
Article:
Thokala, P. orcid.org/0000-0003-4122-2366, Dodd, P. orcid.org/0000-0001-5825-9347, Baalbaki, H. et al. (3 more authors) (2020) Developing Markov models from real-world data: A case study of heart failure modeling using administrative data. Value in Health, 23 (6). pp. 743-750. ISSN 1098-3015

https://doi.org/10.1016/j.jval.2020.02.012

Abstract

Objectives: Markov models, which characterise disease progression as specific health states based on clinical or biological measures. However, these measures are not always collected outside clinical trials. In this paper, an alternative approach is presented that uses real world data to define the health states and to model transitions between them, specific to a local setting to estimate the cost-effectiveness of telemonitoring (TM) versus no TM for heart failure.

Methods: Incidence of hospitalisation for usual care was estimated from hospital episode statistics (HES) data in the UK and converted into a monthly transition matrix with five health states (four states are defined based on the number of hospitalisations in the previous year, and death) to estimate cost-effectiveness of TM in a local UK primary care trust (PCT) using probabilistic sensitivity analysis, from a health care perspective.

Results: Geographical variation in hospitalisation rates were present, which led to different health state transition matrices in different localities. In the PCT that was evaluated, TM accrued mean additional costs of £3,610 and 0.075 additional quality adjusted life years (QALYs) compared to usual care per patient, resulting in a mean incremental cost effectiveness ratio of £48,172/QALY.

Conclusions: The use of administrative data to define health states and transition matrices based on health service events is feasible, and TM was not cost-effective in our analysis. Given the increasing emphasis on using real world evidence, it is likely that these approaches will be used more in the future.

Highlights

- Markov models typically characterise disease progression using health states based on clinical or biological measures. This paper presents an alternative way of characterising Markov models using administrative data (i.e. routinely available data) to define health states based on hospitalisations in the previous year.
- Geographical variation in hospitalisation rates were present, which led to different health state transition matrices in different localities. The cost-effectiveness of telemonitoring for heart failure, based on locality specific administrative data, was estimated as £48,172/QALY.
- This approach is shown to be capable of supporting locality-specific cost-effectiveness analyses using real world data.

Keywords

Administrative data, Markov modelling, Cost-effectiveness, Routine data, Health Technology Assessment (HTA)

Introduction

Heart failure (HF) currently accounts for 1–2% of the annual healthcare budget in most developed countries and is associated with high levels of morbidity and mortality [1]. Telemonitoring (TM) can facilitate early detection of clinically significant changes as well as earlier intervention to re-stabilise the syndrome and prevent emergency admissions [2]. There have been studies of cost-effectiveness of TM compared to usual care for HF, estimated using modelling, to help decision makers assess value for money [3].

A range of modelling techniques have been used [4], but cohort-based Markov models have been the most commonly used methods in health technology assessment (HTA) as they are relatively simple to develop, debug, analyse, and communicate [5]. Markov models are described in terms of the conditions that individuals can be in ("health states"), how they can move between such states ("transitions"), and how likely such moves are ("transition probabilities") within a given time period ("cycle length").

Markov models can be specified in a number of different ways using different choices of state definitions, but biological or clinical measures (such as New York Heart Association [NYHA] classifications for HF) are frequently used. Also, simpler 2 health state models (death – alive) focusing on the number of (re)hospitalizations are often developed. However, measures like NYHA are not always collected outside clinical trials and number of (re)hospitalizations in clinical trials do not correspond to the real world hospitalization rate where there can be important local differences in case-mix, disease progression and clinical practice.

The aim of this paper is to provide a proof of concept case study of using local administrative data to define health states and to model the transitions between them, specific to a given local setting. This is exemplified by the development a Markov model of HF that a) allows classification of HF patients into the different health states by the local decision makers and b)

allows estimation of the transition probabilities from administrative data for their local setting. This approach facilitated the production of results that represent the cost-effectiveness of TM services at the local level, without the necessity of additional data collection.

The next section describes the methods including the data sources and the modelling methodology. In the subsequent section, the results of a case study of TM for HF in a local primary care trust (PCT) are presented. In the discussion section, the key issues in modelling using routine data are highlighted along with recommendations for future researchers who are interested in developing similar models.

Methods

Model structure

Based on the background work conducted to understand how researchers approached modelling HF previously and what information local decision makers would like to see in the modelling framework (see Appendix for more details), the measure of severity used needed to be related to available data on mortality and resource use, and identifiable in routine clinical practice of the local setting. As such, the number of hospitalisations in the previous year were used to define the states in the Markov model to allow easy classification of HF patients into the different states. This structure also includes an important deviation from the previous hospitalisation based models, namely, transitions are not uni-directional; patients can move to health states with lower numbers of hospitalisations. This was considered important by the stakeholders as it captures 'stabilization' of many patients following hospitalisation. The model used a monthly cycle length and life time horizon.

