Comments on the ACD Received from the Public Through the NICE Website

Name	[redacted]
Role	other
Other role	Academic gastroenterologist (Emeritus Professor of Clinical Medicine at UCLA) and previous Chief of Gastroenterology at a UCLA affiliated hospital (Olive View-UCLA Medical Center) which is a public hospital that is part of the Los Angeles County system
Location	US
Conflict	no
Notes	I have had a career-long experience in using evidence to assess various interventions, mostly for gastrointestinal disease. Â I am currently one of the editors of the Cochrane HepatoBiliary Group (Cochrane Collaboration).
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	There have been at least 8 randomized trials of alpha-interferon vs no treatment that have assessed clinical outcomes (Valla, Hepatology 199929:1870-5 Mura, Hepatology 199929:A1251 Ikeda, J Hepatol 199828:910-1 Testino, Recenti Prog Med 200293:302-7 Fartoux, Clin Gastroenterol Hepatol 20075:502-7 Di Bisceglie, N Engl J Med 2008359:2429-41 [HALT-C] Hofer, Hepatology 200950:680A (EPIC3) Afdhal, Hepatology 200440:239A [early CO-PILOT report] as well as two using other types of interferon (Bernardinello, Hepatogastroenterology 199946:3216-22 [&#946-interferon] Pockros, Hepatology 2007 45:569-78 [&#947-interferon]) and only one of them has shown a possibly favorable benefit (Mura). Curiously, this trial was published as an abstract in 1999 and, to my knowledge, has never appeared as a final paper. (The other allegedly randomized trial, Nishiguchi, Lancet 1995346:1051-5, has a disproportionately longer followup in the control arm and may not truly have been randomized.) Where is the evidence to justify treatment for anybody? This is particularly the issue since the vast majority of infected patients will never get into trouble even if they are not treated.
Section 2 (clinical need and practice)	The endpoints of therapy that are used in hepatitis C treatment trials are surrogate ones that have never been validated. Data that have emerged from the three large long-term treatment trials of patients with severe histologic disease (HALT-C, EPIC3, CO-PILOT) have indicated that the endpoints could improve even though the patients did not, observations that would be incosistent with the surrogates being valid. The focus on sustained viral responses (SVRs) is an incorrect extension of the HIV model. Â (The vast majority of hepatitis-C infected patients will never get into trouble even if not treated and the serum level of virus may be an epiphenomenon if the virus infects hepatocytes by being in the neighborhood). Since there are prognostic factors for SVRs (little fibrosis, recent infection, female gender, normal weight, etc.), it is incorrect to assume that a 50% SVR rate translates into a 50% reduction in future morbidity. (Many of these factors identify people less likely to get into trouble and disease progression may largely be

	confined to those who do not respond.) There is insufficiant evidence to recommend treatment based on improvements in these surrogate markers.
Section 3 (The technologies)	The medications clearly have toxicities, including occasional deaths. They are expensive. Why are we asking patients to undergo all of this if we do not know that we are providing benefit, especially since the vast majority of them will never get into trouble even if they are not treated? A number of inception cohort studies (long-term followup of an entire population of infected individuals, including my own (Ann Intern Med 1993119:110-5) have indicated that the risk of decompensated cirrhosis or cancer is closer to 10%. Furthermore, epidemiologic data indicate that most infected individuals will never get into trouble. Â (For example, if there are 4,000,000 carriers in the United States, as well as 10,000 annual deaths [the figures that are widely cited to indicate the impact of these infections], the average time that it would take to get into trouble [latent phase] is 400 years.) We also know that not everybody who has an SVR is protected from the subsequent development of end-stage liver disease or hepatocellular carcinoma (e.g., Hofer, Hepatology 200950:680A).
Section 4 (Evidence and interpretation)	See above for other comments. The various cost analyses with which I am familiar all suffer from biases that favor the intervention. It is often assumed that non-responders will have the same natural history as would those who had never been treated. Â Since responders tend to have more favorable characteristics, non-responders likely have a worse long-term course. Â It cannot be assumed that the life expectancy of hepatitis-C-infected individuals is the same as the normal population, since these people are infected for some reason (typically either a high-risk behavior or a blood transfusion given for some underlying disease such as arteriosclerosis). Some models assume that hepatitis C can only progress in a more severe direction, discounting the possibility of spontaneous recovery or at least the cessation of further inflammation and fibrosis. The natural history of hepatitis C is often derived from studies from tertiary referral centers. Â Studies of large inception cohorts, as well as epidemiologic considerations discussed above, suggest that the natural history will be less severe.
Section 5 (implementation)	The enthusiasm for treating hepatitis C has largely been based on marketing campaigns rather than convincing data for true (clinical) efficacy. Even the statement that the purpose of treatment is to get rid of the virus misses the point that the real purpose of treatment is to prevent end-stage liver disease. These are not the same. Perhaps NHS funding would be better spent mounting a public education campaign explaining the true risks of the disease, namely the low probability of developing liver failure, and the lack of information about any known true benefits from treatment.
Section 6 (proposed recommendations for further research)	The data would suggest that consideration should be given to restricting, rather than expanding, treatment programs for hepatitis C.
Section 7	

(related NICE guidance)	
Section 8 (proposed date of review of guidance)	
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