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NHS ENGLAND SUBMISSION TO QUESTIONS RAISED BY NICE FOLLOWING CONSULTATION RESPONSES TO HEPATITIS C DRUG APPRAISALS

BACKGROUND

NHS England is supportive of expanded new treatment options for people with Hepatitis C, and has already begun funding their care. However, we also want to ensure that unresolved questions about the best treatment strategies are answered and that phased investment in Hepatitis C services does not cause damaging cuts elsewhere.

The National Institute for Health and Care Excellence (NICE) Appraisal Committee is in the process of considering three products for the treatment of hepatitis C; sofosbuvir plus ledipasvir (Harvoni®) [ID742], daclatasvir (Daklinza®) [ID766], and paritaprevir/ritonavir/ombitasvir (Viekirax®) +/- dasabuvir (Exviera®) [ID731]. In the context of consultation on the preliminary recommendations for sofosbuvir/ledipasvir NHS England submitted a comment that relates to NICE's general duties to 'have regard to the broad balance between benefits and costs of the provision of health services or of social care in England and the degree of need of persons for health services or social care in England'.

The introduction of the oral treatments for hepatitis C is a major change in the management of this disease and NHS England is supporting the implementation of these treatments in a stepwise fashion with:

a) the early access scheme for decompensated cirrhosis;
b) the access scheme for all patients with cirrhosis soon to be available; and
c) the formation of the work programme to establish access to oral drugs for patients with F3 liver fibrosis in conjunction with an effective program of surveillance for other patients and a focus on the specific needs of the complex patient groups with hepatitis C.

The potential publication of the NICE guidance for sofosbuvir plus ledipasvir (Harvoni®) [ID742] as a single technology appraisal has led to a number of concerns that were described in the consultation response. All stakeholders who have advised NHS England have indicated the importance of forming a multiple technology appraisal evaluating the new suite of medications, their combinations, the previously available treatments and the potential for shorter treatment durations. It is understood that a multiple technology appraisal would be best achieved in approximately 18 months time when the full range of these new medications has been licensed.

In the meantime NHS England is confident that treatment strategies through commissioning policy can be formed to substantially reduce the burden of liver disease associated with hepatitis C.

Until a NICE multiple technology appraisal can be carried out, NHS England would support with their Access Scheme Programmes a NICE 'Recommended with Research' position for patients without cirrhosis. These schemes would harness substantial 'real world' data on the effectiveness of treatments and their combinations to deliver much greater value for money for the NHS than proceeding with a NICE recommendation through a single technology appraisal at this stage.

Prioritisation strategies

In establishing the best way to implement NICE guidance, NHS England can consider a number of prioritisation strategies. NICE evaluative processes do not explicitly consider particular prioritisation strategies, such as watchful waiting and treatment sequencing. *Treatment sequencing* involves initially treating people with a less costly and less effective treatment (e.g. response guided pegylated interferon with ribavirin), then retreating people who do not achieve SVR (treatment failures) with more expensive and more effective treatment (e.g. ledipasvir-sofosbuvir or others). *Watchful waiting* consists of monitoring the patient until their disease progresses to a more severe stage then treating.

Watchful waiting strategies may be particularly cost-effective for patients with mild disease and a low likelihood of onward transmission. For example, it is estimated that 70% of patients will not develop cirrhosis, and among the 30% who do, time to progression is 40 years on average (3). If the aim of treatment is to reduce the incidence of events with a high health burden and/or health care costs (decompensated cirrhosis, end stage liver disease, liver transplant), then making new drugs available to all patients with chronic hepatitis C could represent overtreatment as up to 70% of those receiving high cost drugs would, in the absence of those drugs, have experienced little or no ill health consequences from their disease.

An example of a watchful waiting strategy is making ledipasvir-sofosbuvir available for patients with METAVIR score F3 but not for patients at F2-F0. This issue was not discussed at the NICE appraisal committee meeting but has direct relevance to the value of the new treatments for chronic hepatitis C. The model for ledipasvir-sofosbuvir, for example, does not use METAVIR score and instead classifies the disease stages into cirrhotic and non-cirrhotic.