Data analysis

Data

Hospitalisation data for HF patients in England were accessed from national Hospital Episodes Statistics (HES), which is a centralized dataset containing details of all admissions, outpatient appointments and accident and emergency (AE) attendances at NHS hospitals in England. Data were obtained for individuals who suffered at least one hospital admission for heart failure (ICD10 code I50) between March 2005 and March 2010. Mortality data were obtained from the Office for National Statistics with a pseudonymised identifier to allow linkage to HES data. In addition to hospital admissions, records for individuals' AE attendances (which were further disaggregated into HF or OC attendances), GP attendances, and nurse visits were also extracted.

Definition of health states

The health states were based on the number of HF hospital admissions over the past year. Thus, state 0 described a population with no admissions to hospital for the condition over the past year; state 1 described a population with one HF admission in the past year; state 2 described a population with 2 HF admissions in the past year; and state 3 described a population who had been admitted 3 or more times for HF in the past year. Death is represented as state 4.

Identifying individual patient histories

HES data were used to reconstruct individuals' history of hospital use and mortality, and to categorize them into health states at each point of time according to the number of admissions for HF in the preceding year (Figure 1)**Figure** . If an individual is admitted to hospital over the course of a year, their severity state will increase – that is, they transition up the chain of states. If they suffer no further admissions during a year they would be categorized as 0 – that is,

transitions down the chain of states are also possible. Individuals leave the modelled population upon death.

Figure 1 shows how the hospitalisation data are used to estimate the patient's severity states over time. This (hypothetical) patient had hospital admissions at months 6, 20, 23, 25 and 27 respectively. Up until 6 months, the patient is allocated to state '0' i.e. no hospitalisations in the previous year. After 6 months, the patient is in severity state '1' (i.e. one hospitalisation in the previous year) and remains in that state until after 18 months, where the patient goes back to state '0' as it has been more than 12 months since their last hospitalisation. The patient stays in state '0' until month 20, after which they go to state '1'. The patient then moves on to state '2' after month 23 as they had two hospitalisations in the previous year. And, then to state '3' after month 25 as they had three hospitalisations in the previous year. A further hospitalisation in month 27 means they had four hospitalisations in the previous year so the patient is still in state '3'.

Figure 1: Derivation of health states from hospitalisation data for a hypothetical patient

Cohort data

Individual patient data were then combined as cohort data, with the cohort at any time point being defined into different health states as described above. The number of admissions (HF & OC), emergency department attendances (HF & OC), and deaths that occurred in a given severity state were also calculated. Figure 2 shows the data derived from four PCTs accessed through a query run on HES data. The population in each PCT is categorised into states and the number of admissions, emergency department attendances (HF & OC) and deaths that occurred among individuals of a given severity state are presented.

Figure 2: Data from four sample localities in UK by severity state

This figure highlights two key constructs: a) defining disease severity using administrative data and b) need for modelling a given local setting. The frequency of all the outcomes increase with severity state, highlighting the relevance of classification of the severity states based on hospitalisations in the previous year. The figure also shows the variation of hospitalisation, mortality and resource use between the different PCTs, highlighting the need for local models.

Estimating the transition probabilities

Monthly Markov transition matrices were computed using a multi-step process. The hospital admissions data were analysed first to derive estimates of the rates, from which monthly probabilities of transition between states were calculated. The intervention effects (specified in terms of hazard ratios) were applied to the baseline event rates, to estimate the transition matrices for the TM patients. The R code together with hypothetical data can be found in the technical appendix and the reader can follow the steps in the code to operationalising this method, which is described in detail in subsections below.

Calculating the rates

Information on individual patient histories was aggregated to derive dynamics through time. The total number, $n_{a\varepsilon}$, of events of type ε occurring to individuals in a state a, and the total person-time spent in this state, T_a was counted. The ratio of the count and the total person-time gives an estimate of the rate (hazard), $r_{a\varepsilon}$, at which event ε occurs to those in state a:

$$r_{a\varepsilon} = \frac{n_{a\varepsilon}}{T_a}$$

Estimating the transition matrix for usual care

The transitions between states were treated as a continuous-time Markov process and writing $\varepsilon = b$ for the event transition to state b, and with the convention that $r_{ab} = 0$ when $a = b$, the

master equations (Kolmogorov forward equations) determining the probability, $P_a(t)$, of occupying state a at time t can be stated as follows

$$\frac{dP_a}{dt} = \sum_{b=0}^{4} (r_{ba}P_b - r_{ab}P_a).$$

Since the r_{ab} are constant in time, the equation can be solved using the matrix exponential of the transition rate matrix, R

$$R_{ab} = r_{ab} - \sum_{c=0}^{4} r_{bc}\delta_{ab}$$

where δ_{ab} is the Kronecker delta function (1 if $a = b$ and 0 otherwise). This results in estimation of the probabilities as

$$P_a(t) = \sum_{b=0}^{4} (e^{Rt})_{ba} P_b(0)$$

Using this approach, the usual care Markov monthly transition matrix, M was computed numerically in a software package supporting matrix exponentiation as $\mathrm{M} = \exp(R)$. Uncertainty in these rates was included by modelling event counts as following Poisson distributions, using a cycle length of one month (i.e. R is measured in units of events per person per month).

