such as incorporating history, but would still require the use of health states. A discrete event simulation is another approach that simulates individual patients, and so can incorporate history, but models events rather that states and uses functions like BCVA to reflect outcomes rather than fixed states.

2.4 Introduction to discrete event simulation models

Discrete event simulations are structured around a set of mutually exclusive events and model the pathway of individual patients (or 'entities') through those events, according to the time at which each event happens[8]. Each individual patient has specific characteristics (or 'attributes') that may influence which events happen and when, and the history is recorded and can influence if and when future events happen. Events can occur at any time. Discrete event simulations are so-named because they model a discrete sequence of events, but they operate in continuous time (rather than in discrete time intervals).

2.5 Advantages of a discrete event simulation for LEAVO

A discrete event simulation overcomes the limitations of a state-transition model for LEAVO:

1. Health states are not required – each individual patient's visual acuity can be tracked over time on a continuous scale.
2. The study eye and non-study eye can be modelled separately, using data from LEAVO (and other sources) on the change in visual acuity over time.
3. The follow-up visits times can be modelled by fixing the time to milestone visits and using rules and variation to determine other visit times.

4. Each patient's history (previous visits and visual acuity) can be tracked, so the retreatment algorithm can be used.
5. Individual patients can have different baseline characteristics to incorporate heterogeneity.

3. LEAVO DISCRETE EVENT SIMULATION MODEL

In designing a discrete event simulation model, consideration should be given to which events should be included, and characteristics/attributes should be assigned to the patients/entities.

3.1 Events

The following events will be included in the model:

- Visit
- Specific Adverse Events as defined in the HEDMAP
- New onset macular oedema in the non-study eye
- Death

At each event, the patient's characteristics will change, and costs and quality of life outcomes will be updated.

The Visits to the ophthalmologist are the key stage in LEAVO at which changes to the patient's characteristics will be identified (such as changes in visual acuity including blindness), and this is assumed to be the same in clinical practice and beyond the trial period. While these characteristics may change between visits, the changes would not be recorded so no data is available.

AEs and new onset macular oedema involve changes to the patient's characteristics that may be identified not at a Visit. For example, AEs may require hospitalisation, or new onset macular oedema may be identified through a GP visit.

3.2 Characteristics

The following characteristics will be included in the model:

