Social Values and Health Priority Setting Case Study

Title of Case Study	**Telaprevir for chronic hepatitis in the UK**
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Case Summary (approx. 350 words) Please include information here about why the case is of particular interest	The assessment of Telaprevir for chronic hepatitis by the National Institute for Health and Clinical Excellence (NICE) in the UK demonstrates the application of a variety of social value judgments by NICE even in a case where cost-effectiveness was shown to be well below the established threshold. Thus it indicates that social values are taken into consideration by NICE not only in 'controversial' cases where interventions provide clinical benefit but where cost-effectiveness is not demonstrated, but also in cases where cost-effectiveness is easily proven. While the good quality of the clinical evidence and the favourable ICER per QALY undoubtedly played a role in the decision to recommend Telaprevir, public health considerations around reducing hepatitis C transmission rates and concerns related to stigmatization also influenced the decision. The case thus reflects NICE's commitments to non-discrimination and equality, and adherence to the principles set out in its 'Social Value Judgments'. To what extent close adherence to these principles was furthered by the favourable cost effectiveness calculations remains an unanswered question that is worthy of future consideration.
1. Facts of the case	**Facts of the case**
Please include information on as many of the following as are relevant to the case: • At what condition is the intervention, program or service aimed? • What are its effects? Eg. Is it curative, preventative, palliative, life-prolonging, rehabilitative? • Is there a relevant comparator? If so how does this intervention, service or program compare to the alternative? Include ICER estimates/QALY costs if relevant. • What are the significant features about the condition and/or about the patient population in this case? Eg. patient population is very young, very old, condition is rare, life-threatening, life-limiting etc. • How are the benefits of the intervention distributed across the patient population and/or across	• Telaprevir is a treatment for chronic hepatitis C. Its manufacturer, Janssen-Cilag International N.V., obtained a UK marketing authorisation in 2011 for Telaprevir to be used 'in combinnation with peginterferon alfa and ribavirin for the treatment of genotype-1 chronic HCV in adult patients with compensated liver disease (including cirrhosis) who are treatment naïve, or who have been previously treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders' (NICE 2012). • Two large Phase III randomised controlled trials (RCTs) demonstrated Telaprevir's ability to increase sustained virological response (SVR) rates when it is used in combination with peginterferon alfa and ribavirin (PR) (NICE 2012a). SVR rates are considered a significant outcome in treatments for hepatitis C as they are an indication of the clearance of the virus from the blood (NICE 2011). • The ADVANCE trial (Telaprevir plus PR compared with PR only, included patients who were previously untreated) showed an increase of SVR rates by 31% in the Telaprevir arm (75% of patients achieved a SVR in the Telaprevir plus PR arm vs. 44% of patients in the PR alone arm) (NICE 2011).

time? • What is the cost or budget impact of the intervention/service/ programme? • What is the nature and strength of the evidence about the outcomes of the intervention, service or programme? Eg. randomized clinical trials, evidence on patient-related outcomes. • How did the issue about this case arise - for example, from clinical practice, from a policy setting, from a topic selection process?	• The REALIZE trial (Telaprevir plus PR compared with placebo plus PR, included patients who had been previously treated with PR but whose disease did not respond or only responded partially or has relapsed) showed an increase of SVR rates by 47% in the Telaprevir arm (64% of patients achieved a SVR in the Telaprevir plus PR arm vs. 17% of patients in the placebo plus PR arm) (NICE 2011). • Significant features of the treatment: 1) By increasing SVR rates Telaprevir increases the chances of stopping the progression of the disease to more disabling stages of liver disease and the follow-on complications that arise 2) It offers a promising treatment option to a group of patients with a type of the hepatitis C virus that is most resistant to treatment (genotype-1) and 3) it offers opportunities for a shortened duration of treatment by means of response-guided therapy if the response of patient's disease is positive (NICE 2011). • The benefits of the intervention (i.e. increased SVR rates) are consistent across the subgroups of patients (i.e. prior relapsers and null responders) although the numbers of these subgroups are small (Jones et. al., 2011). • ICER as calculated by the manufacturer: £13,553 per QALY for treatment-naïve patients and £8,688 per QALY for treatment-experienced patients (NICE 2011). The Evidence Review Group (ERG) conducted 8 additional cost-effectiveness analyses which resulted in a highest ICER of £18,360 per QALY for the treatment-naïve patients and of £10,388 per QALY for treatment-experienced patients. The ERG concluded that its additional analyses showed no substantial impact on the presented ICER (Jones et. al., 2011).
2. Policy decision: process	**Policy decision: process**
Please include information on as many of the following as are relevant to this case: • What stages/institutions were involved in the decision making process? • Is legal context important in this case? If so, in what way? • Who was involved? Eg. key stakeholders, the public, professionals, industry, patients, governmental or non-government policy actors. • How were they involved, and at what stages of the process? • Was there disagreement between any of the parties involved in the decision process? • Do any rules or frameworks exist to guide decision making? If so, were they followed in this instance? • Do mechanisms exist for challenging the decision at any stage of the process? • How, if at all, is the decision process or the decision itself publicized?	The guidance on Telaprevir was developed using by the UK National Institute for Health and Clinical Excellence (NICE) according to the rules of its Single Technology Appraisal process. The process in this case was as follows: • Evidence on Telaprevir was obtained by NICE from the pharmaceutical product's manufacturer, Janssen-Cilag International N.V. • The evidence was critically reviewed by an independent Evidence Review Group (ERG) (in this case the Southampton Health Technology Assessments Centre). • An Equality Impact Assessment was carried out as part of the scoping process. This included the view expressed by consultees that treatment availability for patients with mild/moderate hepatitis C who use drugs and/or misuse alcohol and are co-infected with HIV is a concern that affect equality (NICE 2011a). Any future guidance should address this concern and aim to remove inequalities (ibid.). • NICE invited clinical specialists, NHS commissioning experts and patient experts to attend Appraisal Committee meetings to consider the intervention, and to provide their views in writing. Details of all stakeholders invited to attend meetings were made available on the NICE website. • The Appraisal Committee at NICE met to consider the evidence for the intervention as well as the review of the evidence - the meeting was open to the public and the press (NICE publishes a notice of the meeting and a draft agenda on its website 20 days before the