Incorporating effectiveness of interventions using hazard ratios

The effects of TM on reductions in hospitalisations and mortality are included by computing a new transition matrix for TM via exponentiation, using new transition rates r'_{ab}. The hazard ratio for hospitalisation, HR_{hosp}, was applied to the upward state transitions relating to hospitalisation, i.e. states with $a \in \{0,1,2,3\}$ and $a < b$:

$$r'_{ab} = HR_{hosp}.r_{ab}$$

The hazard ratio for death, HR_{mort}, was applied to transitions to the dead state (i.e. state 4):

$$r'_{a4} = HR_{mort}.r_{a4}$$

As such, this captures both the instantaneous direct reduction in mortality rates in each state due to TM, and also the indirect reductions in mortality over time due to slowed progression towards more severe disease. The transition matrices for the TM arm are estimated in the same manner (as for the usual care arm) using matrix exponentiation described in the sub-section earlier.

Evaluation scenario

The methodology outlined above was used to develop a Markov model to compare TM with usual care for a cohort of 2,825 HF patients representative of the case-mix for an anonymous local PCT (named PCT1). The model used a monthly time cycle, a life time horizon (i.e. patients are followed until death) and National Health Service (NHS) health care perspective. Utilities and costs for each health state were based on published sources and primary data (described in more detail in Appendix). Costs and quality adjusted life years (QALYs) were discounted at a rate of 3.5%, in line with the NICE methods guide [9].

Results

Estimating the transition rates

Using the set of reconstructed individual histories for PCT1, the transition rates are estimated using the methods described in section 2 (*Calculating the rates*). The transition rates estimated for PCT1 are provided in Table A1 in the appendix. Within PCT1, it can be seen that not all patients transition from their current state to a state with a higher number of hospitalisations, which lends support to our choice of model structure. The number of admissions and emergency department attendances that occurred among individuals of a given severity state

for PCT1 are shown in Table A1 in the appendix. It can be seen that the rate of events increases with severity state, suggesting that the health states capture disease progression.

Estimating the transition matrix for usual care

Given the transition rates, the transition matrix M was estimated numerically in R software package using methods described in section 2 (Estimating the transition probabilities). The transition matrix for PCT1 is provided in Table 1 below. Uncertainty was included by modelling event counts as following Poisson distributions i.e. we assumed $n_{a\varepsilon} \sim Po(r_{a\varepsilon}.T_a)$, sampled new counts and re-computed rates as $r_{a\varepsilon} = \frac{n_{a\varepsilon}}{T_a}$.

Incorporating effectiveness of telemonitoring

The effect of TM on disease progression (i.e. progression through our severity states based on hospital admission frequency) and mortality was informed based on data from a meta-analysis by Pandor et al [10]. This estimated that medical support during office hours had the following hazard ratios: all-cause mortality of 0.76 [CrI: 0.49-1.18], and hospitalisation of 0.75 [CrI: 0.49-1.1]. We modelled the uncertainty in these intervention effects with log-normal distributions with parameters chosen to match the mode and credible intervals: (μ, σ) = (-0.274, 0.170), (-0.288, 0.151), and (-0.051, 0.159), respectively.

The hazard ratios for mortality and condition-specific hospitalisation were applied to the instantaneous rates of these events derived from the HES data. New transition matrices representing monthly progression between disease states for those on TM were then derived i.e. mortality, disease progression, and hospital admissions on TM were all estimated incorporating these hazard ratios. It should be noted that the hospitalisations occur at a lower rate on TM. However, it is assumed that emergency department attendances for a given severity state are independent of the treatment i.e. whether the cohort is on usual care or TM.

Table 1. Monthly transition matrices for usual care and telemonitoring, and monthly rates for associated events

Markov traces

Figure 3 presents the evolution of the patient cohort of PCT1 (n=2825) through time, on usual care and with TM. The model predicts that over the course of five years, the HF patients on TM have a better prognosis compared to those not on TM.

Figure 3: Case-mix through time with for usual care and telemonitoring.

Cost effectiveness analyses

Costs and QALYs can be estimated by using the information on the number of people in each state over the time horizon (i.e. Markov trace) with costs and utilities of each given state. Appendix 1 presents further details of the case study; the data on costs and utilities associated with each health state are used to estimate the overall costs and QALYs. TM accrued mean additional costs of £3,610 and 0.075 additional quality adjusted life years (QALYs) compared to usual care, resulting in a mean incremental cost effectiveness ratio of £48,172/QALY.

