Actuarial approaches to modelling and mitigating financial uncertainty in recommending new drugs and health technologies

June 2016

An illustrative case study of hepatitis C antiviral therapies recently approved by NICE

Prepared by:
Joanne Buckle, FIA
Principal and Consulting Actuary

Didier Serre
Actuarial Associate

11 Old Jewry
London, EC2R 8DU, UK

Tel +44 (0)20 7847 1500
Fax +44 (0)20 7847 1501

uk.milliman.com

ACKNOWLEDGMENT

We would like to thank the National Institute for Health and Care Excellence (NICE) for providing assistance and guidance in this project, and comments on preliminary draft versions. We also wish to thank Dr. Helen Blumen, MD, MBA for clinical guidance and Jill Van Den Bos, ASA, MAAA for technical peer review.

This white paper was funded entirely by Milliman.

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I. EXECUTIVE SUMMARY

Our analysis uses actuarial principles to illustrate a theoretical framework for handling uncertainty and variability in modelling the financial impact of recommending new drugs and health technologies for routine commissioning in England. Recognising the strong influence of the mean incremental cost-effectiveness ratio (ICER) in current appraisals and reimbursement decision-making, we consider some alternative approaches that build on the current analytical process of the National Institute for Health and Care Excellence (NICE), considering risk and uncertainty in ultimate decision-making.

Using the evidence from manufacturer submissions to NICE for treating chronic hepatitis C, we replicate, within reasonability, the Markov disease state transition model for three of the treatment regimens for ledipasvir-sofosbuvir, all recently recommended for reimbursement by the English National Health Service (NHS), and use that as a basis to illustrate an actuarial theoretical framework for handling uncertainty. We identify key assumptions from one-way sensitivity analysis and model them stochastically.[1] As the tolerance level for risk varies across the methodological approaches that we explore, only one scenario results in an ICER above the current implicit threshold for recommendation, as illustrated with cost-effectiveness acceptability curves. Through simulation, we derive a distribution of ICER points for each treatment regimen and rely on key statistics and other measures of variability to develop a basis for risk sharing. The risk mitigation strategies presented are designed to reduce uncertainty around the ICER and the budget impact. Particularly, we demonstrate examples of possible one-way and two-way risk sharing arrangements developed around the assumptions that have the greatest effect on the potential financial impact, split by population, treatment, and patient-specific levels.

We further propose an actuarial cost model as a robust tool to monitor the resource implications and overall budget impact of new NICE guidance. This model, designed as a proof of concept, has built-in capacity to integrate revised assumptions reflecting actual experience against projections, provide key metrics against which to measure performance, and present various scenarios over time and for specified subpopulations. It also allocates costs and gains to the various health and social care payers within the NHS, both at a population level and specific to a treatment population.

Overall, this paper communicates a framework for assessing uncertainty in the ICER in a way that the multidisciplinary stakeholders can understand. It ultimately relies on stochastic modelling and simulation. It also demonstrates how key model assumptions can be derived empirically using 'real-world' data of medical services utilisation to inform the NICE guidance review process.

[1] In a health economics context, the term "probabilistic" may also be used interchangeably to refer to "stochastic".

II. BACKGROUND

The appraisal of new medical technologies is central to any value-based health system that seeks to maximise health benefits given a fixed budget. Since 1999, NICE is responsible for producing national guidance on new drugs and devices in England through its technology appraisal process and clinical guidelines, using a well-defined and broadly accepted academic methodology.[2] While there is no explicit cost-effectiveness threshold for acceptance, in practice it is estimated to lie somewhere between £20,000 and £30,000 per quality-adjusted life-year (QALY), with very few technologies recommended above £30,000/QALY. Another of NICE's responsibilities is to strike a balance between timely access to innovative technologies and the relative cost-effectiveness of different treatments. To this extent, NICE adopts the perspective of the NHS as a third-party payer, yet does not typically take into account other direct costs (social care) or indirect costs (sickness absence, or patient opportunity costs for instance).

Currently, the models produced by the manufacturer form the basis to evaluate the clinical and cost-effectiveness evidence used by the NICE Appraisal Committee to inform the decision-making process. The onus is on the manufacturer to provide clinical and cost-effectiveness evidence that justifies premium pricing of the technology. In recent years, England, like many other countries in Europe, has witnessed an increase in the number of submissions for new drugs and technologies with no therapeutic alternative. These received regulatory approval, and sometimes even reimbursement approval, on the basis of initially very promising evidence from mature Phase II clinical data.[3]

The recent changes to the regulatory system and associated expected increases in the number of submissions based on less than perfect information are likely to require ongoing monitoring of evidence and mitigation strategies which limit the financial risk for the NHS.

In parallel, manufacturers can also apply for Patient Access Schemes (PAS) and other managed entry agreements to secure access to high-cost drugs for patients. These usually involve confidential pricing arrangements, and aim to improve the cost-effectiveness of new technologies. Recent changes to the regulatory system and resulting expected increases in the number of submissions based on less than perfect information are likely to require ongoing monitoring of evidence. Risk mitigation strategies can offer to limit financial risks to the NHS (and potentially social care budgets, as they become more interlinked with healthcare budgets).

The potential NHS budget impact of adopting a new technology is not considered explicitly in the final Appraisal Committee's decision, although we recognise that it is considered implicitly. However, more importantly, the explicit determination of the budget impact if key assumptions that affect the financials turn out to be incorrect is not considered within a consistent framework that highlights critical financial risks. Developing robust mechanisms for mitigating and monitoring financial risks and uncertainties around outcome measures can therefore prove essential to whether or not a technology actually meets cost-effectiveness criteria when in use.

While recognising that the actuarial contribution to medical and technology appraisals has historically been limited, there exist nevertheless some opportunities for us to explore alternative methodological approaches and perspectives. Precisely, this report will aim to illustrate some applications of actuarial techniques in handling uncertainty and projecting future cost implications in a context of health technology appraisals.

[2] NICE (April 2013). Guide to the methods of technology appraisal 2013. Retrieved March 18, 2016, from https://www.nice.org.uk/article/pmg9/chapter/foreword.

[3] Two common examples are the *Early Access to Medicines Scheme*, which allows access to drugs to patients before securing a full licence, and adaptive licensing, which initially grants authorisation to a small, well defined group of patients with the possibility to extend its use to wider groups.

III. THEORETICAL FRAMEWORK

CONSIDERATIONS RELEVANT TO THE CURRENT NICE APPRAISAL PROCESS

One of NICE's ongoing challenges includes modelling and quantifying uncertainty around the clinical and cost-effectiveness of technologies in a way that is both meaningful to the various stakeholders and commensurate with the expected risk/benefit ratio. Where the expedited regulatory approval process described previously is used to promote the preliminary adoption of potentially very effective drugs, it can nevertheless be subject to high levels of uncertainty around long-term outcomes such as survival and side effects, and around their associated costs. Note that these estimates are usually extrapolated from clinical trial data with low sample size and projected forward at a very early stage of the drug development. For treatments likely to offer a cure, for instance, the levels of financial and clinical uncertainty can be quite considerable.

In addition, head-to-head comparisons are rarely carried out in clinical trials, thus relying on naïve indirect comparison to assess the incremental cost-effectiveness of a technology or drug relative to a comparator. Finally, despite NICE's strongly stated preference for stochastic modelling in estimating the ICER, many drug and technology manufacturers prefer to present their health technology assessment (HTA) submission, and any modifications to it, using deterministic scenario testing, which is due to the computationally demanding nature of the probabilistic model. The deterministic approach precludes attributing probabilities to the economic and outcome metrics and analysing the distribution of the ICER. Given the computing power now available, this argument becomes increasingly invalid.

One approach we could take is to discard the use of the mean ICER and instead dictate that the ICER at a higher percentile must be below a specified threshold.