- Age
- Sex
- Study eye OCT CST
- Study eye BCVA
- Non-study eye OCT CST

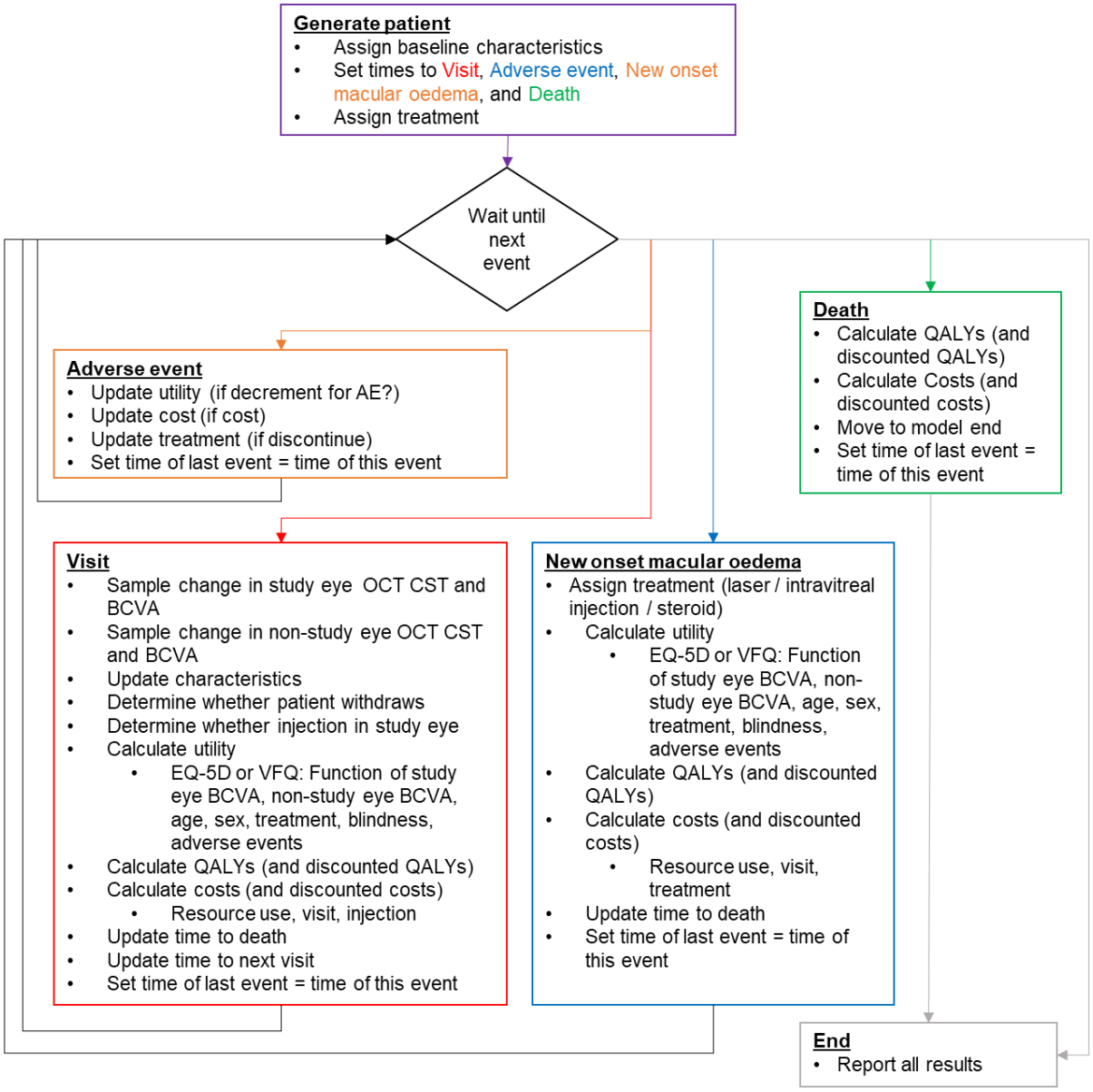
- Non-study eye BCVA
- Disease duration

Age, sex, and BCVA in both eyes have been shown to influence quality of life[6]. The inclusion of OCT CST is important as it is considered in the retreatment algorithm.

3.3 Model structure

A simplified model structure is shown in Figure 1. Once a patient is generated and has baseline characteristics and a treatment assigned, their times to events are set – these times may be fixed (for example the milestone visits) or sampled from a distribution. The event with the shortest time is the next event that the patient experiences, at which point their characteristics, QALYs and costs are updated. The patient then waits until the next event. The model ends when either the patient has died, or the model time horizon is reached. The process is repeated for a large number of patients, and the total costs and QALYs calculated. The same patients are then simulated through the model again, but with a different treatment. The total costs and QALYs are compared for each treatment to calculate cost-effectiveness results.

Figure 1: Model structure



4. MODEL DATA

The model will use data analysed from LEAVO and additional sources.

4.1 Baseline characteristics

The baseline characteristics will be sampled from the LEAVO population, unless there is evidence to suggest that the LEAVO trial population is not representative of the UK population and an alternative dataset is identified. Two approaches exist for using the LEAVO baseline population data:

1. fitting distributions to the baseline characteristics and sampling hypothetical patients, modelling the relationship between characteristics
2. using the baseline characteristics of actual LEAVO patients.

Whether the first approach is possible will depend upon the data from LEAVO and the statistical models available (whether there are enough patients with different characteristics to determine relationship between characteristics). The second approach may be necessary to preserve the relationship between characteristics, and has been used in previous ophthalmology simulation models[7]. The second approach may be preferable for transparency and for aligning the economic model with the trial based analysis. Clinicians should consider which approach is preferable and have suggested a preference for option 2.

Non-study eye macular oedema at baseline will also be analysed from LEAVO.

4.2 Change in OCT CST and BCVA at Visit

The retreatment algorithm assesses both OCT CST and BCVA, so both must be modelled. However, they are expected to be somewhat related, and so a joint statistical model is required. A recent study of ranibizumab in RVO found that increasing macular thickness was a negative predictor of visual acuity[9]. The trial team advised that OCT CST is assessed accurately at all visits, but the BCVA assessment is non-refracted at non-milestone visits (although the difference between refracted and non-refracted BCVA scores are likely to be small). The relationship between OCT CST and BCVA will be based on the measurements at milestone visits. The statistical model will be presented to and discussed with clinicians before it is used in the final economic model.