Table 2 presents the costs, consequences and QALY results for 1 year and 5-year time horizon. The cost elements include the A&E and hospital admissions (reported separately for HF and other causes), costs for GP attendances, nurse visits and TM. This allows the decision makers to see where the costs are accrued and where there are potential cost savings. Cost-effectiveness results in the form of an incremental cost-effectiveness ratio (ICER) of TM compared to usual care are also presented. Scatterplot of costs and QALYs estimated from the probabilistic sensitivity analyses are presented in the appendix (see Figure A1), which suggest that the ICER is higher than the threshold of £20,000 per QALY. The cost-effectiveness acceptability curve (see Figure A2) shows that TM is the most cost-effective option at thresholds greater than £50,000 per QALY.

Table 2: Costs, Consequences and QALY results for 1 year and life-time horizon

Discussion

In this paper, we presented an approach that uses routine hospitalisation data to define the states in a Markov model and estimate the transition probabilities for heart failure patients specific to a given local setting. The novel aspect of this approach is the derivation of the transition matrix from administrative data, which requires categorization of the cohort into disease severity states and calculate event rates by severity. Our method was then used to assess the cost-effectiveness of TM, by including the evidence on TM intervention's effectiveness in the form of hazard ratios concerning multiple, competing events (i.e. disease progression and mortality) incorporated into our Markov model.

In the PCT that we evaluated, TM had a mean ICER of £48,172/QALY compared to usual care, suggesting that it is not cost-effective at the threshold of £20,000 per QALY. These analyses can be also performed at other local settings to capture local differences in case-mix, progression and resource use as long as the required data is available on a reasonable number of patients. Many organisations do have administrative datasets or electronic medical records (EMR) that utilise the ICD10 classifications, upon which our analyses are based, and these should be able to adapt the code and methods to their context. The administrative data needs to cover all hospitalisations and outpatient contacts related to the patient cohort. This will be difficult to achieve if patient data are not routinely linked i.e. this type of analyses is not possible for settings that lack this kind of data.

Our framework allowed for the inclusion of uncertainty based on the observed event counts and person-time in each locality. In combination, these features enabled us to generate locality-specific projections of costs, consequences, QALYs, and cost-effectiveness analyses for regionally specified decision problems. This functionality was made freely available as a web

model [11], where the users could log in, select a locality in the UK and perform the analyses for that setting.

However, there are some limitations to the approach used in this paper. Firstly, administrative data needs to be available in order to implement the approach used in this paper. These data may not always be available (e.g., in low resource settings) or forthcoming (e.g. if there are confidentiality issues), in which case this approach cannot be implemented. Also, as highlighted above, the hospitalisation-based Markov modelling approach applies best to chronic diseases where hospitalisation is a useful measure of both effectiveness and disease progression. Each HF hospitalisation is treated as the same in our analysis, independent of intensity or length of stay on the assumption that they average out at the population level. However, this may not be case for all situations and as such, it may not be sensible to use this approach for all conditions and interventions.

The differences in event definitions and clinical practice may mean that measures of effectiveness based on service events (e.g. hospitalisations) are non-transferable between countries or providers. This is less of a problem for physiological or functional health states (e.g. NYHA) which are more independent of clinical behaviours and health system characteristics. If this is the case, then models based on more robust health proxies will be required, together with compatible measures of effectiveness.

In our case study, the treatment effect was estimated from published literature and assumed to be applicable to the usual care arm specific to the local setting. If the treatment effectiveness parameters also need to be estimated from routine data, issues of heterogeneity, lack of reporting or selection bias due to confounding need to be addressed. The randomised controlled trials (RCTs) do not have these same drawbacks associated with observational studies. However, there are methods such as propensity score matching, inverse probability weighting

and instrumental variable methods to tackle issues associated with the use of observational data to inform estimates of treatment effectiveness [12,13].

Populating a hospitalisation-based model with utilities (and costs) may be more difficult as the requisite data are typically reported by patient sub group defined in terms of physiological severity such as NYHA. The costs in the model presented in this paper have been estimated from the resource use associated with each health state (derived from HES data) and the unit costs associated with resource use (derived from published literature). However, the health-related quality of life (HRQoL) values associated with each health state were not available in the HES data and thus, primary data needed to be collected. If such data on costs and HRQoL for the health states are not available from the routine data, the model needs to make assumptions about these parameters based on published literature and/or expert opinion. As with any modelling assumption, the validity of these model parameters needs to be checked with an expert group.

However, this approach has many advantages over traditional Markov models that characterise disease progression by specific states based on clinical/biological measures. Whilst these clinical/biological measures are collected in randomised controlled trials, they are not always collected in the routine clinical practice. As a result, models based on clinical/biological measures are limited in their applicability to several decision-making contexts. In particular, these approaches are not suited for estimating cost effectiveness in settings (e.g. local areas/hospitals) where access to detailed, locally specific information on clinical/biological measures is not routinely available. Using routine data to populate the Markov models such as the hospitalisation-based model presented in this paper overcomes this limitation and allows the users to perform analyses specific to a local setting.