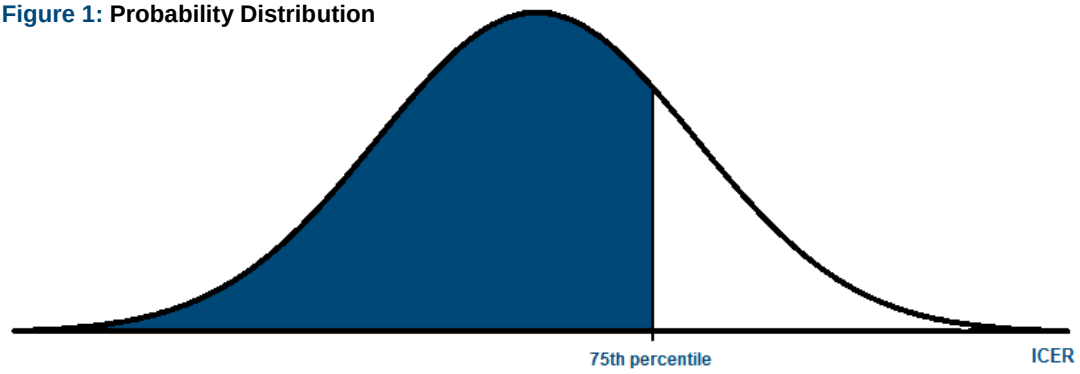
Other factors, such as the strength of supporting evidence, the robustness of the model, and the plausibility of inputs, are also included into the final recommendation's considerations, but they are not considered with an objective framework in the same way as the mean ICER. Judgements about the cost-effectiveness of new technologies are strongly influenced by a static central estimate as the most plausible ICER. In this context, we consider some alternative approaches towards handling uncertainty to support NICE's decision-making process. All require assigning probability distributions to cost and effectiveness metrics and focus on shielding the NHS budget from downside risk.[4] It is important to emphasise that, whatever the approach, consistency of methodological approach and application remains critical to ensuring comparability across appraisals.

PROPOSED APPROACHES: KEY ELEMENTS

Scenario 1: Using a higher percentile ICER than the mean

One approach we could take is to discard the use of the mean ICER and instead dictate that the ICER at a higher percentile must be below a specified threshold. Under this scenario, the mean as a measure of central tendency is no longer used to inform reimbursement decisions as we ultimately move towards a more one-sided measurement. The choice of percentile is a matter for public policy discussion rather than actuarial science, but for the purposes of illustration, we used the 75% percentile (Figure 1), because this is a widely used and well-understood percentile. It is also referred

Figure 1: Probability Distribution



[4] Downside risk generally refers to the overall risk that the financial impact to payers for providing care is greater than initially modelled.

to as the upper quartile in probability distributions. This approach considerably reduces the amount of uncertainty around the cost-effectiveness of the technology, because it leads to only recommending those drugs and technologies for which at least three-quarters of the modelled ICER distribution falls below a predetermined threshold. This approach will generally result in a higher rejection level of new technology appraisals relative to the current NICE method, unless the threshold for acceptance is also increased.

One of the applications of this approach can be illustrated with the following example. Using two hypothetical mean ICERs of £15,000/QALY and £17,500/QALY, and a 75th percentile of £21,000/QALY and £19,000/QALY respectively, we notice that the second treatment presented, though associated with a higher mean ICER, represents a potentially smaller financial risk to the NHS than its counterpart, which is due to the lower variability in the cost per QALY. It is possible, though not always, that this treatment offers greater value for money for more patients than the treatment showing the lowest mean ICER. Understandably, this variability cannot be observed by simply looking at the mean ICER and requires a range of ICERs to be produced using a stochastic method.

The coefficient of variation provides an indication of the dispersion of the distribution of the ICER and allows comparison of distributions with different means.

As we commented above, the choice of the 75% is arbitrary and depends on the NHS's appetite for risk—a higher percentile of say 90% or even 95% would limit downside risk further, but would have the consequence that few highly uncertain technologies would ever be recommended. As uncertainty is often linked with small patient populations, this approach is potentially discriminatory against patients with rare diseases.

Scenario 2: Using a combination of median and a measure of variability

One other approach is to consider the median of the distribution in combination with a standardised measure of variability to inform the decision-making process. Similar to the current NICE methodology, the median ICER would be compared against a predefined threshold. This measure, which can take many forms, is defined here for illustrative purposes as the ratio of the standard deviation over the mean ICER, also commonly known as the coefficient of variation or relative standard deviation. It provides an indication of the dispersion of the distribution of the ICER and allows comparison of distributions with different means. For instance, in an insurance context, this ratio can be used to classify treatment costs as low, medium, or high risk, in terms of 1) how expensive they are (looking at average cost only), and 2) how variable that cost is likely to be. While a high average cost and a high coefficient of variation is considered high risk, treatments with high average cost, yet showing a low coefficient of variation, are deemed low or medium risk because, although the cost is high, it is more predictable.

$$\textit{Measure of variability} = \textit{Coefficient of variation} = \frac{\sigma}{\mu} \quad \textit{(for illustrative purposes)}$$

While the standardised measures for two or more technologies can be assessed relative to one another, another application includes comparing them against a fixed value. Generally, this value is industry-specific and can be adjusted up or down in accordance with the prespecified tolerance level. Once it is set, consistency of use is fundamental. Note that lowering this threshold value will impose stricter acceptance levels of variation in outcomes for a given technology (smaller variation allowed per one unit of the mean), which should result in higher rejection rates. Alternatively, when the measure of variability is above the fixed threshold value, recommending a new technology may be tied to risk sharing agreements being implemented to limit financial downside risk. One of the objectives of these arrangements is to bring the coefficient of variation within the mandated bounds, seen in Figure 2.

Scenario 3: Using a combination of mean and a measure of variability

In line with the current NICE framework, we present a variation to Scenario 2, which builds on the current methodology of relying on the mean ICER. As two technology appraisals with the same mean may not necessarily represent the same degree of risk to payers (Figure 3), we also incorporate a measure of variability in this approach and select the coefficient of variation for illustrative purposes. Of the three options presented here, this approach is the most compatible with the current NICE methodology; however, it represents a more stringent decision process relative to the one currently in place, as the additional condition to be met (i.e., measure of variability to be within bounds) is likely to reduce the number of technologies that are recommended. This

consequence can nevertheless be addressed by recommending a drug for routine commissioning provided that risk mitigation is put in place. We explore this in more detail in Section V.

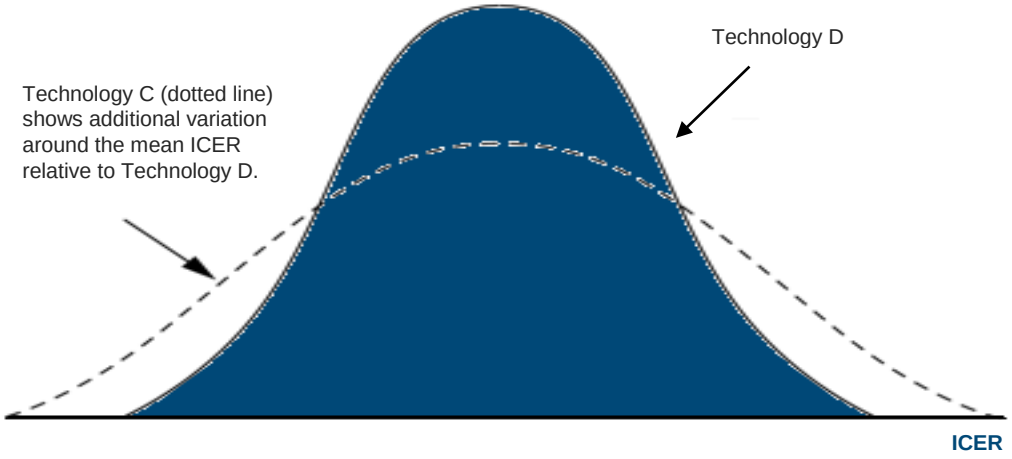
Figure 2: Measure of Variability, Examples