	meeting date). • Professional groups and patient experts agreed that the use of Telaprevir in combination with PR increases SVR rates (NICE 2012b). Consultee comments on the draft scope included patient views that treating people for hepatitis C offers a further potential economic benefit through reducing future transmission (ibid.). Consultees highlighted that there is a huge need for alternative treatment to those who have failed current standard of care (ibid.). Patient groups highlighted that the removal of fear of long-term progression of the disease, transmission, discrimination and stigma (because of a link between chronic hepatitis C and intravenous drug use) currently connected to having chronic hepatitis C is a positive effect of the use of Telaprevir (ibid.). The manufacturer highlighted that the magnitude SVR improvement represents a step-change and demonstrates the innovative nature of Telaprevir; furthermore by potentially reducing future transmission rates Telaprevir should be considered positively in the light of public health interests (NICE 2011). • An appraisal consultation document summarising the evidence and views that were considered by the Appraisal Committee and its provisional recommendations were published for public consultation. • The Appraisal Committee decided to approve the intervention for its licensed indication as a treatment for genotype-1 chronic hepatitis C. The Final Appraisal Document containing the Committee's decision was sent to relevant stakeholders, offering them the opportunity to appeal. • No appeal was raised, so the Final Appraisal Document was published on the NICE website in March 2012.
3. Policy decision: content	**Policy decision: content**
Please include information on as many of the following as are relevant to this case: • What decision was made about the intervention, service or program, if any? • What values were relevant in the case or in the decision itself? For example, values of cost-effectiveness, clinical effectiveness, justice/equity, solidarity or autonomy. How did they affect the decision itself? • Was the way in which these values were balanced affected by any specific features of the case? For example, end of life considerations, age of patients, impact on carers, disease severity, innovative nature of the intervention, social stigma or cultural sensitivity? • Did the case challenge established guidance or 'decision rules'? Eg. on cost-effectiveness, cost thresholds, age discrimination etc. If so, in what	The intervention was approved. The main considerations taken into account were as follows: • *Clinical effectiveness* Based on data from the RCTs the Appraisal Committee "[…] noted that the teleprevir-containing regimen statistically significantly increased sustained virological response rates for 'standard' treatment (48 weeks) and response-guided regimens. […] The Committee included that telaprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone on inducing a sustained virological response in previously untreated patients" (NICE 2012a, p. 22-23). It also concluded that Telaprevir plus PR was more clinically effective than PR alone on previously treated patients (ibid.). The Committee considered that the more adverse reactions observed in the Telaprevir arms of the trials could be managed with current standard of care (ibid.). • *Cost effectiveness* At an ICER of £13,553 per QALY gained for treatment-naïve patients and £8,688 per QALY gained for treatment-experienced patients, the ICER was within the range that NICE would usually call cost effective, namely below £20,000 per QALY gained (NICE 2008). The Committee considered the manufacturer's base-case results as well as the deterministic ICERs for previously untreated