Whilst we have applied the approach to hospitalisation data relating to HF, this approach may also be suitable to be used for other conditions. The main requirements for the measures used to define health states (e.g. by hospitalisation count) are: a) that counts of this event strongly correlate with costs and or outcomes, and adequately capture disease progression; b) that the effectiveness of the intervention can be summarised as a hazard ratio applied to these rates. Based on our work we have identified the seven key steps in the use of administrative data to generate Markov models, which are summarised in Table 3.

Table 3: Recommendations for analysing administrative data to generate Markov models

This use of routine hospitalisation data for populating Markov models can also be generalised to other types of routine data and other modelling techniques. The dataset can be chosen based on type of disease under consideration - for example, registry data can be used to develop breast cancer Markov models [14]. The models need not always be Markov models and the technique that best suits the decision problem can be chosen – for example, statistical techniques such as multi state modelling [15, 16] can be used to incorporate the effect of key risk factors (such as age, gender, comorbidities, etc) or discrete event simulation [17] can be used for modelling based on time to event data from claims databases. These approaches, given they are dependent on routinely available data, allow the consideration of regional variation in the disease progression [18].

This work has identified several advantages and disadvantages associated with the use of administrative data to structure and populate health economic models, and future research should seek to validate such models against more conventionally structured models. Key issues to consider would be the applicability of the approach to other conditions, and the role that regional variation plays in disease progression and cost-effectiveness.

Conclusions

This paper demonstrates the feasibility of using administrative data to define health states and transition matrices based on health service events. In the PCT that we evaluated, TM accrued mean additional costs of £3,610 and 0.075 additional quality adjusted life years (QALYs) compared to usual care per patient, resulting in a mean incremental cost effectiveness ratio of £48,172/QALY, suggesting that it is not cost-effective at the threshold of £20,000 per QALY. This approach has many advantages over conventional Markov modelling approaches, especially in chronic disease areas where hospitalisation is a useful measure of both effectiveness and disease progression. Given the increasing emphasis on using real world evidence, it is likely that these approaches can prove a valuable addition to traditional approaches in cost-effectiveness modelling.

References

1. Riley, J.P. and M.R. Cowie, Telemonitoring in heart failure. Heart, 2009. 95(23): p. 1964-1968.

2. Thokala, P., Baalbaki, H., Brennan, A. et al., Telemonitoring after discharge from hospital with heart failure: cost-effectiveness modelling of alternative service designs. BMJ Open, 2013. 3(9): p. e003250.

3. Roberts, M., Russell LB, Paltiel AD et al., Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2. Med Decis Making, 2012. 32(5): p. 678-89.

4. Brennan, A., Chick S.E., and Davies R. A taxonomy of model structures for economic evaluation of health technologies. Health Econ, 2006. 15(12): p. 1295-310.

5. Caro, J.J., Briggs AH, Siebert U., et al. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. Value Health, 2012. 15(6): p. 796-803.

6. Goehler, A., et al., Decision-analytic models to simulate health outcomes and costs in heart failure: a systematic review. Pharmacoeconomics, 2011. 29(9): p. 753-69.

7. Di Tanna, G. L., Bychenkova, A., O'Neill, F., Wirtz, H. S., Miller, P., Hartaigh, B. Ó., & Globe, G. (2019). Evaluating cost-effectiveness models for pharmacologic interventions in adults with heart failure: a systematic literature review. *PharmacoEconomics*, *37*(3), 359-389.

8. Raphael, C., Briscoe C, Davies J., et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart, 2007. 93(4): p. 476-82.

9. National Institute for Health and Care Excellence - Guide to the methods of technology appraisal 2013 Process and methods Published: 4 April 2013 nice.org.uk/process/pmg9

10. Pandor, A., Thokala P, Gomersall T., et al. Home telemonitoring or structured telephone support programmes after recent discharge in patients with heart failure: systematic review and economic evaluation. Health Technol Assess, 2013. 17(32): p. 1-207, v-vi.

11. ScHARR, H.E.D.S. MALT Online Financial Model. 2016; Available from: https://malt.shef.ac.uk/.

12. Berger, Marc L., Sox H., Wilke RJ., et al. "Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making." Pharmacoepidemiology and drug safety 26.9 (2017): 1033-1039.

13. NICE Decision Support Unit Report - The use of real world data for the estimation of treatment effects in NICE decision making (updated December 2016)

14. Pobiruchin, M., Bochum, S., Martens, U. M., Kieser, M., & Schramm, W. (2016). A method for using real world data in breast cancer modeling. Journal of biomedical informatics, 60, 385-394.

15. Ieva, F., Jackson, C. H., & Sharples, L. D. (2017). Multi-State modelling of repeated hospitalisation and death in patients with Heart Failure: the use of large administrative databases in clinical epidemiology. Statistical methods in medical research, 26(3), 1350-1372.