NHS England believes it is essential for NICE to revisit the cost effectiveness analysis for the hepatitis C drugs now that policies have been formed by NHS England. Patients with cirrhosis now are unlikely to progress to End Stage Liver Disease as they will be treated, patients with F3 fibrosis will be unlikely to progress to cirrhosis once a F3 treatment strategy is in place. The probability of disease state progression will be substantially changed for an F0 patient with the change in the clinical pathway.

NICE asked NHS England to clarify aspects of its comment through the following questions.

QUESTIONS SPECIFIC TO THE APPRAISALS

Q1. Confirmation as to the extent of the impact on its budget

The key variables in defining budget impact are:

- the numbers of patients coming forward for treatment on an annual basis;
- the relative genotype frequencies;
- the treatment durations;
- the real world viral responses taking into account treatment compliance, and;
- the costs of the drugs to the NHS, including discounts offered by the companies for higher annual patient numbers.

The budget impact of the annual costs covering all drugs, all genotypes and all stages of disease for diagnosed patients is estimated to be between £285-772 million per year. However, if a hypothetical but unrealistic 100% of the estimated 80,000 population with confirmed chronic HCV comes forward for treatment our analysis suggest budget impact up to circa £1.9 billion.

Numbers coming forward for treatment

Although there is no patient registration system or national activity audits, the clinical advice to NHS England accurately predicted the uptake for treatment of end stage liver disease in relation to our first Early Access Scheme and so we have confidence in the estimates regarding the second access scheme for those with cirrhosis soon to be launched pending final approvals. Our confidence is related to the fact that most of these patients (F4) are already accessing specialist healthcare. For these two schemes NHS England is planning to treat 4,600 patients in 2015/16.

If there is access to all patients of all stages of disease (F0-4) with chronic HCV NHS England estimated this could move patient treatment numbers to range from 7,000 (manageable but not currently affordable within current clinical services) to 20,000 patients per annum which will require significant service transformation along the entire pathway (from diagnosis to treatment) in order to meet expectation generated by the guidance even if this were affordable, which it is currently not. NHS England believes it is unlikely that calls for treatment access will exceed 20,000 per annum, but there are international examples where annual access rates have increased to 40% of the 80,000 known infected patients (which would be 32,000 per annum).

The budget impact model

The model and figures presented are based on the following assumptions:

	Assumptions used
Patient population	In the NICE ACD the total population figure of 167,000 is used, within which it has been taken that 28,500 are known to the health system. 21% of the known patients have cirrhosis of which one third are decompensated cirrhotics. 14% of non cirrhotic patients are F3, 14% of patients are interferon

	unsuitable. Similar proportions have been applied to the unknown (de novo) patients.
Genotypes	The split between genotypes are GT1 - 45%; GT2 - 7%; GT3 - 44%; GT4 - 2%; GT5 - 1%; GT6 - 1%
Drugs	Clinical opinion supports the proposal that GT3 non cirrhotic naïve patients will be offered pegylated interferon plus ribivirin as the first line treatment Daclatasvir plus sofosbuvir will be used in those patients unsuitable for interferon The NHS will only fund a maximum of 12 weeks treatment in ALL cases For GT1 non cirrhotics the course length for the Gilead FDC is assumed to be 8 weeks
Costs	All medicines costs are based on full list price with the exception of ribivirin and pegylated interferon which are based on average discounted prices. Costs have been adjusted by 11% to reflect the average impact of VAT (based on data from the early access scheme in 2014/15).

