Commissioning Business Service

"Informing Decisions, Improving Care"

HEPATITIS C IN GREATER MANCHESTER

REPORT ON DECISION MODEL FOR CHANGING CARE PATHWAYS

Author – Carl Ashworth, Commissioning Business Service

Background

The population of Greater Manchester has amongst the highest prevalence of Chronic Hepatitis C virus (HCV) infection in the UK, and the associated health problems are escalating. Increasing prevalence is driven by high numbers and high infection rates amongst injecting drug users, although there is increasing evidence of high rates amongst ethnic minority groups who acquire the infection abroad. Untreated chronic HCV infection is closely linked with cirrhosis and hepatocellular carcinomas and with associated premature mortality.

Greater Manchester health services face a problem of a large undiagnosed chronic HCV population, whilst at the same time increasing numbers of individuals who are tested are testing positive, causing increased pressure on treatment services. Increasing numbers of patients are being admitted to hospital with complications at high cost, whilst there is a social impact arising from the fact that the majority of people affected are male and of working age, leading to increased worklessness and incapacity benefit claims.

HCV services in Greater Manchester do not meet the population need. There is no clear care pathway and the referral process is inefficient. High numbers are infected with HCV but not diagnosed – it is estimated that there are currently 20,000 people with HCV in GM, although only a small proportion are in contact with services. Service delivery is inequitable, with poor access to services for some parts of the population.

In order to overcome these current shortfalls, a proposal has been put to GM PCTs to introduce changes to patient pathways and service models. This HCV decision model is intended to establish the cost effectiveness of the key changes:

- Increase the level of HCV antibody testing amongst the exposed population to identify undiagnosed infected individuals
- Put in place a clear referral pathway with community based diagnostic testing to improve management of referral into treatment
- Increase capacity in treatment services to meet increased demand
- Improve exit management strategy to reduce numbers of patient retained by specialised hepatology and infectious disease services in the longer term by passing maintenance care to generalist services, thereby reducing ongoing support costs.

Hepatitis C

The HCV decision model has been built from an NHS-perspective intended to inform a decision by the ten Greater Manchester PCTs on the implementation of improvements to the HCV treatment pathway. The outputs of the model – in terms of an incremental cost effectiveness ratio (ICER) compared to the current pathway – demonstrate the cumulative effect of implementing each stage of improvement as described above.

Hepatitis C is an infectious disease whose consequences - in terms of both service costs incurred and impact on individual health - are significant over the medium to longer term, with around 80% of people exposed to HCV going on to develop chronic disease. HCV is the cause of between half and three quarters of all liver cancers and two thirds of liver tranplants.

HCV disease pathway

In the UK, the main route of acquisition of HCV is through recreational Intravenous drug use. In developing countries, blood transfusion and exposure to unclean surgical and other practices (e.g. body piercing, tattooing) is also important (Nash et al 2009), and it is known that there are individuals from UK ethnic minority populations who are infected abroad and return with the virus.

Acute HCV infection is usually unsymptomatic, with 80% progressing towards chronic infection (NICE 2006). Of these, 20% will progress to cirrhosis over a period of up to 20 years (Nash et al 2009), leading to increased risk of liver cancer and liver failure, when transplantation is indicated.

Initial screening undertakes a test for HCV-specific antibodies, although the risk of false positives requires a follow-up with a Polymerase Chain Reaction (PCR) test for HCV RNA. For those who test positive for chronic infection, the NICE-recommended treatment is anti-viral therapy – a combination of Peginterferon Alfa and Ribavirin, tailored to genotype (NICE 2006). Treatment can be seen to be successful when HCV RNA is undetectable at six months after commencement of treatment, termed a sustainable virological response (SVR). SVR is seen in around 67% of patients treated (NICE 2006).

Building the model

It is recognised that a *deterministic* approach to model building (such as using a decision tree) is suitable for acute interventions but that it cannot usefully model the recurrence of disease. A

stochastic Markov approach is usually applied for simple recurring chronic conditions (Cooper et al 2007). However Markov models require much greater levels of data, including transition probaibilites from state to state, and it is accepted that insights from simpler models are usually similar to those deriverd from more complex calcluations (Detsky et al 1997). As a further point, it is often recommended that beginners build the simplest models (Detsky et al 1997). Consequently, the model structure chosen for the HCV analysis is that of a decision tree.