16. Gasperoni, F., Ieva, F., Barbati, G., Scagnetto, A., Iorio, A., Sinagra, G. and Di Lenarda, A., 2017. Multi-state modelling of heart failure care path: A population-based investigation from Italy. PloS one, 12(6), p.e0179176.

17. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J., 2012. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–4. Value in Health, 15(6), pp.821-7.

18. Bottle, A., Ventura, C.M., Dharmarajan, K., Aylin, P., Ieva, F. and Paganoni, A.M., 2017. Regional variation in hospitalisation and mortality in heart failure: comparison of England and Lombardy using multistate modelling. Health care management science, pp.1-13.

Table 1. Monthly transition matrix for usual care and telemonitoring patients and monthly rates for associated events

		Health state					**Events**			
Usual Care		**0**	**1**	**2**	**3**	**4 (Death)**	**ED_HF**	**ED_OC**	**HA_HF**	**HA_OC**
Health state	0	0.981	0.004	0.000	0.000	0.015	0.007	0.036	0.004	0.055
	1	0.068	0.872	0.017	0.000	0.043	0.016	0.062	0.020	0.124
	2	0.004	0.094	0.777	0.041	0.084	0.032	0.097	0.053	0.178
	3	0.000	0.006	0.095	0.777	0.122	0.055	0.098	0.085	0.274
	4	0.000	0.000	0.000	0.000	1.000	0.000	0.000	0.000	0.000
TM		**0**	**1**	**2**	**3**	**4**	**ED_HF**	**ED_OC**	**HA_HF**	**HA_OC**
Health state	0	0.986	0.003	0.000	0.000	0.011	0.005	0.036	0.003	0.055
	1	0.068	0.885	0.013	0.000	0.033	0.012	0.062	0.015	0.124
	2	0.004	0.096	0.804	0.032	0.065	0.024	0.097	0.040	0.178
	3	0.000	0.006	0.098	0.801	0.094	0.041	0.098	0.064	0.274
	4	0.000	0.000	0.000	0.000	1.000	0.000	0.000	0.000	0.000

Key: ED_HF: Emergency department attendances for heart failure, ED_OC: Emergency department attendances for other causes, A_HF: Hospital admission for heart failure, APC_OC: Hospital admission for other causes, TM: Telemonitoring

Table 2: Costs, Consequences and QALY results for 1 year and life-time horizon

Consequences	**Telemonitoring**	**Usual Care**
1-year time horizon		
HF A&E attendances	273 (264 - 282)	263 (255 - 271)
Other A&E attendances	1,139 (277 - 1,302)	1,211 (1,184 - 1,236)
HF hospitalisations	228 (197 - 253)	225 (218 - 232)
Other hospitalisations	1,571 (1,394 - 1,726)	1,998 (1,959 - 2,038)
GP attendances	7,382 (1,534 - 8,535)	17,601 (8,006 - 23,818)
Nurse home visits	55,223 (23,573 - 71,481)	46,620 (21,855 - 62,813)
Life time horizon		
HF A&E attendances	466 (443 - 490)	426 (410 - 440)
Other A&E attendances	1,999 (487 - 2,267)	2,010 (1,956 - 2,059)
HF hospitalisations	360 (309 - 400)	338 (325 - 350)
Other hospitalisations	2,697 (2,384 - 2,973)	3,251 (3,172 - 3,332)
GP attendances	13,394 (2,768 - 15,541)	30,268 (13,686 - 40,763)
Nurse home visits	100,345 (43,158 - 127,283)	80,156 (37,509 - 107,630)
Costs	**Telemonitoring**	**Usual Care**
1-year time horizon		
HF A&E attendance costs	£39,628 (£38,326 - £40,944)	£38,164 (£37,004 - £39,317)
Other A&E attendance costs	£165,123 (£40,161 - £188,756)	£175,569 (£171,691 - £179,264)
HF hospitalisation costs	£381,999 (£79,381 - £441,692)	£910,833 (£414,317 - £1,232,565)
Other hospitalisation costs	£643,835 (£556,568 - £715,221)	£636,688 (£616,650 - £656,409)
GP attendance costs	£2,702,212 (£2,397,726 - £2,968,452)	£3,436,607 (£3,370,273 - £3,506,090)
Nurse home visit costs	£2,360,768 (£1,007,732 - £3,055,829)	£1,993,021 (£934,312 - £2,685,240)
Telemonitoring costs	£6,101,729 (£5,955,135 - £6,246,069)	0 (0 - 0)