Estimated budget impact

	Patients numbers	Cost £m	Patients numbers	Cost £m	Patients numbers	Cost £m
Decompensated Cirrhosis	1,100	60	1,100	60	1,100	60
Compensated cirrhotic	3,500	153	3,922	172	3,922	172
Non cirrhotic (known to system)	2,400	72	14,978	286	22,095	422
De Novo					4,883	119
Total	**7,000**	**285**	**20,000**	**518**	**32,000**	**772**

Q2. What other areas of treatment would be impacted by the need to find the cost of this technology

NHS England will have to cut expenditure on other specialised service developments being considered for 2015/16 and 2016/17. In addition, on the scale of budget impact, further savings will need to be delivered to maintain the budget position for specialised services. This will require service delivery restraints for other services (the specific services are yet to be defined). To illustrate the opportunity cost York University have modelled that a budget impact of £700 million is associated with 3,598 additional deaths elsewhere in the NHS, which represent 16,308 years of life lost and 54,128 lost QALYs. If the incremental cost-effectiveness ratio (ICER) for NICE recommended hepatitis C treatment is less than £13,000 (see below), the health gains to patients receiving the new treatments for hepatitis C may exceed the health losses elsewhere in the NHS.

The NHS England Mandate from government requires us to deliver within resource allocations made available by parliament. Therefore all other investment decisions will be impacted by decisions relating to Hepatitis C. The impact will be felt across 70 Specialised Clinical Reference Group areas and over 130 services. It would not be appropriate to identify where we would need to make reductions to other services at this stage, and a very careful process would have to be followed before deciding what cuts would have to be made. Therefore the information in this section must be understood as contextual only. It serves to illustrate the complex nature of reprioritising financial allocations to clinical services. We are emphatically not saying that these are the reductions in other services that would actually be made. The calculations are illustrative only and are used to give a feel of the scale of reductions in other services that might be required.

For high budget impact scenarios it is impossible to manage large changes in budget demand in year. The annual budgeting for 2015/16 was set in December 2014. For high budget impact scenarios the 90-day rule of mandated compliance with a NICE TA becomes very problematic to implement at all. We would have to carry out sufficient modelling, engage with the public, take a decision to our Board, and then wait for the implementation of whatever new policies are adopted to begin to deliver savings in order to begin the process of delivering the necessary savings. Achieving full savings would then take a further period of time depending on how quickly existing patients end the courses of treatment we have had to withdraw or reduce. We would in particular wish to avoid any situation where cuts to be made were dictated not by where those cuts would do the least harm but where savings would begin to be seen the most quickly.

For context, a growth in hepatitis C demand of up to £772m per annum within 12 months of implementation would be greater than the total funded growth in expenditure within the total specialised services allocation in 2015/16 of £592m (4.4%). This level of underlying growth within specialised services gives little scope for spend over and above that required to deliver core activity growth within provider contracts.

The opportunity costs from funding new interventions

The opportunity cost of funding new medications is the health forgone as a result of those resources being unavailable to fund other alternative competing priorities [(1)]. Recent empirical research on the cost-effectiveness threshold to inform NICE decisions has estimated that the additional cost which results in 1 QALY being forgone by NHS patients is approximately £13,000 (central estimate) [(2)], lower than implied by the existing NICE threshold range.

Furthermore, this research highlighted that technologies with non-marginal budget impacts on the NHS budget are likely to displace disproportionally more health, implying an even lower cost-effectiveness threshold. The opportunity cost considered by NICE is represented by the NICE threshold, at £20,000 to £30,000 per quality-adjusted life year (QALY) gained. The empirical evidence of the lower threshold suggests that when NICE approves medicines with ICERs £20,000 or more and/or that have a large budget impact, the services that are displaced may

have generated more health for NHS users than that which is gained with the NICE approved therapy.

The opportunity costs of the new treatments for chronic hepatitis C

The new treatments for chronic hepatitis C have the potential to reduce morbidity and mortality as well as making a significant public health impact. However, these treatments represent a significant budget impact given their high acquisition cost and large patient population. For the purposes of illustration assuming a budget impact between £300 million and £700 million per annum it is possible to describe the health that could have been generated with existing NHS services without those funds being diverted to new treatments for hepatitis C; in other words, it is possible to quantify the health that other types of patients will forgo given the displacement of their services to release budget for the hepatitis C products. The work that was undertaken to estimate the cost-effectiveness threshold also produced a calculator that would break down the impact on displaced services in terms of reduction in NHS spend per disease area and associated additional deaths, life years lost, total QALYs lost, QALYs lost due to premature death and QALYs lost due to reductions in health-related quality of life [1, 3].