Derivation of the coefficient of variation	Value for comparison	Interpretation
Technology A μ_A = £18,000/QALY σ_A =£10,000/QALY $\frac{\sigma}{\mu} = \frac{£10{,}000/QALY}{£18{,}000/QALY} = 0.556$	**Technology B** μ_B = £14,000/QALY σ_B =£9,000/QALY $\frac{\sigma}{\mu} = \frac{£9{,}000/QALY}{£14{,}000/QALY} = 0.643$	The standard deviation of the ICER for Technology B is smaller than for Technology A, yet the coefficient of variation of Technology B shows the ICER is more variable compared with Technology A after adjusting for differences in the mean.
Technology B μ_B = £14,000/QALY σ_B =£9,000/QALY $\frac{\sigma}{\mu} = \frac{£9{,}000/QALY}{£14{,}000/QALY} = 0.643$	**Fixed threshold value** = 0.5 *This is set as 0.5 for illustrative purposes and will reflect the level of risk that the organisation is willing to take. A decrease in the value results in stricter approval rules.*	**No risk sharing** The coefficient of variation of Technology B is above the threshold value set by the organisation (0.643 > 0.5), resulting in the rejection of the technology if applied as a blunt instrument.
		With risk sharing The coefficient of variation of Technology B (0.643) is above the threshold value of 0.5. Under a risk sharing agreement, the standard deviation decreases as uncertainty in the ICER is reduced, however movements in the mean will depend on the way risk sharing is designed.* Ultimately, the ratio of the standard deviation to the mean will be within the fixed threshold value.

* Risk sharing can be one-way or two-way. One-way risk sharing generally is designed to protect the healthcare payer against adverse deviation; therefore reduction in variability is one-sided, and the mean is expected to decrease. Conversely, in two-way risk sharing, both the manufacturer and healthcare payer share in parts of the risk. Any reduction in the standard deviation therefore occurs across both sides of the mean.

Risk sharing agreements can be suggested to limit financial downside risk to payers and bring the measure of variability within the mandated threshold value.

Figure 3: Variability Around the Mean



All of the options have benefits and disadvantages, summarised in Figure 4. Our role as actuaries is not to recommend one option over another, or recommend thresholds, but rather to illustrate the potential financial and other consequences of each approach, which in turn suggests the potential risk mitigation strategies available to the NHS.

Two technology appraisals with the same mean may not necessarily represent the same degree of risk to payers; a measure of variability can help highlight the differences in risk and ensure that appropriate mitigation measures are considered.

Figure 4: Summary of Proposed Methodological Approaches

Factors to consider	75th ICER percentile	Median ICER+ measure of variability	Mean ICER+ measure of variability
	Scenario 1	**Scenario 2**	**Scenario 3**
Rejection rate of new health technology	Likely to be higher than current method.*	Depending on the appraisal, the median may be lower than the mean, resulting in a lower decision criterion. However, the measure of variability is likely to increase the rejection rate.*	Same or higher; magnitude of change will ultimately depend on the value of the measure of variability.*
Compatibility with current NICE approach	Likely to require changes to current methodology.	Likely to require changes to current methodology.	Builds on the mean ICER used currently.
Required use of probabilistic sensitivity analysis (PSA)	Yes. Distribution of ICER is required.**	Yes. Distribution of ICER is required.**	Yes. Distribution of ICER is required.**
Combined use with risk sharing	Yes.	Yes. The measure of variability can be used to inform the magnitude of the risk sharing.	Yes. The measure of variability can be used to inform the magnitude of the risk sharing.

* Assuming the same threshold for acceptance used currently is applied to all three approaches presented.

** The distribution of the ICER could in principle be inferred from deterministic modelling using various scenarios. However, generally stochastic modelling is required.

PARAMETRISING MODELS WITH EMPIRICAL DATA

Submissions to NICE typically rely on assumptions derived from patient studies during clinical trials, which are usually based on small sample sizes. In addition, cost assumptions are often several years out of date and require the use of the Hospital and Community Price and Pay Index to standardise costs to current levels. While the principles underlying this approach are clear, it nevertheless represents an important source of uncertainty as it implicitly assumes that health state costs have steadily increased over time and that no changes in utilisation patterns, mix of resource usage, or schedule of care has occurred. In fact, rarely do the models make use of large (existing) empirical databases to derive patient costs and transition probabilities to parametrise the underlying Markov model. This is partly because of a lack of access to databases such as the HES and SUS[5] data at a national level, but also because of the difficulty of linking data from primary care and other care settings in England. However, if data do not need to be linked at a patient-level, there are more possibilities for deriving resource estimates for specific clinical populations.

Empirical population-level assumptions such as annual transition probabilities and health state costs can offer alternatives to data inputs from clinical studies usually characterised by small patient populations.

One of the key features of an approach that is consistent with actuarial techniques would be to carry out much larger observational studies to determine costs and resource use in each health state, and derive transition probabilities. When granular information such as medical services utilisation and costs is available, it is desirable to model the cost distribution of specific population groups for each of the various health states. While recognising that this approach may require some additional resources, it is likely to provide more accurate estimates of mean transition probabilities and costs and the likely variation in assumptions, leading to a greater appreciation of financial uncertainty and mitigation. Even apparently modest differences between estimates from the current and proposed methods can become significant at a population level. In an insurance setting, parametrising the cost distribution would typically be done using 'real-world' data pulled from the 'claims' database of medical resource utilisation, mostly through a retrospective cohort study. Using the definition for stages of a particular disease based on International Classification of Diseases (ICD) diagnosis coding and diagnosis codes found in large data medical bases, we can calculate the annual costs by stage of disease. Additional filters can also be used to identify patients currently undergoing treatment (using drug codes for oral treatments for instance) from patients off treatment. Last, we would fit the cost information to an appropriate statistical distribution to simulate disease costs as traditionally performed in health economic evaluations.

Equally, empirical population-level annual transition probabilities can also be derived through a longitudinal study of claims data. This is relatively simple to produce as it again relies on analysing diagnosis codes of each patient from one year to the next to establish the transition to more severe stages of the disease. When disease prevalence is relatively small, these probabilities can be estimated using data from across the country rather than be CCG[6]-specific. Ultimately this provides 'real-world' data on disease progression and, as the data is typically regularly collected, a mechanism to monitor against initial assumptions on an ongoing basis.

As an example, the Institute and Faculty of Actuaries in the UK funded earlier this year a team of researchers at the University of East Anglia to develop a model predicting individuals' longevity based on risk factors such as diseases and lifestyle.[7] This four-year project aims at understanding the impact of various diseases and conditions, but also preventive treatments, on life expectancy. More importantly, this research highlights the potential of aggregating population-level health data sets collected over the long term from healthcare providers to improve health outcomes. This may represent a way of addressing some of the shortcomings associated with clinical trial studies, notably with respect to the small patient populations and relatively short study time frame.

[5] Hospital Episode Statistics (HES) and Secondary Uses Service (SUS).

[6] Clinical commissioning groups (CCG) are responsible for the local delivery of NHS care services in England.

[7] Institute and Faculty of Actuaries. Use of Big Health and Actuarial Data for Understanding Longevity and Morbidity Risks. Retrieved May 1, 2016, from https://www.actuaries.org.uk/learn-and-develop/research-and-knowledge/arc-actuarial-research-centre/research-programmes/use-big-health-and-actuarial-data-understanding-longevity-and-morbidity-risks.

IV. SIMULATION RESULTS AND RECOMMENDATION

To illustrate the various theoretical approaches, we rely on three treatment regimens from the recently recommended hepatitis C drug ledipasvir-sofosbuvir as a case study. For each of these regimens, we replicate a time-dependent Markov model using the evidence from the manufacturer submission to NICE. We also model uncertainty around key assumptions, which are presented here but described in more detail in Appendix A. Deterministic scenario testing illustrated that the ICER was particularly sensitive to changes in the transition probability from non-cirrhotic to cirrhotic stage, to the discount rate applied to both costs and outcomes, and to the disease health state costs for non-cirrhotic patients, and therefore we assigned each of these a probability distribution to model stochastically.

The treatment arm consists of ledipasvir-sofosbuvir; the control arm does not have any treatment assigned. In total, we simulate 1,000 runs for each of the treatment regimens below.