4.2.1 Study eye

Change in OCT CST is expected to be dependent upon treatment (although the effect of ranibizumab or aflibercept versus bevacizumab may not be significant), duration of treatment, time since last injection, and previous/baseline OCT CST. A recent study of ranibizumab found that patient age, the duration of RVO, presence of intraretinal fluid and

other factors were predictive of change in visual acuity[9]. These factors, as well as baseline and previous BCVA and OCT CST will be considered in developing the statistical model and discussed with clinicians. These will be analysed from the LEAVO trial data. Any variables included in the statistical model will be included as characteristics in the economic model and added to the list in Section 3.2

4.2.1 Non-study eye

Change in OCT CST for the non-study eye can be analysed from the LEAVO data, since it is also recorded. However, since the non-study eye is not treated, it would be expected to be dependent only on time and previous/baseline OCT CST. Beyond the trial period, the same data could be used (as it is a function of time), or external data sources could be identified from the systematic review.

4.3 Adverse events

The HEDMAP lists the systemic and ocular adverse events that will be included in the model. In the trial-based analysis, the adverse events reported in the trial will be analysed and included, but it is anticipated that some adverse events will be rare and not reported in the trial, but may occur in a large patient population over a longer time period. Therefore, the systematic review will identify the incidence of these adverse events. The model will use trial data as far as possible, supplemented with published data for rare events. The sources of AE data will be discussed with clinicians after we have analysed the trial data and reviewed the literature. The incidence and time period will be analysed to estimate the time to each adverse event occurring.

4.4 New onset macular oedema

The incidence of new onset macular oedema in the non-study eye will be analysed from adverse event data in LEAVO to estimate the time to new onset macular oedema. If this is rare in LEAVO, published data will be used.

4.5 Death

Mortality is expected to be related to age, sex, and BCVA. As deaths in LEAVO will be relatively rare, external mortality data will be used, identified through the systematic review.

4.6 Utility (VFQ-UI, EQ-5D)

A mapping function will be produced to convert BCVA in both eyes to utility. In the primary analysis, utility will be measured using the VFQ-UI. In secondary analyses, utility will be measures using the EQ-5D-5L, EQ-5D-5L with bolt-on and EQ-5D-3L (using the algorithm to convert from EQ-5D-5L by van Hout et al[10]). It is expected that this will incorporate age, sex, blindness, a relationship between study and non-study eye BCVA, adverse events, and

treatment. The EQ-5D is NICE's preferred measure of health-related quality of life in adults, and currently NICE recommends the 3L valuation system[11].

Utility scores could also be estimated from published mapping functions.

Adverse events may be associated with a disutility. For common adverse events in LEAVO it may be possible to analyse this directly from the trial data. For rarer events, disutilities will be estimated from the published literature.

4.7 Costs

Resource use data, including staff training, equipment, medications, and contacts with NHS healthcare practitioners, are being collected as part of the LEAVO trial. Unit costs for treatment will be taken from the British National Formulary[12] (or Moorfields Eye Hospital for bevacizumab) and applied each time treatment is given. The average cost of an ophthalmologist visit will be taken from NHS reference costs[13] and applied at each visit. The cost of administration for intravitreal injection will be taken from NHS reference costs and applied each time treatment is given.

Additional resource use, reported in the resource use questionnaire, will be analysed from LEAVO and related to BCVA. This will be costed using NHS reference costs and applied in the model.

Adverse events will be costed using NHS reference costs, using either the resource use reported in LEAVO for adverse events occurring in the trial, or published estimates/clinician opinion for those reported in the literature.

Resource for treatment of macular oedema in the non-study eye will be analysed from LEAVO concomitant procedure data and costed using the BNF and NHS reference costs.

4.8 Data beyond the trial period

LEAVO will provide data for 100 weeks (the duration of the trial), but the model will consider a lifetime horizon (until all modelled patients have died). The model could use the trial data beyond the trial period, since change in OCT CST and BCVA is expected to depend on duration of disease, treatment and time since last treatment, or external data sources could be identified from the systematic review. It is important to establish what the expected treatment pathway will be beyond the trial period – whether the same treatment continuation rule would be used until the patient dies, or if the pathway differs. This will require discussion with clinicians, who have suggested that it is reasonable to assume patients who have not had injections for 12 months in LEAVO will not need future treatment, and that patients who do need treatment in year 2 of LEAVO will require fewer injections each year,

to a limit of 5 years. Longer term data, such as the 48 month RETAIN study will be used to inform the assumptions beyond the trial period.