Table 1 shows the health forgone from activities that are likely to be displaced in the NHS from funding the new hepatitis C treatments assuming a budget impact from those products of £300 million and £700 million using the opportunity cost calculator [1]. Again, we stress that these are illustrative only and do not imply any decision about how we would actually respond to a recommendation.

Table 1 also shows the detailed breakdown of the disease areas where the health losses are likely to occur in the NHS. A budget impact of £300 million is associated with 1,542 additional deaths for other types of patients elsewhere in the NHS, which represent 6,989 years of life lost and 23,198 lost QALYs. A budget impact of £700 million is associated with 3,598 additional deaths elsewhere in the NHS, which represent 16,308 years of life lost and 54,128 lost QALYs.

Table 1. Estimates of health displacement elsewhere in the NHS from funding the new treatments for chronic hepatitis C. This reflects a central estimate of the cost-effectiveness threshold of approximately £13,000

	Additional deaths		**Life years lost**		**Total QALYs lost**		**QALYs lost due to premature death**		**QALYs lost due to effects on quality of life**	
Budget impact (million)	£300	£700	£300	£700	£300	£700	£300	£700	£300	£700
Total	1,542	3,598	6,989	16,308	23,198	54,128	4,493	10,484	18,704	43,643
Cancer	112	262	1,125	2,625	790	1,843	732	1,707	58	136
Circulatory	683	1,595	3,479	8,118	3,235	7,548	2,211	5,159	1,024	2,389
Respiratory	401	936	482	1,124	6,881	16,055	302	704	6,579	15,350
Gastro-intestinal	78	183	740	1,726	1,317	3,072	485	1,132	831	1,940
Infectious diseases	22	50	159	372	470	1,097	108	252	363	846
Endocrine	20	47	149	348	1,817	4,240	97	227	1,720	4,013
Neurological	36	84	194	453	3,272	7,635	128	299	3,144	7,336
Genito-urinary	67	157	98	229	317	741	62	145	255	596
Trauma & injuries	-	-	-	-	-	-	-	-	-	-
Maternity & neonates	0	0	13	30	14	32	9	22	4	10
Disorders of Blood	11	26	50	116	655	1,529	34	79	621	1,450
Mental Health	85	198	385	899	2,858	6,669	249	582	2,609	6,087
Learning Disability	1	3	6	14	21	48	4	10	17	39
Problems of Vision	2	4	7	16	127	297	5	12	122	285
Problems of Hearing	1	2	4	10	420	981	3	7	417	973
Dental problems	0	0	0	1	204	476	0	0	204	475
Skin	7	17	33	78	58	136	21	50	37	86
Musculo-skeletal	12	27	53	124	696	1,625	35	81	662	1,544
Poisoning and AE	1	3	6	14	25	57	4	9	21	48
Healthy Individuals	1	2	5	11	20	47	3	7	17	40
Social Care Needs	-	-	-	-	-	-	-	-	-	-

The ability to undertake further research to support future care of HCV

The evaluations NHS England suggests should be carried out by a 'recommended with research' appraisal include:

- A direct comparison of all the relevant treatment options, including new treatments, watchful waiting, and treatment sequences.
- Subgroup analyses by patient characteristics that affect the costs or benefits of treatment, such as genotype, prior treatment experience, interferon eligibility and severity of disease.
- The impact of uncertainty in the effects of treatment on the costs and benefits of the optimal strategies.
- The costs and benefits of reducing onward transmission and reinfection.
- The implications of current NHS England commissioning policy for treating those with decompensated cirrhosis and its impact on extending access for people with cirrhotic and non-cirrhotic disease.
- The level of investment to increase treatment uptake that is warranted alongside the optimal strategies in each of the patient groups.
- The characteristics required of any further new treatment in order for it to offer value to the NHS (threshold levels of effectiveness and cost).