For the HCV model, the point of infection, treatment interventions and viral clearance can be modelled as acute episodes, with the development of chronic infection and consequent development of cirrhosis shown as potential longer term consequences. The model is intended to demonstrate the potential impact of changing treatment pathways on costs to the NHS and Quality Adjusted Life Years (QALYs) gained by individuals in targetted populations through achieving viral clearance rather than developing chronic HCV infection. This is demonstrated through a model that utilises optional branches to reflect shifts in patient pathways. Whilst this approach has generated a fairly complex structure to the model, overall the chioce of using a decision tree approach can be seen to be justified.

Model Assumptions

The model takes as a starting point an exposure to HCV, followed by screening for HCV antibodies on a proportion of the exposed population. The unscreened proportion will not know they have the virus and will either naturally clear it or develop a chronic infection, with a subsequent risk of cirrhosis. For those who test positive for antibodies, there are two treatment arms in the model that are mutually exclusive for the sake of analysis – one for the current pathway, where PCR is undertaken in secondary care; and one for a community-based

assessment, including PCR. The key difference between the two arms at this stage is that, within the current pathway, some 50% of PCR-positive patients drop out before treatment and will develop chronic disease. Under the planned community pathway, appropriate controls will be put in place through the assessment and community support process to ensure a much lower drop out rate.

The first sheet of the Excel workbook containing the model describes the current treatment pathway. Of the population exposed to HCV, 80% will develop chronic infection, of which 20% will eventually develop cirrhosis. Only some 10% of the estimated 20,000 exposed GM population are picked up through antibody testing at present, and for some of these patients subsequent PCR testing is undertaken in primary care. Upon referral to secondary care, PCR testing is again carried out, followed by multi-disciplnary team assessment – on the path towards treatment, however, some 50% of patients drop out. Capacity constraints mean that only 50% of the remaining patients get access to treatment in-year, with the remainder put on a watchful wait approach until a treatment 'slot' becomes available. Treatment gives an increase in viral clearance rates from those seen naturally, with 67% of patients treated avoiding chronic infection. The model calculates costs and QALYS for each decision branch and produces overall average cost per patient per annum and QALY score per patient for the current pathways.

The second sheet varies only the proportion of patients undergoing antibody testing from 10% to 50%, then calculates the costs and QALY score from the revised situation.

The third sheet maintains these scores, whilst also shifting from the secondary care treatment arm to the community assessment arm, thereby reducing drop out rates from 50% to 10% and calculating the combined impact on overall average cost and QALY score.

The fourth sheet takes the above scenario and adds to it a shift in treatment rates from 50% to 90% through increased treatment capacity, then calculating combined impact on costs and QALY scores.

Finally, the fifth sheet reduces the costs associated with treatment of those patients with chronic infection, reflecting a shift of care back to other specialties away from hepatology and Infectious diseases, where tariffs are higher.

For ease of utilisation by decision makers of the outcomes of the model, the time horizon has been set at twelve months. This is far enough into the future to reflect the impact of treatment on viral clearance rates (six months), though not enough to reflect the longer term impact of chronic disease leading to cirrhosis (up to 20 years). To take account of the latter, the estimated cost of treating cirrhosis, including liver transplant, has been discounted over 20 years at 3.5% per year.

Model data

Data used to populate the model were as follows:

Data field	Value	Source	Justification
Current proportion of exposed population tested	0.10	Harrison & Verma 2010	From GM Joint Strategic Needs Assessment
Proportion of exposed population developing chronic infection	0.80	NICE 2006	NICE acknowledged estimate
Proportion of chronically infected developing cirrhosis	0.20	Nash et al 2009	Internationally ackowledged estimate
Current proportion of patient 'drop out' prior to treatment	0.50	Local service estimate	
Current proportion of ready & willing patients treated in-year	0.50	Local service estimate	
Proportion of HCV positive patients achieving CVR with combination therapy	0.67	NICE 2006	NICE acknowledged estimate
Cost of average cirrhosis patient service use per year	£50,818	Author's estimate	£100,000 cost of treating cirrhosis discounted at 3.5% over 20 years
Cost of average infected non-cirrhosis pt service use per year	£5,000	Local service estimate	
Cost of combination therapy treatment per year	£6,000	Local service estimate	
Current costs of antibody/ PCR testing	£600	Local service estimate	Assumes PCR testing duplicated; OP attendance plus MDT f-up
Revised cost of community based assessment & PCR test	£350	Local service estimate	Assumes more efficient assessment and testing pathway
QALY for cirrhosis – no treatment	7.71	**Grishchenko et al 2009** Genotype non-1 patients aged 40 with cirrhosis	Taken from CEA of combination therapy for chronic HCV patients in routine clinical practice
QALY for cirrhosis post treatment	9.45		
QALY for moderate HCV – no cirrhosis, no treatment	11.15	As above. Genotype non-1 pts aged 40, mod HCV	
QALY for moderate HCV – no cirrhosis, with treatment	13.43	As above.	As above.
QALY for SVR	19.38	**Cure et al 2010** Mean QALY associated with SVR	Estimate derived from literature review of published economic evaluations of antiviral treatment

Pre-model data analysis

Data analysis in advance of incoropration into the model was undertaken on the costing of treatment. It was estimated that patients who develop cirrhosis would make substantial use of hospital care at this point (estimated to be £10k) prior to liver transplant (at a cost of £90k). Given that it could take 20 years to develop cirrhosis, this estimate of £100k cost was discounted over 20 years at a rate of 3.5% per annum, giving an in-year estimate for the model of £50,818.

Other costs were calculated as follows:

- Current secondary care test: OP attendance (£150) + PCR test (£100)x2 + MDT f/up (£250)
- Proposed community care assessment: GP attendance (£100) + PCR test (£100) + nurse assessment (£150)
- Cost of average infected non-cirrhosis pt service use per year: OP attendances (£1k), IP attendances & treatment (£4k)
- Cost of combination therapy treatment per year: OP attendaces (£2k); drug costs (£4k)

Assessment of uncertainty

Decision makers need to understand the extent of any variation in the model that will impact on the number and quality of lives saved per measure of investment (Brennan et al 2006). Uncertainty can be found in patient variability and population heterogeneity; parameter uncertainty; choice of appropriate model of disease; or alternative treatment paths available

(O'Hagan et al 2005), most of which could be said to apply to the HCV model. The model is based upon estimates of population prevalence that take only some account of the fact that the target population lead fairly chaotic lifestyles and display little heterogeneity. Also, given that HCV is an infectious disease, a more complex infectious disease model could have been built to reflect population interaction.

Whilst models can be made probabilistic to capture parameter uncertainty, using distributions for parameters (Briggs et al 2009), such distributions were not available to populate the HCV model. However, scenario analysis could be used to test the impact of parameter uncertainty, looking at variations in costs and QALYs, potentially using results from Genotype 1 moderate HCV patients from Grishcenko et al 2009 (which indicated lower QALY benefits for combination treatment), and minimum/maximum QALYs associated with SVR (14.53 and 36.41 respectively) from Cure et al 2010 . However, such sensitivity analyses have not been applied to the model before submission.

Consistency

The model can be seen to be externally consistent with NICE guidance 106, which recommends Peginterferon alfa and ribavirin for the treatment of mild chronic HCV as being cost effective compared to no treatment.

Outputs from the model

Hepatitis C Virus - GM Decision Model
Cost benefit analyses

2. Improved diagnosis thru AB testing		
Incremental analysis		
	QALY	Cost
Testing @ 10%	12.38	£ 11,321
Testing @ 50%	12.91	£ 11,282
Difference	0.54	-£ 39
ICER (cost per QALY)		**-£ 73**

3. Plus Community Assessment inc PCR		
Incremental analysis		
	QALY	Cost
No assessment	12.38	£ 11,321
Assessment	13.45	£ 10,878
Difference	1.07	-£ 443.34
ICER (cost per QALY)		**-£ 414**