way? • Were any health system-wide considerations influential in the decision? For example, displacement of old technologies, professional practice issues, or infrastructure/feasibility considerations.	and previously treated patients. It noted that the ICERs appeared to be robust in the manufacturer's sensitivity analyses (NICE 2012a). Considering the ERG's comments and analyses the Committee accepted that the most plausible ICERs were £18,000 and £10,000 per QALY gained for previously untreated and previously treated patients respectively. Furthermore the Committee noted a number of health-related benefits, which, if taken into account, would decrease the ICERs, i.e. the public health benefit of reduced transmission and the reduction of stigma associated with having hepatitis C (ibid.). There was uncertainty around utility values, however, sensitivity analysis showed that variation in these values was unlikely to increase ICER above £20,000 per QALY gained (ibid.). • *Public Health Impact* The public health impact connected to the effect of a SVR on reducing transmission of the hepatitis C virus to uninfected people was highlighted by patient experts and acknowledged as significant by the Committee (ibid.). • *Equality Considerations* Patients co-infected with HIV and intravenous drug users had been excluded from the clinical trials. According to clinical specialists, the treatment of these patient groups is considered on an individual basis (ibid.). "The Committee concluded that although these patients were not represented in the pivotal clinical trials, based on the current evidence available, there was no reason to make any different provision for these patients" (ibid., p. 29). • *Innovation* The Committee agreed that Telaprevir is a major development due to its potential for shortening treatment durations. It accepted that Telaprevir is a valuable new therapy and that there were health benefits not captured in the QALY calculation which had been included in the Committee's considerations (public health and stigma considerations) (ibid.).
4. Discussion	**Discussion**
Please use this space to reflect on, for example: • The reasons or values explicitly used in making the decision. Do these reflect any institutional decision rules or statements of value, for example commitments to equality, non-discrimination or fairness? Do they reflect wider social, moral, cultural, religious values, and if so how? • Considerations not explicitly taken into account in the decision, but which may nonetheless have been important 'background' factors. These might include, for example, public opinion, political sensitivity, moral sensitivity, and international reputation, as well as cultural, social, moral, religious or institutional norms.	The following were the key positive reasons for accepting the intervention: • Statistically significant results in the RCTs in favour of Telaprevir plus PR (=clinical effectiveness considerations) • Potential of Telaprevir plus PR to cure (i.e. to achieve a SVR) patients with genotype-1 hepatitis C who were previously very difficult to treat (=clinical need/clinical effectiveness consideration) • ICERs well below the per QALY threshold from the beginning and robustness of ICERs to sensitivity analyses by the manufacturer and to additional analyses by the ERG, meaning the treatment could be considered a cost effective use of NHS resources (=cost effectiveness consideration) • Reducing transmission rates of the hepatitis C virus to uninfected people, hence having a positive impact on public health and future health care costs (=public health impact) • Reducing stigma and discrimination associated with being hepatitis C-positive (=social value judgement, i.e. reduction of stigma and promotion of non-discrimination) • Innovation provided due to potential of shortening treatment durations for patients who respond well to the treatment, hence

- The impact of the decision making process on the decision itself, if any.
- Any issues relating to implementation. For example, whether access may be restricted by capacity issues, even if the intervention, service or programme is provided on a 'universal' basis.
- Anything else you think significant or interesting about the decision.

enabling them to return to their daily activities sooner and increase their quality of life (=social value judgement, i.e. innovative nature of intervention has a positive impact on lives of patients)

The evidence the clinical effectiveness data on Telaprevir seems to have been one of the key factors driving the positive recommendation in this case. The clinical effectiveness results from the RCTs were statistically significant and considered applicable to the licensed patient population as well as being generalisable to the UK population (Jones et.al., 2011). The comparator products were also considered appropriate by the ERG. All in all, the clinical evidence can therefore be described to be of good quality, a feature which NICE itself points out is not always the case, hence giving rise to the inevitability of NICE having to make judgements about the 'best available evidence' (NICE 2008, p. 4).

In comparison to other technology appraisals, the appraisal of Telaprevir is an example of how a lack of controversies and questions surrounding the clinical effectiveness results and/or the quality of the evidence in terms of issues such as appropriate comparators and patient populations can contribute to a more favourable and straightforward appraisal process. However, the nature of many diseases and thus the treatment thereof is complex and does not render itself easily to an uncontroversial interpretation of scientific data. Clinically significant outcomes, the division of patients into appropriate subgroups and the choice of an appropriate comparator largely depend on the scientific knowledge we have of the 'workings and progress' of a disease, its characteristics and the health policy context under which a treatment is supposed to operate. Thus, while the Telaprevir case is a good example of the advantages of comparatively 'good quality evidence', in the daily practice of health technology assessments the availability of such evidence seems to be the exception rather than the rule.