References

1. Claxton KP, Martin S, Soares MO, Rice N, Spackman ED, GHinde S, et al. Methods for the estimation of the NICE cost effectiveness threshold. Health Technology Assessment. 2015;19(14).
2. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. London: NICE2013.
3. Claxton K, Martin NK, Soares M, Rice N, Spackman DE, Hinde S, et al. Opportunity cost calculator How much and what type of health is lost2014.
4. Faria R, Barbieri M, Griffin S, Palmer S, Sculpher M. Economic Analysis to Support NHS Implementation of Hepatitis C Drugs: Scoping Study (draft)2015.

Q3. What difference would it make if the timeframe was extended?

Although we stand by our observation above that it is in fact impossible for us to accommodate positive guidance within the usual timescale, because of the scale of changes in other services that would have to be considered and consulted on, NHS England is not specifically seeking to extend the timeframe for mandatory guidance as this in itself would not address the concerns raised. It is seeking a more substantial revision to the strategy to deliver care for hepatitis C that includes a managed market entry and a cost effective approach to implementation for each patient cohort. To deliver this strategy a pause in the process of the technology appraisals combined with delivery of national clinical policy will secure access for the patients with advanced liver fibrosis and cirrhosis, i.e. those in urgent need of immediate treatment. A pause would allow a re-working of the cost-effectiveness models to include watchful waiting and the formation of multiple technology appraisal

that this complex mix of drugs, genotypes, treatment durations, and access to care demands.

However, if NICE proceeded to give an unrestricted guidance for the oral drugs the work rate of 20,000 patients per year or more could not be absorbed by the current hepatology services. A new service delivery model will need to be defined and commissioned, for example test and treat services coordinated by specialised nurses.

NHS England considers the flexibility of a 'recommendation with research' recommendation to allow some control over choice of treatment relevant to disease presentation and progression and the relative cost of the drug.

NICE recently issued guidance which stated that 'If there is more than one NICE-approved medicine for the condition, providers and commissioners must not recommend that any one of them is used **routinely** in preference to the others (unless an order of preference is stated in the TAs or HSTs). Similarly, they must not recommend that a medicine that has not been assessed by NICE is used **routinely** in preference to a NICE-approved medicine.' By issuing STAs for the different treatments that are available NICE is effectively forcing NHS England down a treatment line which may not be in the best interest of patients or the NHS as a whole.

Q4. Whether there is a possibility of the overall budget being increased to meet the recommendation

NHS England's budget for 2015/16 has been set by parliament and government and our Mandate requires that we operate within it. The growth in hepatitis C demand of up to £772m per annum within 12 months of implementation would be greater than the total funded growth in expenditure within the specialised services allocation in 2015/16 of £592m (4.4%).[1]

In total, specialised commissioning allocations have grown by 12.9% across 2014/15 and 2015/16, whereas other areas of expenditure have grown by only 6.4%. There is therefore no realistic potential to divert further funding from other areas of commissioning.

In summary, there is no spare capacity in the system to afford increased hepatitis C expenditure at the scale potentially suggested by forthcoming NICE appraisal decisions.

[1] Overall allocation growth less funding for the elimination of the structural deficit in specialised commissioning

QUESTIONS NOT SPECIFIC TO THE HEPATITIS C, RAISING GENERIC CONSIDERATIONS FOR FUTURE APPRAISALS

Q5. Is NHSE's key point the % of the budget, which would be required to meet an unrestricted positive recommendation (for all eligible patients)? If so, what %?

NICE decisions for a technology appraisal can be absorbed in commissioning plans either by NHS England (for directly commissioned services) or CCGs where the budget impact is relatively small. The budget impact illustrated by hepatitis C drugs is of a scale where the implementation will displace other services or service development. The specific mitigation proposed in this case is a multi-year implementation that builds on our early access policies, targeting the greatest clinical needs first, avoiding relatively low value treatments, and increasing knowledge of cost effectiveness.

The broader point is to develop the method and means to bring forward consideration of budget impact through closer collaboration in planning the appraisal pipeline, including the use of multiple technology appraisal where indicated.

Our immediate concern is any recommendation that has a severe impact on the overall pattern of expenditure, particularly one that is unforeseen or that must be implemented in a short period. This could be measured as simply the projected cost of implementation expressed as a percentage of the total available resource. We are open to discussion with NICE, and other stakeholders, about what percentage ought to call the wider considerations we refer to above into play.