- **Treatment 1**: Patients without cirrhosis; treatment naïve; eight-week treatment.
- **Treatment 2**: Patients without cirrhosis; treatment experienced; 12-week treatment.
- **Treatment 3**: Patients with cirrhosis; treatment naïve; 12-week treatment.

We summarise the simulation results for each of the three exploratory methods presented previously, as well as the 90th percentile and the percentiles corresponding to a threshold value of £20,000/QALY and £30,000/QALY, seen in Figures 5 and 6. The latter is also equivalent to the probability of being cost-effective relative to the thresholds for acceptance. We also plot the distribution of ICERs on cost-effectiveness acceptability curves[8] to illustrate the results of the probabilistic sensitivity analysis (PSA) because this is a common way of communicating uncertainty in economic evaluations. We observe from simulating each of the three selected model assumptions separately that the transition probability from no cirrhosis to cirrhosis is responsible for the largest increase in the ICER and therefore we represent the results separately on the graph to better understand its impact, seen in Figure 7. Understandably this only applies to Treatments 1 and 2 as the population for Treatment 3 only includes cirrhotic patients.

Not all treatments are shown to be cost-effective relative to a threshold of £20,000/QALY when the 75th percentile ICER is used as the rule for recommending new treatments.

Figure 5: Summary Statistics of Proposed Approaches

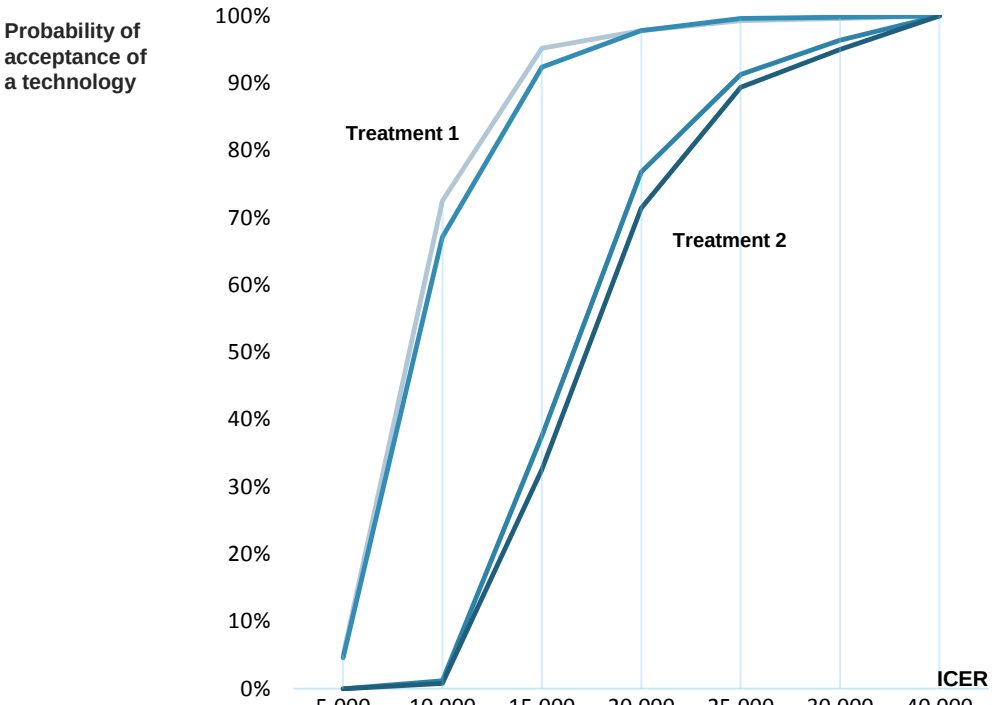
Treatment regimens	Deterministic mean ICER (£/QALY)	Stochastic mean ICER (£/QALY)	Median ICER (£/QALY)	75th percentile (£/QALY)	90th percentile (£/QALY)
Treatment 1	7,978	9,387	8,480	11,050	13,794
Treatment 2	16,089	18,415	16,875	20,722	25,504
Treatment 3	4,464	4,774	4,752	5,127	5,434

Figure 6: Additional Statistics

Treatment regimens	Standard deviation ICER (£/QALY)	Measure of variability ($\frac{\sigma}{\mu}$)	Percentile corresponding to £20,000/QALY	Percentile corresponding to £30,000/QALY
Treatment 1	3,759	0.400	97.7	99.7
Treatment 2	7,172	0.389	71.3	94.9
Treatment 3	524	0.110	100	100

[8] Note that on the graph in Figure 7, only the distributions of simulated ICERs for Treatments 1 and 2 are presented. The entire distribution of ICER points for Treatment 3 is under £10,000/QALY.

Figure 7: Cost-Effectiveness Acceptability Curves



Probability that ICER is under:	5,000	10,000	15,000	20,000	25,000	30,000	40,000
Transition probability only	0.050	0.725	0.952	0.978	0.993	0.996	1.000
All three assumptions *	0.046	0.671	0.924	0.978	0.996	0.998	1.000
Transition probability only	-	0.012	0.376	0.768	0.913	0.964	1.000
All three assumptions *	-	0.008	0.326	0.714	0.894	0.950	1.000

* The three model assumptions include the transition probability of moving from no cirrhosis to cirrhosis, discount rate, and annual health state costs for non-cirrhotic patients.

From the simulation results, we note the sensitivity of the models for Treatments 1 and 2 around the transition probability. This also is captured in the measure of variability, which is substantially higher for these two treatment groups compared with Treatment 3, which does not include any transition probability in the simulation. In addition, while we recognise that the simulation results above continue to point to the cost-effectiveness of all treatment regimens relative to a £20,000/QALY threshold, when either the simulated mean or median are being considered, we observe that the variability and uncertainty around the ICER for Treatment 2 makes the technology for this regimen above the threshold when the 75th (or 90th) percentile is selected. Ultimately, this introduces increased financial and clinical risk to payers that may require ongoing monitoring. Reducing uncertainty through implementing risk mitigation strategies to bring the ICER below the cost-effectiveness threshold can improve the predictability and transparency of the budget impact of recommending new technologies for routine commissioning. Risk sharing designed around sensitive assumptions is discussed with illustrative examples in the next section.

A 2013 review of past NICE decisions for which information about probability of cost-effectiveness is available reveals that a 40% probability of being cost-effective in the PSA would generally be sufficient to secure a positive recommendation in the final assessment.[9] This appears to leave a reasonably high probability that the technology would not be cost-effective, which in turn opens up NHS payers to considerable budget uncertainty.

[9] Adalsteinsson, E. & Toumi, M. (2013). Benefits of probabilistic sensitivity analysis - A review of NICE decisions. *Journal of Market Access & Health Policy, 1*. Retrieved April 26, 2016, from http://www.jmahp.net/index.php/jmahp/article/view/21240.

ACTUARIAL COST MODEL AND BUDGET IMPACT

Actuarial cost models are commonly used risk management tools for projecting future healthcare costs. The modelling of cost per treatment and utilisation can be an effective way for payers (both public and private) to estimate the financial impact of recommending a treatment for routine use. While insurance plans are often interested in estimating the budget impact of adding a new drug or treatment onto their formulary or benefit package, publicly financed systems similarly may want to understand the implications of expanding the range of care services provided to their populations. Often this can be achieved using already existing cost information from health payers.

MODEL SPECIFICITIES

We propose as a proof of concept a five-year actuarial cost model allocating costs to their respective service categories over time. Our original intent was to populate the model from the data inputs of ledipasvir-sofosbuvir appraisal, but because of confidentiality constraints and limitations on data, the model produced is in its generic form. Nevertheless, the methodology to develop such capabilities and various applications are described.

The cost model can present the evidence under a treatment versus control scenario to highlight differences in costs or trends between a new technology and a comparator, and reflect risk sharing agreements in place.