It is interesting that NICE's Appraisal Committee included discussions of factors other than the costs and clinical benefits of Telaprevir even though the ICER per QALY gained was below what NICE usually considers cost effective (i.e. an ICER per QALY gained below £20,000 (NICE 2008)). This indicates that the Appraisal Committee adhered to Principle 3 of NICE's Social Value Judgements which states that "decisions about whether to recommend interventions should not be based on evidence of their relative costs and benefits alone […]" (NICE 2008, p. 18), but that "NICE must consider other factors when developing its guidance" (ibid.), despite the fact that the calculated ICER was already an indication of the cost effectiveness of the intervention. Providing the public and the stakeholders with an overview of the additional factors that contributed to the Appraisal Committee's decision such as the public health impact, the issue of equality and non-discrimination and the innovative nature of Telaprevir thus suggests that the decision-makers went considerable lengths to demonstrate how the decision to recommend this intervention was arrived at, making the value judgements as transparent as possible.

The Appraisal Committee's focus on the positive public health impact that Telaprevir might provide by reducing hepatitis C virus transmission rates is noteworthy in its own right. NICE's remit was expanded to include public health in 2005 (NICE 2008). This includes health promotion and disease prevention focusing on prevention rather than treatment and usually pertains

	to public health interventions (ibid.). The use of Telaprevir is focused on treatment rather than prevention and it is not connected to a public health programme. Nevertheless, its long-term benefits include public health benefits due to the reduction of the transmission of the virus which, as the Appraisal Committee pointed out, is not captured in the QALY method (NICE 2012a). The Telaprevir case is thus both an example of how NICE might adhere to its wider remit when making decisions as well as recognising that some benefits might not be captured by the QALY method. A question that arises in connection with this, however, is what happens in cases where the ICER per QALY gained exceeds the £20,000-£30,000 that NICE will usually consider cost effective. Arguably such a case would have challenged the ERG or the Appraisal Committee to attempt to quantify the health-related benefits that are not captured by the QALY method. While the good quality of the clinical evidence and the favourable ICER per QALY undoubtedly played a role in NICE's decision to recommend Telaprevir, the Telaprevir case is an illustration of how a variety of social value judgements are applied by NICE. The consideration of the reduction of transmission rates reflects a wider concern for the advocacy for public health while the potential of reducing stigmas associated with hepatitis C is a direct reflecting of what NICE aims to do in order to avoid discrimination and promote equality. It is also interesting that the Appraisal Committee decided not to make special provisions for HIV-co-infected patients even though they were not included in the clinical trials. While this might on the surface be considered in violation of Principle 1 of NICE's Social Value Judgements (the principle that NICE should not recommend an intervention if there is no evidence or not enough evidence to make a decision), it is rather a strict adherence to Principle 7, namely that NICE can recommend the use of an intervention is restricted to a particular group of people only within certain circumstances, a principle which aims to promote non-discrimination (NICE 2008). Equality of access to treatment in the interest of non-discrimination was thus a major concern of the Appraisal Committee in making this decision and is yet another indicator that NICE's Social Value Judgement Principles were closely followed in this case. To what extent close adherence to these principles was furthered by the favourable cost effectiveness calculations remains an unanswered question that is worthy of future consideration.
5. References/Links to relevant documents	
	Jones J, Hartwell D, Baxter L, Harris P. (2011) *Telaprevir for the treatment of genotype 1 chronic hepatitis C. A Single Technology Appraisal.* Southampton Health Technology Assessments Centre. NICE (2008) *Social Value Judgements – Principles for the development of NICE guidance.* Available at: http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf NICE (2011a) *Equality Impact Assessment – Scoping. STA: Telaprevir for the treatment of genotype 1 chronic hepatitis C.* Available at: http://www.nice.org.uk/nicemedia/live/13486/56307/56307.pdf NICE (2011) *Manufacturer's submission: Single Technology Appraisal (STA) – Telaprevir for the treatment of genotype 1 chronic hepatitis C.*

	Available at: http://www.nice.org.uk/nicemedia/live/13486/58484/58484.pdf NICE (2012a) *Final Appraisal Determination – Telaprevir for the treatment of genotype 1 chronic hepatitis C.* Available at: http://www.nice.org.uk/nicemedia/live/13486/58478/58478.pdf NICE (2012b) *Premeeting briefing: Telaprevir for the treatment of genotype 1 chronic hepatitis C.* Available at: http://www.nice.org.uk/nicemedia/live/13486/58479/58479.pdf NICE (2012) *TA 252 Hepatitis C (genotype 1) – Telaprevir: guidance*. Available at: http://guidance.nice.org.uk/TA252