The threshold will be a function of the scale of the cost impact, the speed of its uptake, the anticipated growth in available NHS resources and unavoidable competing demands for those resources in the same period. A consideration is whether any impact threshold is at single appraisal level or set against the cumulative effect of all decisions over a time period.

To illustrate the position, in the current economic climate with typical upward pressure on spend from population need, the total new resources available for all non-demographic cost pressures across the whole of specialised commissioning, including funding any new technologies/drugs is approximately £400m. A single decision or group of decisions by NICE within a year with a value of more than £70m brings budget impact into play.

We are concerned of the effect of any recommendation to transfer resources on a significant scale from other treatments or areas into the recommended treatment. This is of particular concern if this is done without a public debate not only about the benefits of the treatment recommended and the needs of that patient population but also about the benefits of other treatments and needs of other patients. We accept that NICE's standard processes, which acknowledge that any recommendation may displace spend elsewhere but that that displacement is acceptable at a cost effectiveness threshold at about £20,000 and up to £30,000 per QALY, are usually fit for purpose. Where the displacement is relatively small in proportion to total spend it is reasonable only to be satisfied that the displacement results in an overall

improvement in cost/benefit. Although there may be reductions in treatments available in other areas as a result of any positive recommendation, they will be in such cases relatively small and manageable.

The requirement to deliver a TA which requires possible transfer of a significant proportion of the available resources for drugs spend away from current investment to one group of patients introduces additional considerations. We stress this is not because those patients are in any way undeserving of treatment and care, nor does it depend on any characteristic of the patients, the condition or the treatment. Rather it is that we do not think it is appropriate in effect to require very substantial reductions in other areas, without that fact being considered and some view taken on what those areas would be, whether reductions on a sufficient scale could be implemented at all, and whether the values of the NHS require some other approach. For such a significant impact we do not think it is adequate simply to focus on the benefits of the treatment being appraised. This is a key consideration and one which would apply to any TAs of this magnitude of impact irrespective of the patient group involved.

Q6. What evidence is required from NHS England or elsewhere to demonstrate that a technology is in this category?

The greater the budget impact the greater the difficulty a commissioner has to define the arrangements for service delivery. Although a threshold is arbitrary NHS England is open to a discussion with NICE about a budget impact where NICE might consider a revised approach in its appraisal position.

The evidence that might be required for any future considerations is the commissioning portfolio size defining the budget on which the technology impacts (for hepatitis C this is specialised services in NHS England), the split between cost of the technology and the cost of the service impact, and the potential gains across the wider health and social care system. In year implementation requires capacity within allocated budgets.

Q7. What evidence would the Committee be seeking from NHS England in order to determine whether its recommendation is appropriate?

NHS England considers that NICE through its appraisal process will gather information on budget impact to support these scenarios. The relative prioritisation of one treatment decision over another remains with the service commissioner and we are not proposing that NICE takes on this role. Managed market entry will aid the implementation of high cost impact technologies through NICE/Commissioner collaboration.

We would not ordinarily expect the cost of implementation to be a particularly contentious issue, and NICE's costing and budget templates can typically be used to give a sufficiently precise figure. The size of the NHS drug expenditure and commissioning allocations are known, and we can provide typical spend in various therapeutic areas to assist a committee to contextualise the impact of, say,

recommending new spend of £300-700m within 12 months. We would not be able to suggest that the effect of a recommendation would be to make specific cuts in specific areas, and invite the committee in effect to make a choice. While that is close to the reality of a decision where a recommendation would have a major expenditure impact, it is not a decision that can be left to an appraisal committee. The process for making such important decisions would have to be carefully considered to maintain public and professional understanding and confidence. NHS England would have to consider how to react to such a recommendation, having in mind its duties of public engagement, to reduce health inequality, and to deliver the NHS Constitution.

However, we would be happy to provide further information and to continue to work closely to ensure that 'real world' commissioning considerations are increasingly fed into appraisals and so frame NICE's appraisal deliberations.