From patient-level data, costs per treatment can be allocated to one of the nine service categories (some categories may be specific to England, but a similar logic could be replicated in other settings). Depending on the granularity of the clinical data submitted by the manufacturer to NICE, the annual utilisation rate per 1,000 patients, average cost per service/admit, and average total costs per patient can be aggregated for each service category, with additional information about the annual hospital admission rate per 1,000 patients (in days) and average length of stay available for inpatient services. Similarly, a cost model can be developed at a population level; rates per 1,000 patients are simply substituted for rates per 1,000 heads of population.

Note that changes in some of the assumptions found in the manufacturer submission (for new drugs and technologies for instance) will be captured by and reflected in the cost model, because it is possible to link the costs accrued over time in the state-dependent Markov model to the actuarial cost model. Our suggested service categories are shown in Figure 8.

Figure 8: Illustrative Actuarial Cost Model for Treated Population

	Annual admission per 1,000 patients*	Annual utilisation per 1,000 patients (days)*	Average length of stay (days)	Average cost per service (£)	Annual costs per patient* (£)
Hospital acute inpatient					
Medical - Emergency - Elective					
Surgical - Emergency - Elective					
Maternity					
Psychiatric					
Subtotal					
Continuing care					
Hospital day case					
Medical					
Surgical					
Maternity					
Psychiatric					
Subtotal					
Hospital outpatient					

Mental health					
Primary and community care					
Prescription drugs					
Social care					
Ambulatory care					

* At a population level, annual rates per 1,000 heads of population and total annual costs per capita would be presented in order to estimate the overall budget impact for a CCG or other NHS payer.

In addition, capturing the impact on social care costs is likely to become increasingly relevant because of the planned full integration of health and social care in England by 2018. The coordination of these historically disjointed services, likely to benefit the elderly and people with chronic conditions and complex health needs, are expected to yield efficiency savings and other financial benefits if implemented effectively. Better coordinated care is also likely to support superior outcomes for these population groups and improve quality of life. Therefore, including social care costs in NICE appraisals, alongside the expected gains in outcomes, may provide a more holistic representation of the cost-effectiveness of new drugs and technologies and be a more consistent methodological approach than the current consideration of 'NHS-only' costs.

APPLICATIONS OF THE COST MODEL

One of the key applications of the actuarial cost model is the ability to project and allocate net healthcare costs (budget impact) and healthcare resources required for new technologies to each payer in the NHS system. Because the model uses existing experience data routinely collected by the NHS, it therefore does not require any substantial additional resources in terms of data collection.

Currently in England, a costing tool or cost assessment impact is typically published by NICE to assist local commissioners in estimating the budget impact of a guidance. This costing template allows for local inputs such as population disease prevalence, expected population treated, and distribution of patients by treatment duration. However, it relies mainly on static estimates of costs and resources. The ability of the actuarial cost model to present information under various scenario generators can ultimately assess more accurately the possible financial impact of a NICE guidance and the resulting opportunity cost of funding new interventions. This can be particularly useful to local care commissioners, as they are mandated to provide new technologies to patients within 90 days following recommendation. The allocation of costs against their respective service categories will facilitate the budgeting and planning of care for the various healthcare payers such as CCGs, NHS England (as a whole but also through specialised services), and other regional commissioning bodies.

An actuarial cost model can support the allocation of healthcare costs among various NHS payers, and the benchmarking of these costs and resource use against the original assumptions found in the manufacturer submission.

Another application of the model lies in its ability to analyse projections under various trend scenarios, which generally include a zero trend and trends that incorporate the current and projected PbR[10] deflator, as well as trends that reflect any financial-based schemes that are put in place, such as cap on volume, discounts, or rebates, for instance. Upon three years of data collection of a given technology, the actuarial cost model can also be useful to establish past cost and utilisation trends by service category and project future cost and activity over a typical five- or 10-year-horizon period. This can highlight service categories responsible for increases in costs, if any, and the stages of the disease for which this is observed.

In parallel, the model can present the evidence under a treatment versus control scenario, where the current standard of care or a combination of the treatments currently dispensed (control arm) is compared against the new health technology. This treatment versus control scenario can also be used to highlight cost differences between two population groups with different underlying characteristics, and where these differences are projected to occur. The model is also generally adjusted for changes over time in population characteristics such as age and sex, and can restrict the analysis to identified subpopulations.

In a context of new technology appraisals, monitoring effects following NICE guidance can be pivotal to ensuring value for money in the long run. When actual experience differs from the assumptions

[10] PbR: Payment by results, a tariff for payment of healthcare providers in England.

underlying the original reimbursement decision (i.e., service utilisation), the model is updated to reflect the new experience and compare against internal or external benchmarks. This forms an integral part of the feedback loop process, a common feature in actuarial approaches, and would assess in this particular situation whether a technology is delivering value as expected. Currently, all NICE guidance is considered for review after three years of being issued, especially upon a change in the inputs suspected to affect the outcome of the appraisal, or recommendation of a new competing technology. Therefore, a potential feature of the actuarial cost model would be to inform the first triannual review process and any subsequent ones, by providing metrics against which to evaluate actual costs and utilisation by service categories.

Overall, we believe that the actuarial cost model, while sharing the same objective as the NICE's current cost template, goes one step further, in exploring variability and uncertainty around key inputs and under various scenarios. It also allocates costs and gains to the current payers within the NHS system, and can integrate the effect of potential risk sharing deals, which represent improvements from the current approach. Lastly, it has the potential to inform NICE guidance revision process using readily available cost information collected by the NHS, and at a minimal additional cost to the healthcare system.

V. RISK SHARING AND UNCERTAINTY

Actuarial approaches are often employed to inform risk sharing arrangements. They are usually designed to mitigate the financial risk of uncertainty, with a particular focus on adverse experience and extreme, more volatile, scenarios. Traditional actuarial involvement in these schemes involves distributing uncertainty more productively, between local commissioners and providers, to those parties best equipped to manage different sources of financial risk. Using a similar logic, this expertise can also be used to better apportion the risk between the NHS and companies responsible for marketing new health technologies.

RISK SHARING AND ASSOCIATED CHALLENGES IN ENGLAND

NHS England has developed in recent years some risk mitigation strategies that aim to reduce its financial exposure to new treatments. Patient access schemes, presented in the opening section, are commonly regarded in England, and other parts of the world, as alternative market access agreements between healthcare payers and manufacturers that address risk in initially promising technologies and for which the uncertainty around the ICER is large. They generally extend to technologies likely to have a sizable budget impact. Currently in England, the majority of these agreements are financial-based, merely consisting of discounts to the NHS or price/volume agreements, as they are relatively simple to implement and maintain from an administrative perspective. The move to more outcomes-based or performance-based schemes, which tie reimbursement to superior outcomes, could benefit from actuarial and other risk mitigation approaches in delivering value-for-money care, but ultimately require additional resources to monitor and record clinical endpoints.

One of the main challenges with implementing risk sharing agreements for new drugs and technologies is often the lack of historical data for treatments newly commissioned by NHS England. The financial risk to payers following recommendation can be substantial, as approval usually extends for a few years, or until a revised decision for funding is issued. In these situations, data collected during clinical trials is normally extrapolated to predict future use of resources, but this comes with some level of uncertainty. Instead, these data inputs could be augmented by 'real-world' NHS data from which empirical transition probabilities, treatment costs, and other health state costs are estimated from claims data, using the process described previously. The confidence and credibility around these cost and probability estimates will ultimately depend on the size of the population utilising healthcare resources, with low-volume treatments or small population groups requiring additional months or years of observation to meet these criteria.

The lack of historical data characterised in new drugs and technologies stresses the importance of monitoring future resource use and other model assumptions over time.

