NHS England response consultation: (Hepatitis C (chronic) - ledipasvir-sofosbuvir) [742]
Comments on the content of the NHS England responses

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DOCUMENT 1B

1. Uncertainty in treatment effects and comparative effectiveness

"*Furthermore, the clinical studies are mainly non-randomised open-label studies without concurrent controls. These studies are at higher risk of bias and additional uncertainty from the lack of randomised control. Evidence from these studies should therefore be interpreted with caution.*"

It is not clear how the lack of randomisation is necessarily as an issue here, as the purpose of these trials has been to establish an absolute SVR rate rather than determine superiority over other treatments. There are well-known issues of treatments being less efficacious in clinical practice compared to clinical trials, but it is simply a case of recognising this; a randomised trial would allow comparative measures such as odds ratios to be calculated with less bias, but a cost-benefits assessment ultimately requires a point estimate of the SVR rate. In any case, it is not clear whether the new oral regimens will be less effective in practice. This was observed for pegylated interferon and ribavirin, but these regimens are harder to tolerate and of long duration, so are less likely to succeed outside the more regimented environment of a trial and its selection procedures. The newer treatments do not have the same drawbacks, so rates may be more comparable in clinical practice.

2. Development of the evidence base

"The small sample sizes for particular patient groups may have implications for external validity. For example, the SVR rate for ledispavir+sofosbuvir (LED+SOF) over 12 and 24 weeks in cirrhotic people with HCV genotype 1 was obtained from the ION-1 study. In this study, 34 patients with chronic hepatitis C genotype 1 and cirrhosis received LED+SOF over 12 weeks, of which 32 (94.1%) achieved SVR. Had the trial recruited an additional patient with those characteristics, and that additional patient had not achieved SVR, the SVR rate would have reduced to 91.4%, a drop of 2.7%. Had an additional 5 patients been recruited who did not achieve SVR, the SVR rate would have reduced to 82.1%. Reductions in SVR rates are likely to affect the cost-effectiveness of the new treatments."

This last sentence in particular is not a very useful line of reasoning, and focus should be on the statistical uncertainty. The 95% confidence interval for the proportion 32/34 is 80.3-99.3%, so a true rate around 80% is unlikely. Put another way, the likelihood of 5 additional patients being recruited with no SVR, given the observed 94% rate in the observed 34 patients, is implausible; the confidence intervals should be considered instead. The question of "external validity" in terms of whether the recruited patients are representative is perhaps more pertinent than the size of the sample and what might have happened in the trial.

3. The static nature of the cost effectiveness models

"The cost-effectiveness models utilised in the ACD did not include reinfections or onward transmission. Excluding reinfection is likely to overestimate the benefits and underestimate the costs of more effective treatments since re-infected individuals require new treatment. Excluding onward transmission may underestimate the benefits of more effective treatments. The impact of excluding reinfection and

onward transmission is likely to be larger and depends on the prevalence of the disease and on the probability of risky behaviours by the patient population."

This is an important limitation of the cost-effectiveness models. However, we understand that work on a HCV dynamic transmission and cost effectiveness model is currently being undertaken by the University of Bristol. Outputs from this modelling work could inform prioritisation of new treatments. As it currently stands, it is not clear that prioritising treatment for patients with fibrosis stage F3 alongside instituting a F3 surveillance programme (after treating cirrhotic patients) is more cost effective than treating those in F0-F2 groups, particularly if patients in F0-F2 are more likely to be current injectors and hence their treatment could prevent onward transmission. In view of the comments by NHSE that the potential financial impact of any treatment strategy is high, so there is minimal room for uncertainties in the assumptions, NHSE should be clearer about the evidence to support an F3 all-oral treatment prioritisation strategy as the preferred option during the proposed evaluation period.

4. The omission of relevant treatment strategies: watchful waiting and treatment sequences

"Treatment sequences include strategies where patients are treated with a cheaper less effective regimen (e.g. Pegylated Interferon and Ribavirin) and patients who do not achieve SVR are re-treated with a more expensive more effective regimen"

Although these strategies are sensible from a cost-effectiveness perspective, they rely on the assumption of being able to implement in practice. Uptake of Pegylated Interferon and Ribavirin (IFN+RIB) has always been low because this drug therapy is of long duration, difficult to tolerate, and its side effect profile makes it difficult to roll out in community settings where those in need of therapy can be accessed. Uptake has also fallen in recent years; speculatively, this may be due to patients waiting for new treatments. Overall, it does not seem likely that large numbers will be treated with IFN+RIB and strategies based on use of these therapies are likely to widen health inequalities as they will be less accessible to those groups who are marginalised, including people who inject drugs. There is also the possibility of deliberate drop-out if it is known that new treatments will be offered in case of failure/intolerance. Therefore strategies of tackling HCV in the long-term that rest on treating large numbers of patients with IFN+RIB, or other regimens that are sub-optimal for the patient, may be untenable.