Further follow-up of patients with macular oedema due to RVO will be incorporated into the model in accordance with guidance from the Royal College of Ophthalmologists. This states that follow-up should be every three months for one year in eyes that have significant ischaemia, and every three months for six months in non-ischaemic eyes[14].

4.9 Withdrawals

The model will consider the intention-to-treat (ITT) population, and it is anticipated that some patients will withdraw from LEAVO. Data on withdrawal will be analysed by treatment arm, and the probability of withdrawal will be included in the model. Patients who withdraw will follow long-term natural history data for change in OCT CST/BCVA – this data will be identified from the review. Their Visits to the ophthalmologist will be in accordance with guidance from the Royal College of Ophthalmologists.

5. MODEL SETTINGS

5.1 Discount rates

Costs and QALYs will be discounted at 3.5% per annum, in line with NICE's Guide to the Methods of Technology Appraisal[11] and Guidelines manual[15].

5.2 Time horizon

In the base case analysis, the time horizon will be lifetime (until all patients have died). Scenario analyses will consider shorter time horizons such as 1 year, and the 100 week trial duration.

6. MODEL OUTPUT

As discussed in the HEDMAP (Section 3.3), the model will report costs and QALYs separately for each arm, and calculate ICERs.

7. SOFTWARE

The discrete event simulation model will be built in Simul8, a specialist programming software for simulation modelling. The development of a discrete event simulation in Simul8 is described in Section 4.4 of NICE's Decision Support Unit report on cost-effectiveness modelling using patient-level simulation[16].

8. REFERENCES

1. Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. *Value Health* 2012; **15**(6): 804-11.
2. Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value Health* 2012; **15**(6): 812-20.
3. National Institute for Health and Care Excellence. Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion [TA299]. 2011. https://www.nice.org.uk/Guidance/ta229 (accessed 01 August 2018).
4. National Institute for Health and Care Excellence. Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion [TA283]. 2013. https://www.nice.org.uk/guidance/ta283 (accessed 01 August 2018).
5. National Institute for Health and Care Excellence. Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion [TA305]. 2014. https://www.nice.org.uk/guidance/ta305 (accessed 01 August 2018).
6. Brazier J, Muston D, Konwea H, et al. Evaluating the Relationship Between Visual Acuity and Utilities in Patients With Diabetic Macular Edema Enrolled in Intravitreal Aflibercept Studies. *Invest Ophthalmol Vis Sci* 2017; **58**(11): 4818-25.
7. Claxton L, Hodgson R, Taylor M, Malcolm B, Pulikottil Jacob R. Simulation Modelling in Ophthalmology: Application to Cost Effectiveness of Ranibizumab and Aflibercept for the Treatment of Wet Age-Related Macular Degeneration in the United Kingdom. *Pharmacoeconomics* 2017; **35**(2): 237-48.
8. Karnon J, Stahl J, Brennan A, et al. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. *Value Health* 2012; **15**(6): 821-7.
9. Chatziralli I, Theodossiadis G, Chatzirallis A, Parikakis E, Mitropoulos P, Theodossiadis P. RANIBIZUMAB FOR RETINAL VEIN OCCLUSION: Predictive Factors and Long-Term Outcomes in Real-Life Data. *RETINA* 2018; **38**(3): 559-68.
10. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; **15**(5): 708-15.
11. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013. https://www.nice.org.uk/process/pmg9/chapter/the-reference-case (accessed 09 July 2018).
12. National Institute for Health and Care Excellence. BNF. 2018. https://bnf.nice.org.uk/ (accessed 01 August 2018).
13. NHS Improvement. Reference Costs. 2017. https://improvement.nhs.uk/resources/reference-costs/ (accessed 01 August 2018).
14. The Royal College of Opthalmologists. Retinal Vein Occlusion (RVO) Guidelines,. 2015. https://www.rcophth.ac.uk/wp-content/uploads/2015/07/Retinal-Vein-Occlusion-RVO-Guidelines-July-2015.pdf (accessed 17 September 2018).
15. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. 2017. https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation (accessed 2 October 2018).
16. Davis S SM, Tappenden P, Wailoo A. NICE DSU Technical Support Document 15: cost-effectiveness modelling usisng patient-level simulation. 2014. http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD15_Patient-level_simulation.pdf (accessed 01 August 2018)