Another area that we believe requires greater focus is the continuous monitoring of highly uncertain initial assumptions, which have a disproportionate effect on the eventual financial and clinical outcomes. We believe embedding model updates into a continuous feedback loop would improve submitted models and better inform the NICE guidance review process. Generally, we advise identifying the key assumptions with potentially large implications for the cost-effectiveness or budget impact of the technology at an early stage of the appraisal. Monitoring actual performance over time against inputs and assumptions found in the manufacturer submission can be crucial to quantifying the magnitude of the discount, rebate or any other financial transfer to the NHS from the manufacturer. This process may highlight resource levels that are different from the estimates used in the technology appraisal. Note that this review should be carried out irrespective of whether a risk sharing deal is put in place. It is also worth commenting that risk sharing can be retrospective, or prospective, or a combination of the two, but it is critical that both parties to the deal understand the level of financial and clinical risk they are exposed to under a variety of scenarios and agree in detail on any methodology used to calculate the risk exposures. Despite the limitations and challenges, entering into risk sharing agreements with the drug manufacturer at an early stage can limit downside risk to the NHS.

EXAMPLES OF RISK SHARING FROM CASE STUDY

In this section, we present some risk sharing examples, using assumptions from the ledipasvir-sofosbuvir manufacturer submission to NICE. These illustrative scenarios are broken out into the following three categories:

- Population-wide
- Cohort-specific
- Patient-centric

In the sensitivity analysis, we identify some assumptions associated with greater variability and uncertainty in the ICER output. Specifically, assumptions related to the probability of transitioning from the non-cirrhotic stage to cirrhosis, the discount rate applied to both costs and outcomes, and the disease health state costs for non-cirrhotic patients. While we recommend that these key data points, with the exception of the discount rate,[11] be closely monitored over time as part of the feedback loop, we also suggest that these estimates serve as anchors for the risk sharing agreement—they represent key sources of financial risk which the NHS should seek to mitigate to address affordability concerns.

Population-Wide or Cohort-Specific

Using the transition probability at age 40 for genotype 1 patients as an example, we present some hypothetical risk sharing scenarios alongside associated outcomes and payments that are due to a deviation of the actual rate from the expected rate (set equal to the rate found in the manufacturer submission to NICE). All assumptions and ICER values in Figure 9 relate to Treatment 2 (patients without cirrhosis; treatment experienced; 12-week treatment). Because the annual probability was derived from METAVIR scores and fibrosis scores where available,[12] it is ultimately subject to some uncertainty. The example below represents a possible risk sharing deal implemented at a population level, as the probability of progressing to cirrhosis from no cirrhosis is independent of the treatment selected and applies across the disease population for a given genotype. Note that two-way risk sharing is presented here, whereby the NHS and the manufacturer are both assuming some financial risk. Any reduction in variability is therefore observed across both sides of the ICER.

Population-wide and cohort-specific risk sharing can in theory rely on estimates calculated using claims data.

We also explore an additional risk sharing scenario designed around another key clinical assumption from the appraisal of ledipasvir-sofosbuvir: SVR12,[13] an efficacy indicator of treatment success. Its high value relative to historical control rates (around 94% for the treatments analysed) plays a critical role in establishing the cost-effectiveness and premium pricing of the drug, yet the Appraisal Committee notes that those SVR12 rates were pre-sampled outside the PSA model rather than sampled from a distribution. This uncertainty may therefore expose the ICER to greater variability when specific circumstances are considered. Because an SVR12 rate varies across treatments, this refers to a cohort-specific risk sharing. We rely on assumptions from Treatment 1 to discuss one-way risk sharing in Figure 10. Note that the interpretation of the various rules outlined in Figures 9 and 10 are specific to the appraisal and treatment regimens being analysed.

Figure 9: Two-Way Risk Sharing at a Population Level: Transition Probability

Rule	Outcome	ICER and payment transfer
No risk sharing Expected annual rate of transition: p=0.009 Actual annual rate of transition: p=0.016 Expected rate < Actual rate	The actual rate of transition from no cirrhosis to cirrhosis is higher than the rate found in the manufacturer submission to NICE (expected). This benefits the NHS as the hepatitis C treatment, through halting disease progression in most cases, becomes more cost-effective relative to the no treatment arm.	Expected ICER: £16,009/QALY Actual ICER: £10,453/QALY As no risk sharing is in place, there are no payment transfers.

[11] The choice of the discount rate for appraisals is found in the *Green Book* produced by the UK Treasury.

[12] METAVIR scores provide a model to interpret liver biopsies while fibrosis scores measure the degree of scarring in the liver.

[13] SVR12, or sustained virologic response, establishes whether hepatitis C virus is undetectable 12 weeks after treatment ended.

No risk sharing Expected annual rate of transition: p=0.009 Actual annual rate of transition: p=0.006	The actual rate of transition from no cirrhosis to cirrhosis is below the rate found in the manufacturer submission to NICE (expected). This makes the hepatitis C treatment less cost-effective, as disease progression under both arms is slower than expected.	Expected ICER: £16,009/QALY Actual ICER: £20,472/QALY As no risk sharing is in place, there are no payment transfers.
Two-way risk sharing Risk corridor for the annual rate of transition: 0.007 < p < 0.011 Actual annual rate of transition: p = 0.008	The manufacturer and the NHS establish a risk corridor for the transition probability. This corresponds to a level of risk (range of values) that the NHS is willing to take responsibility for without additional compensation to/from the NHS. Typically, the risk corridor includes a margin for deviation from the expected estimate. It is set symmetrical around the rate found in the submission for illustrative purposes, but may not always be set that way.	Risk corridor ICER*: £13,937/QALY - £18,746/QALY Actual ICER: £17,276/QALY No payment transfer as the actual rate is within the risk corridor.
Two-way risk sharing Risk corridor for the annual rate of transition: 0.007 < p < 0.011 Actual annual rate of transition: p = 0.006	The lower-than-expected rate of transition makes the hepatitis C treatment less cost-effective than initially appraised. However, because of the risk sharing agreement, the NHS will absorb full costs of the technology until the lower bound of p=0.007 is reached, with costs below partly or fully borne by the manufacturer, according to the risk sharing terms.	Risk corridor ICER*: £13,937/QALY - £18,746/QALY Actual ICER: £20,472/QALY Manufacturer to compensate the NHS for an amount equivalent to the difference between the upper bound of the risk corridor ICER (£18,746/QALY) and the ICER based on the actual annual rate of transition (£20,472/QALY). This corresponds to a retrospective rebate of £1,726/QALY.
Two-way risk sharing Risk corridor for the annual rate of transition: 0.007 < p < 0.011 Actual annual rate of transition: p = 0.016	It is also possible that the NHS benefits from favourable experience. As more people are transitioning from no cirrhosis to cirrhosis, the hepatitis C treatment becomes increasingly more cost-effective. Similar to the scenario right above, but in reverse, the NHS will now bear additional costs subject to the risk sharing terms.	Risk corridor ICER*: £13,937/QALY - £18,746/QALY Actual ICER: £10,453/QALY The manufacturer receives from the NHS an additional payment** equivalent to the difference between the lower bound of the risk corridor ICER (£13,937/QALY) and the ICER based on the actual annual rate of transition (£10,453/QALY). This corresponds to a retrospective payment of £3,484/QALY.

* The risk corridor ICER represents the range of ICER values that correspond to the lower and upper limits of the model assumption being analysed (i.e., annual rate of transition). Note that a symmetrical risk corridor for the transition probability may not necessarily result in a symmetrical range of ICER values.

** Under this specific two-way risk sharing, there appears to be an incentive for manufacturers to underestimate the expected annual rate of transition to increase the likelihood of receiving later an additional payment from the NHS upon conducting a retrospective review.

Figure 10: Cohort-Specific One-Way Risk Sharing, SVR12 Rate

Rule	Outcome	ICER and payment transfer
One-way risk sharing Treatment 1: Patients with no cirrhosis; treatment naïve; eight-week duration Expected SVR12 p=94.0% 95% confidence interval for SVR12 p= [89.9% , 96.7%] Actual SVR12 p=87.0%	In the appraisal of ledipasvir-sofosbuvir, the manufacturer provided the 95% confidence interval for SVR12. Therefore the lower bound of the interval (p=89.9%) can be used as a threshold below which a full refund of the drug and on-treatment monitoring costs would be expected from the manufacturer. Note that the NHS would continue to be responsible for the maintenance and health state costs of the disease in this example. Because only adverse deviation is being considered, this represents an example of one-way risk sharing that limits downside risk to the NHS only.	Drug treatment costs (8 weeks) £25,986 On-treatment monitoring costs (8 weeks) £1,000 Manufacturer discount per treatment dispensed = (89.9% - 87.0%)* (£25,986 + £1,000) = £783

As some of the examples suggest, risk sharing arrangements can be designed in ways that make both parties assume parts of the financial risk. They can also be developed focusing only on shielding the NHS from adverse experience. For the purposes of illustration we look at risk sharing scenarios developed around individual assumptions alongside their resulting financial implications. However, in practice, these risk sharing schemes may be designed around multiple assumptions simultaneously.