5. The opportunity costs of high cost medications affecting large populations

6. The capacity constraints to offer treatment to all eligible patients

7. Implementation of 'recommended as option' guidance

8. Investment in increasing uptake of cheaper treatments vs investment in expensive treatments

It is not known whether any efforts to increase uptake of traditional therapies (Peg IFN & Ribavirin) would be successful (See previous comment).

"*It is clear from the clinical trial evidence that for many patient groups sofosbuvir/ledipasvir is an excellent treatment. However for others, who fell outside the relatively restrictive clinical trial programme, it is difficult given the currently available data to say with certainty how and in whom the sofosbuvir/ledipasvir combination should be used*"

"*The place of sofosbuvir/ledipasvir in the treatment of some HCV groups is inadequately defined by the published literature*."

There are a number of trials in different patient groups showing high efficacy in most of the main patient groups that would be treated under the NICE recommendations. The question really is whether alternative strategies are nearly as good that may be delivered at lower prices for some groups, not the uncertainty of the efficacy and suitability of the regimen itself.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
"Drug treatment for hepatitis C could be commissioned on an evaluative basis for a fixed two year period, with robust data collection and analysis included as an integral part of the programme delivered by regional treatment networks. This would allow thorough evaluation of available therapies ahead of a more long term commissioning strategy".

For this to be possible NHS E would need to ensure that they gather the national HCV Rx monitoring minimum dataset ***from all centres*** providing treatment, ***from the point that new therapies are rolled out*** (the content of this dataset has already been agreed with NHS E SC). NHS number will be critical for future linkage of this minimum dataset to other data in the future, subject to the necessary governance arrangements. The HCV national Rx monitoring dataset represents the minimum dataset that could support such an approach and these data should be made available to PHE for PH health monitoring purposes on an annual basis.

NHSE should also clarify the time period of the evaluation as in the final section "Any other comments" a five year time period is referred to:

"It is for this reason coupled with the uncertainties highlighted above that NHS England wish to propose an evaluative process to take place over the next five years".

DOCUMENT 3

"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."

This strategy has not been evaluated in terms of the potential for failing to reduce preventable disease compared with more widespread treatment strategies. In particular, the following are not known:

1) Whether SVR rates are as high once cirrhosis has developed.
2) Whether liver damage is fully reversible and the potential for continued poor health/loss of life once SVR is achieved for those that have developed cirrhosis compared to SVR at earlier stages.
3) How many patients may be "missed" that develop cirrhosis before they are indicated for treatment by fibrosis staging; this may occur due to rapid disease progression in some patients, and/or due to imprecise grading of fibrosis stage, i.e., mistaking F3 grades patient for an earlier stage.

The generic issue of affordability is a real one. Where treatments are proven to be cost effective by NICE but there are insufficient resources within the NHS to fund them, then broader discussions are required as to whether additional funds should be sought from elsewhere to meet these costs or whether some cost effective therapies (according to current NICE thresholds) will no longer be made immediately available on the NHS. That said, since hepatitis C is a life threatening liver disease

principally of marginalised populations, it would presumably remain an NHS priority in view of current government policy to tackle health inequalities and premature mortality from liver disease.

"Prioritisation strategies
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".

This rationale for the watchful waiting strategy assumes that those "waiting" for treatment have a low likelihood of onward transmission and does not offset the "gains" from a low disease progression rate. However, since the majority of HCV infection is among current or past injecting drug users - and most infection is acquired early on during an individual's injecting history - then it follows that those who have mild disease are likely well and still injecting as opposed to those who have cirrhosis, are older, have poorer health and therefore less likely to be injecting. If not treated, the group with mild disease who inject may continue to transmit and the expected reductions in incidence in high health burden events may not be observed. As mentioned earlier, dynamic transmission and models need to be used evaluate the cost-effectiveness of treatment on preventing end-stage liver disease and cancer both directly on an individual's disease progression and indirectly by interrupting onward transmission.

*"**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)".*

To a greater or lesser extent, all these areas of work will require data on HCV treatment uptake and outcome from all clinical centres. This further reinforces the need for a national HCV treatment monitoring dataset with mandatory submissions from all clinical centres. These data should be made available to PHE for public health monitoring of equitable access and health outcomes.