4. Plus increased treatment rates		
Incremental analysis		
	QALY	Cost
50% treatment	12.38	£ 11,321
90% treatment	14.41	£ 10,375
Difference	2.03	- 945.84
ICER (cost per QALY)		**-£ 465**

5. Plus improved exit management		
Incremental analysis		
	QALY	Cost
Current	12.38	£ 11,321
Shift to other specialties	14.41	£ 10,229
Difference	2.03	-£ 1,092
ICER (cost per QALY)		**-£ 537**

The results indicate that each step in the proposed changes to the treatment pathway will both reduce overall costs and increase the generation of QALYs. Combined together, the proposal

generates a cumulative saving to the NHS of £1,092 per patient for an increase of 2.03 QALYs, giving an Incremental Cost Effectiveness Ratio of **-£537 per QALY**.

Conclusion

The proposed changes to the GM HCV treatment pathway can be seen to be cost effective – not only does the model indicate that the changes will increase QALYs amongst the treated population but it also suggests that this will be achieved at reduced cost. Overall, the changes can be seen to generate savings of £537 per QALY gained amongst the treated population.

Whilst the HCV decision model can be seen to be relatively simple, the logic behind its structure is sound. Some sensitivity analysis could be applied to test parameter uncertainty, although the inputs to the model have been tested and confirmed as appropriate with local subject matter experts.

On that basis, this cost benefit analysis recommends the adoption of the following changes to the local HCV treatment pathway:

- Increase the level of HCV antibody testing amongst the exposed population to identify undiagnosed infected individuals
- Put in place a clear referral pathway with community based diagnostic testing to improve management of referral into treatment
- Increase capacity in treatment services to meet increased demand

- Improve exit management strategy to reduce numbers of patient retained by specialised hepatology and infectious disease services in the longer term by passing maintenance care to generalist services, thereby reducing ongoing support costs.

REFERENCES

Brennan A, Chick SE, Davies R (2006) **A taxonomy of model structures for economic evaluation of health technologies**. *Health Economics.*15:1295-1310

Briggs A, Claxton K, Sculpher M (2006) **Decision Modelling for Health Economic Evaluation**. Oxford University Press 2006

Cure S, Bianic F, Cawston H, Dartois L, Zhang H (2010). **Impact of sustained virological response after antiviral treatment in chronic hepatitis C patients on life expectancy and quality adjusted life years**. *European Association for the Study of the Liver (EASL) 45th Annual Meeting – April 2010. Conference report for National AIDS treatment Advocacy Project (NATAP).*

Detsky AS, Naglie G, Krahn MD, Naimark D, Redelmeier DA (1979) **Primer on Medical Decision Analysis: Part 1—Getting Started** *Medical Decision Making* 1997; 17; 123

Duffell E (editor) (2009) **Hepatitis C in the North West Region.** *Health Protection Agency* July 2009

Grishchenko M, Grieve RD, Sweeting MJ, De Angelis D, Thomson BJ, Ryder SD, Irving WL (2009) **Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice.** *International Journal of Technology Assessment in Health Care* 25:2 (2009), 171-180

Harrison K, Arpana V (2010) **GM HCV Prevention Joint Strategic Needs Assessment – core report.** *Health Protection Agency, Manchester University* January 2010

Nash KL, Bentley I, Hirschfield GM (2009) **Managing Hepatitis C virus infection.** *BMJ* 2009; 338;b2366

National Institute of Health & Clinical Excellence (2006). **Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C**. *NICE technology appraisal guidance 106,* August 2006.

O'Hagan A, McCabe C, Akehurst R, Brennan A, Briggs A, Claxton K, Fenwick E, Fryback D, Sculpher M, Speigelhalter D, Willan A (2005). **Incorporation of uncertainty in health economic modeling studies**. *Pharmacoeconomics* **23(6)**: 529-536

Philips Z, Ginnelly L, Scuplher M, Claxton K, Golder S, Riemsma R, Woolacott N, Glanville J (2004). **Review of guidelines for good practice in decision-analytic modeling in health technology assessment.** *Health Technology Assessment* 2004; Vol 8; No 36