Commissioners can benefit from risk sharing targeting extreme and volatile scenarios. This will improve certainty around budgeting.

Patient-Centric

Risk sharing agreements can also be developed around extreme and more volatile scenarios. Additionally, they can focus on individual patients. Currently, commissioners carry the financial responsibility to provide care to their respective local populations and may be ill-equipped to absorb full downside risk, especially as the costs of providing care for some of these patients may be particularly high and may require displacement of current resources directed at other patients. An approach similar to a stop-loss insurance is explored, whereby the 95th percentile of the lifetime cost distribution for the treatment arm is used to inform reimbursement decisions, seen in Figure 11. In this example, costs in excess of the 95th percentile would fall under the sole or shared responsibility of the manufacturer, subject to the risk sharing terms, with costs below that percentile expected to be borne by the NHS, as is currently the case.

For technologies presenting a mean ICER around the threshold for acceptance and showing signs of variability, an alternative approach can be considered, whereby total discounted cost per patient for the treatment arm is set to an amount that equates the ICER with the fixed monetary threshold, such as £20,000/QALY. As in the previous example, individual patient costs in excess of that value would be borne, partly or fully, by the manufacturer, according to preestablished terms.

Figure 11: Risk Sharing With a Stop-Loss Design

Treatment regimens	Smallest value of lifetime cost distribution (£)	Stochastic mean of lifetime cost distribution (£)	95th percentile of lifetime cost distribution (£)
Treatment 1	28,875	29,236	29,480
Treatment 2	40,967	41,413	41,633
Treatment 3*	55,712	61,798	65,764

* We assign a probability distribution to costs for cirrhotic patients using the parameters of a PSA referenced in the manufacturer submission.

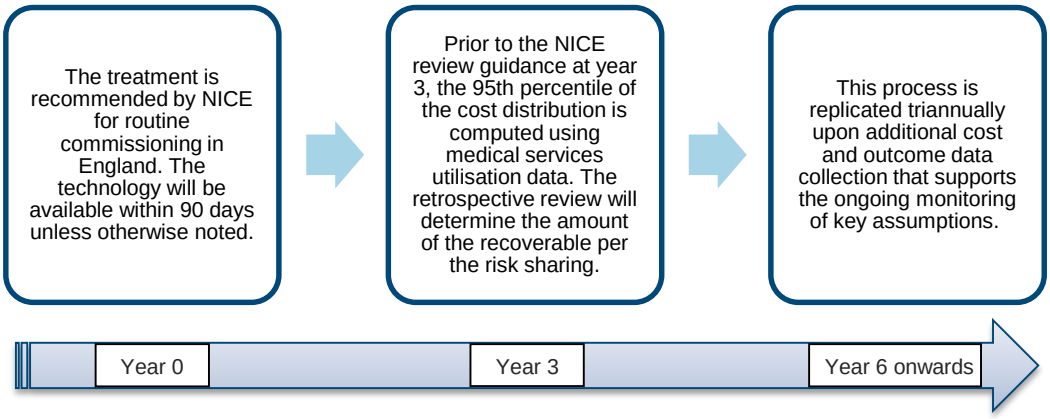
As we note from Figure 11, Treatments 1 and 2 are showing limited variation in their respective lifetime discounted costs, which could be partly explained by the effectiveness of the treatment in halting progression to the cirrhosis stage. Treatment 3, however, is subject to greater variability, as patients who achieve SVR12 continue to incur annual maintenance and health state costs after year 2, in contrast with Treatments 1 and 2. Therefore, such a method could be more appropriate for treatment regimens with a larger range observed over the total cost distribution.

As most economic models are presented using a 30-year or even lifetime horizons, an alternative approach may be considered whereby the time frame is partitioned into multiple intervals and costs analysed separately within each of these segments. This ultimately will require conducting retrospective reviews of historical medical services utilisation data at preestablished intervals to identify the 95th percentile (or any other percentile agreed upon in the risk sharing terms agreement), and to calculate the amount of the recoverable, seen in Figure 12.

A stop-loss insurance design can be implemented at a patient or population level using a similar approach.

In addition, this method may be more relevant to curative treatments, such as ledipasvir-sofosbuvir, as it better reflects the distribution of costs over time. Generally, these treatments are associated with high up-front costs in early years and lower maintenance costs in later years as more people are cured. Outliers may therefore be identified in a relatively short time frame. Increased costs and resource use for treating complications and other adverse outcomes may also be more easily connected to treatments in the early stages of treatment rather than in later years. While we note that some high-cost patients may benefit disproportionately from treatment (higher-than-expected utility gain), these individuals should nevertheless be included in the cost distribution unless they can be identified through the collection of outcome measures. As NICE reviews the guidance and as 'real-world' data is collected, these percentile values will vary over time.

Figure 12: Illustrative Timeline for the Retrospective Review of Total Costs



Lastly, it is worth mentioning that a stop-loss risk sharing may be implemented in aggregate (over the entire treatment population), either in isolation or in combination with an individual stop-loss scheme. A major benefit of this approach is to limit the overall budget to payers such as the NHS for delivering care to a particular treatment group. Ultimately, maximising the potential for success of these risk sharing contracts will require, among other factors, a solid understanding of the needs of the patient population under analysis, an accurate estimate of the disease prevalence and the proportion of people eligible for treatment, and an incentive structure that is well aligned with the profile of the risk bearing entity.

Overall the examples discussed above represent possible ways of tackling uncertainty about cost and outcome measures in recently approved drugs and technologies. As an alternative to simple, predetermined discounts (which ultimately reduce the mean ICER but do not necessarily address variability in the ICER), we present various options for payers, like the NHS, to enter where appropriate into risk sharing agreements with the manufacturer. We illustrate them using population-wide, cohort-specific, and patient-centric risk sharing mechanisms. This framework is also compatible and consistent with both NICE's current triannual review cycle and with a commitment to ensuring timely access to innovative drugs in a context of scarce resources and uncertainty.

VI. CONCLUDING REMARKS AND NEXT STEPS

The recommendation in recent years of high-cost health technologies such as interferon-free hepatitis C drug regimens heightens the importance to healthcare payers of addressing the economic implications of recommending new treatments for routine commissioning. As some NICE guidance involves diverting resources away from existing services, it is important to understand and quantify the degree of uncertainty in each appraisal and design, where appropriate, mechanisms to mitigate risk going forward. This is consistent with the view of delivering value-for-money care.

In this report we apply actuarial approaches to handling uncertainty to the health technology appraisal process, using recent hepatitis C drug submissions to NICE as a basis to develop a proof of concept. These new treatment regimens, undeniably characterised by increased adherence levels that are due to a more favourable side effect profile, require however considerably more economic resources, the level of which is relatively uncertain. Using the lens of health and social care payers, we propose an actuarial cost model against which to monitor future resource use and cost to better estimate the budget impact of new drugs and technologies. We also acknowledge that this approach could be replicated for treatments currently commissioned within NHS England and help commissioners and other relevant payers estimate their share of the cost.

Quantifying uncertainty around the ICER is critical as new drugs and technologies eventually divert resources away from currently funded treatments and health services.

In addition, we present a theoretical framework which aims to address some of the ongoing challenges faced by NICE, particularly around the modelling and quantifying of uncertainty in technology appraisals. The three approaches presented rely on stochastic modelling and the attribution of probability distributions to sensitive model assumptions. While proposing the ongoing monitoring of these assumptions over time, we also discuss how empirical data or 'real-world' data can be used where applicable to model the effects of recommending a drug for routine commissioning and inform the NICE review guidance process.