Life time horizon		
HF A&E attendance costs	£67,607 (£64,205 - £71,110)	£61,717 (£59,466 - £63,872)
Other A&E attendance costs	£289,879 (£70,634 - £328,778)	£291,386 (£283,656 - £298,545)
HF hospitalisation costs	£693,144 (£143,265 - £804,271)	£1,566,354 (£708,241 - £2,109,494)
Other hospitalisation costs	£1,016,594 (£874,140 - £1,129,641)	£954,603 (£918,178 - £988,052)
GP attendance costs	£4,638,483 (£4,099,914 - £5,112,923)	£5,591,644 (£5,455,328 - £5,730,187)
Nurse home visit costs	£4,289,756 (£1,844,992 - £5,441,343)	£3,426,679 (£1,603,529 - £4,601,171)
Telemonitoring costs	£11,096,584 (£10,629,586 - £11,575,420)	0 (0 - 0)
Cost effectiveness results		
QALYs	2,548 (1,853 - 3,318)	2,336 (1,681 - 3,028)
Costs	£22,092,046 (£19,375,262 - £23,727,195)	£11,892,384 (£9,869,820 - £13,313,259)
ICER	£48,172/QALY	

Table 3: Recommendations for analysing administrative data to generate Markov models

Step	Description
Choose model states	Identify event that is related to effectiveness data, and which will form the basis of the Markov health states.
Specify model structure	Identify data variables relating to exposure to intervention, risk-stratification and other covariates that are related to costs and utilities.
Gather patient data	Acquire individual patient linked data over a time period which captures medium-to-long term disease progression.
Map individual patient histories	Generate patient histories across time.
Allocate patients to different states	Identify health states base on event counts, considering number of patients within each health state, and difference in costs and utilities between states.
Data analysis	Generate baseline transition matrix.
Apply effectiveness parameters	Apply hazard ratios for the intervention to the hazard matrix.

Appendix 1: Conceptual modelling

Background work was conducted to understand how researchers approached modelling HF previously and what information local decision makers would like to see in the modelling framework. As such, a targeted literature search was conducted to understand the state of the art of modelling in HF and an elicitation task was performed to understand the modelling requirements from the stakeholders.

Reviews of previous HF models

A systematic literature review by Goehler et al [6], which described the different decision analytic modelling approaches used to estimate the cost effectiveness of health technologies for HF, identified 34 modelling studies with the majority of them Markov models (n=27) along with three discrete-event simulation models and four mathematical equation sets models. Of the Markov models, seven studies used the NYHA functional classification system to model disease progression, ten studies applied a two state Markov model consisting of an 'alive' and a 'death' state whilst six studies applied a Markov model comprising hospitalisation states and a death state. The remaining four studies used combinations of the above or alternative clinical classification systems.

A more recent review by Di Tanna et al [7], evaluating cost-effectiveness models for pharmacologic interventions in adults with HF, also reported similar findings. They identified 64 publications with the majority of them Markov models (n=28) and trial-based evaluations (n=22), along with six discrete-event simulation models, seven partitioned survival models and one decision-tree model. Of the Markov models, seven studies focused on a two-state Markov approach based around the "alive" and "dead" states, five studies used the NYHA functional classification system to model disease progression whilst seven studies applied a Markov model comprising hospitalisation states and a death state (with the rest modelling HF alongside other cardiovascular events).

Most models identified in these reviews were two state models (i.e. 'alive' and 'death' states), but they do not provide enough granularity to model the progression in disease severity. As seen above, and highlighted in the original reviews, most of the other models depend on NYHA class or number of hospitalisations as a proxy for disease severity and progression. These hospitalisation models only allowed maintenance of the same health state or progression to a higher number of hospitalisations (with higher costs and lower utilities).

Elicitation of model requirements

In order to identify the requirements for the model, a formal qualitative elicitation exercise was also conducted. Twenty-nine participants from four National Health Service (NHS) Trusts and eight commercial companies involved with manufacturing or supporting TM devices in the UK took part in the semi-structured, face-to-face and telephone interviews. The key findings from these interviews clearly demonstrated that functional classification systems (such as NYHA) are rarely used in routine practice and a requirement for the model to be capable of using locally specific data was highlighted. In particular, the model parameters needed to capture differences in burden of disease, case mix, hospitalisation rates and mortality.

Issues in choosing the model structure

Given the need to model disease severity, the two state models (i.e. 'alive' and 'death' states) are excluded as they do not provide enough granularity on disease severity. As such, the choice of model structure came down to either using NYHA classes or hospitalisations. The pros and cons of these approaches are briefly described below.

The NYHA classification system is a clinical assessment tool that rates, on a four-point scale, patients' heart failure according to the severity of their symptoms and can be used for measuring disease progression. NYHA classes are appealing from a modelling perspective as there are a number of studies that link the different NYHA classes to resource use and quality of life

(QoL). However, it is suggested that the NYHA classification is subject to some limitations as there is no consistent method for assessing NYHA class [8]. More importantly, whilst NYHA classes are usually assessed in clinical trials, they are not so common in routine clinical practice i.e. the patients are not always assessed using NYHA. This makes the estimation of cost-effectiveness of interventions in real clinical practice using NYHA based models difficult.