Finally, we explore some risk sharing arrangements which can limit downside risk to the NHS in delivering new drugs and technologies to the population. Whether they are designed across the whole disease population, specific to treatments, or at a patient level, they can assist commissioners with budgeting, especially as more volatile and extreme scenarios are observed.

CAVEATS AND LIMITATIONS

The findings reflect the research of the authors; Milliman does not intend to endorse any product or organisation. Milliman does not intend to benefit or create a legal duty to any third party recipient of its work. If this report is reproduced, it should be reproduced in its entirety as pieces taken out of context can be misleading. As with any economic or actuarial analysis, it is not possible to capture all factors that may be significant. Because we present illustrative data, the findings should be interpreted carefully before they are applied to any particular situation.

In carrying out the modelling, we relied on data from publicly available sources and on actuarial judgement. We have not audited or verified this data or other information. If the underlying data or information is inaccurate or incomplete, the results of our analysis may likewise be inaccurate or incomplete. The projections presented in this report are based on assumptions derived from historical data and our actuarial judgement. If different assumptions were used, the projections would be materially different. Actual experience will differ from our estimates, perhaps materially.

APPENDIX A: DATA, METHODOLOGY AND ASSUMPTIONS

Using a recently approved hepatitis C drug as a case study, we develop a theoretical framework from which we illustrate a potential handling of uncertainty and variability in the ICER. Rather than critiquing the manufacturer model submitted to NICE, we replicate, within reasonability, a time-dependent Markov model relying on the clinical and cost evidence of the drug produced as part of the submission process. This was done using publicly available information and therefore does not include any confidential price arrangements agreed between NHS England and the manufacturer. In addition, the submission to NICE includes a weighted average base case analysis whereby the cost-effectiveness of the drug is assessed jointly for both non-cirrhotic patients and patients with cirrhosis, and across several treatment durations. In this report, we adopt the view of analysing the two hepatitis C virus (HCV) population groups separately in order to remove some of the uncertainty in estimating, for instance, the proportion of cirrhotic patients in the HCV population, or even the allocation of patients between the different treatment durations, a view also shared by NICE. Last, we rely on the assessment of the Appraisal Committee for further insights.

The treatment arm consists of ledipasvir-sofosbuvir; the control arm does not have any treatment assigned. For simplicity we focus exclusively on a treatment HCV population with genotype 1, the most common genotype in England, for the following treatment regimens (all approved by NICE):

- **Treatment 1**: Patients without cirrhosis; treatment naïve; eight-week treatment.
- **Treatment 2**: Patients without cirrhosis; treatment experienced; 12-week treatment.
- **Treatment 3**: Patients with cirrhosis; treatment naïve; 12-week treatment.

The basis of this report consists of presenting actuarial techniques in a context of health technology appraisals. We define the incremental cost-effectiveness ratio in the most traditional way, represented by the formula below:

$$\text{ICER} = \frac{\Delta\text{Cost (£)}}{\Delta\text{Outcome (QALY)}} = \frac{(\text{Cost treatment} - \text{Cost control})}{(\text{Outcome treatment} - \text{Outcome control})}$$

KEY PARAMETER ASSUMPTIONS

We recognise that uncertainty can take many forms and that each requires relying on different techniques. For instance, uncertainty around the choice of data sources typically arises when alternative sets of plausible data on costs and outcomes are available and for which the variability is significant. Sensitivity analysis of key assumptions is usually performed and their effects on the ICER are usually monitored. However, in this report we focus more specifically on parameter uncertainty, which is usually best handled through PSA. It has the advantage of showing the probability that a technology is cost-effective at various thresholds, as it assigns a probability distribution to key assumptions. It also provides the most accurate mean and other statistics estimates, and ultimately allows uncertainty associated with key model parameters to be reflected in the results. Under this method, a high probability of a technology being cost-effective should lead to a higher probability of acceptance of the technology.

Per the company submission, the transition probability from non-cirrhotic to compensated cirrhosis is age-specific, with estimates provided for ages 30, 40, and 50. Rather than simply conducting sensitivity analysis on this probability using point estimates provided by the manufacturer, we use a normal distribution to model this key assumption, as an illustration of the approach. Precisely we assign the value of the lower and upper bounds for this probability to correspond to the 1st and 99th percentile of the distribution, and run the simulation 1,000 times. We rely on the normal distribution to reflect the symmetrical confidence interval provided in the submission but recognise nonetheless that this could be replicated using other probability distributions, notably the beta distribution, which is often used to model transition probability.

Similarly, under the different scenarios that we explore we observe that the ICER is very sensitive to changes in the discount rate. As the rate increases the ICER progressively moves upwards and becomes less cost-effective. This is expected, given that the benefits associated with treatment are accrued over the long run.

In line with the NICE guidance on technology appraisals, a discount rate of 3.5% is applied to both costs and outcomes in the base case analysis, as this is the rate used by convention in economic evaluations in England. However, to reflect uncertainty in the model, Figure 13 breaks out the discount rate into three parts, using the methodology described by the UK Treasury in determining this rate.[14]

Figure 13: Breakdown of the NICE Discount Rate

Components of NICE discount rate	Description	Percentage
Growth per capita	Average growth rate per capita in the UK from 1950 to 1998.	2%
Catastrophe risk	Likelihood that there will be some catastrophic event that will radically eliminate all returns from policies or programmes. Examples include technological improvements, natural disasters, and other major threats such as wars.	1%
Pure time preference	Individuals' preference for consumption now rather than later.	0.5%
Total	Discount rate used by NICE for costs and benefits.	3.5%

Acknowledging that the 1% and 0.5% loads represent catastrophe risk and pure time preference respectively, we focus on the remaining 2% and model it using the normal distribution for the purposes of illustration. We compute the standard deviation of the growth per capita in the UK from 1960 to 2010 using public data, validate that the mean growth rate over this period is around 2%, and use both values in the simulation. The simulated discount rate therefore includes a simulated value for the growth per capita in the UK and a fixed 1.5% load.

Last, we note that most of the health state costs referenced in the NICE technology appraisal of ledipasvir-sofosbuvir (along with other previous appraisals related to hepatitis C) are featured in 2002-2003 and 2006-2007 studies, from which the Hospital and Community Price and Pay Index is applied to standardise costs to current levels. Although we recognise the principles underlying this approach and its widespread use in the face of imperfect information, it nevertheless represents an important source of uncertainty, as it implicitly assumes that health state costs steadily increase over time and that no changes in utilisation patterns, mix of resource usage, or schedule of care has occurred. As these costs refer to annual maintenance costs for patients in each of the disease stages, more recent, 'real-world' NHS data is available and could be used to derive empirical estimates as presented in the main body of the text. Because of limitations on accessing these inputs, we rely on the gamma distribution to model the initial, pre-inflated costs for non-cirrhotic patients using the parameters from a PSA referenced in the manufacturer submission.[15] We also apply to the simulated costs the same inflation factor as the one found in the submission.

The high level of uncertainty of the cost parameters is recognised in the sensitivity analysis conducted by the drug manufacturer, as total lifetime costs for non-cirrhotic patients are varied by a seemingly arbitrary value of 25% above and below. Though we acknowledge that this represents one potential way to look at variability in the ICER, we believe this is not informed by a robust data-driven process but rather represents an attempt to define a crude, but ultimately arbitrary confidence interval.

[14] HM Treasury (2003). The Green Book: Appraisal and Evaluation in Central Government. Retrieved March 30, 2016, from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/220541/green_book_complete.pdf.

[15] Shepherd, J., Jones, J., Hartwell, D., Davidson, P., Price, A., & Waugh, N. (March 2007). Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: A systematic review and economic evaluation. *Health Technol Assess*; 11(11):1-205, iii.

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CONTACT

If you have any questions or comments on this paper, please contact:

Joanne Buckle
joanne.buckle@milliman.com

+44 20 7847 1630

Didier Serre
didier.serre@milliman.com

+44 20 7847 1507