Hospitalisations, on the other hand, can be easily captured from administrative datasets, making them more readily available to local decision makers. In chronic conditions such as HF, where multiple hospitalisations are common, this characterisation allows multiple health states to be defined by frequency of hospitalisations. Furthermore, hospitalisations could be considered an objective measure, although caution needs to be taken to ensure that there is consistency in definition. For instance, HF-related hospitalisations should be separated from other cause (OC) hospitalisations i.e. hospitalisations due to other comorbidities.

Appendix 2: Cost-effectiveness of telemonitoring compared to usual care in PCT1

The methodology outlined in the manuscript was used to develop a Markov model to compare telemonitoring with usual care for a cohort of 2,825 HF patients representative of the case-mix for PCT 1. Using the set of reconstructed individual histories, the transition rates are estimated using the methods described in section 2 (*Calculating the rates*) as shown in Table A1 below.

Table A1: Transition rates between health states and associated event rates

		Health state					**Events**			
		0	**1**	**2**	**3**	**4 (Death)**	**ED_HF**	**ED_OC**	**HA_HF**	**HA_OC**

Health state	0	0.000	0.004	0.000	0.000	0.015	0.007	0.036	0.004	0.055
	1	0.073	0.000	0.021	0.000	0.045	0.016	0.062	0.020	0.124
	2	0.000	0.114	0.000	0.053	0.090	0.032	0.097	0.053	0.178
	3	0.000	0.000	0.123	0.000	0.133	0.055	0.098	0.085	0.274
	4	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Key: ED_HF: Emergency department attendances for heart failure, ED_OC: Emergency department attendances for other causes, A_HF: Hospital admission for heart failure, A_OC: Hospital admission for other causes

Given the transition rates, the transition matrices were estimated using methods described in section 2 (Estimating the transition probabilities). The transition matrices (presented in Table 2) are used to estimate the number of people in each state over the whole time horizon (i.e. Markov trace presented in Figure 3), and the costs and utilities can be attributed to each given state to estimate the overall costs and QALYs.

The next sub-section describes the costs and quality of life data used. Then, the costs and QALYs estimated for usual care (UC) and telemonitoring (TM) are presented before presenting the cost-effectiveness results in the form of an incremental cost-effectiveness ratio (ICER) of TM compared to usual care UC (see Table A1). The scatterplot of the costs and QALYs based on the probabilistic sensitivity analysis results are presented in Figure A1.

Costs and Utilities

Cost data was sourced from the HTA report by Pandor et al [9], and inflated to current 2018 values using the health services index reported by Personal Social Services Research Unit. We used the following unit costs: £145 for an A&E visit (regardless of cause); £2,826 for a hospitalisation for HF; and £1,720 for a hospitalisation due to another cause and the cost of TM was £200 per month.

Quality of life was modelled by health state, based on EQ5D scores elicited from HF patients in the participating NHS sites in the broader research project [10]. Participants were recruited via a postal survey between mid July 2013 and September 2013. The patient survey was sent to 713 patients in 6 community services in England; there were 261 responses. Patients were being treated in the community for chronic diseases, with these primarily being heart and/or respiratory conditions. In addition to the EQ-5D, the questionnaire asked about their use of telehealth and wider health services. This information was then used to classify patients into each of the model's health states (in terms of frequency of hospitalisation in the last year) and generate a mean EQ-5D score. Missing data meant that EQ-5D scores could be produced for 254 patients. The mean EQ-5D scores were 0.588, 0.523, 0.457, and 0.392, for the 0, 1, 2, and 2+ health states, respectively. Quality of life as a function of health state was taken to follow a linear trend, with a variation in the intercept modelled as a normal fitted to the regression residuals. The intercept, slope and noise were $(a, b, \sigma) = (0.589, -0.065, 0.23)$.

Given the EQ5D questionnaire is equally likely to be administered after a recent hospitalisation as it is to any time in over the past year (the time period used to define the model health states), the disutility of the hospitalisation is already included in the mean utilities estimated for each of the health states. As such a separate disutility during times of hospitalisation was not included the model.

The inflow into the TM-eligible cohort was calculated from HES data that a mean of 64 new people per month were entering the cohort (i.e. experiencing a first hospital admission for HF). We compared a policy of permanent deployment of TM for all those with HF, vs no TM over a life-time horizon, with a discount rate of 3.5% per year.

Cost-effectiveness results

Scatterplot of costs and QALYs estimated from the probabilistic sensitivity analyses are presented in Figure A1, which suggest that the ICER is higher than the threshold of £20,000 per QALY. The cost-effectiveness acceptability curve (see Figure A2) shows that TM is the most cost-effective option at thresholds greater than £50,000 per QALY.

Figure A1: Cost-effectiveness plane for PCT1*

* Red line indicates a cost-effectiveness threshold of £20,000 per QALY

Figure A2: Cost-effectiveness acceptability curve for PCT1