Antiviral Combination Therapy with Interferon/Peginterferon Plus Ribavirin for Patients with Chronic Hepatitis C in Germany: A Health Technology Assessment Commissioned by the German Agency for Health Technology Assessment

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation

Published Version
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2703229/pdf/

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:4584560

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Antiviral combination therapy with interferon/peginterferon plus ribavirin for patients with chronic hepatitis C in Germany: a health technology assessment commissioned by the German Agency for Health Technology Assessment

Abstract

Objective: The purpose of this health technology assessment (HTA), commissioned by the German Agency for HTA at the German Federal Ministry of Health and Social Security, was to systematically review the evidence on effectiveness and cost-effectiveness of antiviral treatment (AVT) for initial chronic hepatitis C (CHC) and to apply these data in the context of the German health care system.

Methods: A systematic literature search was conducted to identify randomised controlled trials (RCTs), meta-analyses, and HTAs that evaluated initial AVT for CHC. A modified version of the German Hepatitis C Model (GEHMO) – a decision-analytic Markov model – was used to determine long-term morbidity, life expectancy, quality of life, costs and cost-effectiveness of different treatment strategies. Model parameters were derived from German databases, international RCTs, and a Cochrane Review.

Results: Overall, 9 RCTs, 2 HTA reports, 1 Cochrane review, and 2 meta-analyses examining medical effectiveness of antiviral combination therapy, as well as 7 economic evaluations, met the inclusion criteria. These studies indicate that combination therapy with peginterferon plus ribavirin produced the highest sustained virological response rates (54-61%), followed by interferon plus ribavirin with 38-54%, and interferon monotherapy with 11-21%. Based on international cost-effectiveness studies, interferon plus ribavirin is cost-effective compared to interferon monotherapy. No published articles were available regarding cost-effectiveness of peginterferon plus ribavirin. In our decision analysis, these findings were confirmed and the discounted incremental cost-effectiveness ratio for peginterferon plus ribavirin was € 9,800 per quality-adjusted life-year gained compared to interferon monotherapy (as the next best non-dominated strategy). Sensitivity analyses showed robust results across a wide range of model parameters.

Conclusions: This HTA suggests that initial combination therapy prolongs life, improves quality of life, and is cost-effective in patients with CHC. Combination of peginterferon and ribavirin is the most effective and efficient treatment strategy among the examined options.

Zusammenfassung

Ziel: Gegenstand dieses Health Technology Assessments (HTA), welches im Auftrag der Deutschen Agentur für HTA (DIMDI/Bundesministerium für Gesundheit und Soziale Sicherung) durchgeführt wurde, war die...
systematische Bewertung der medizinischen Effektivität und der Kos
teneffektivität antiviraler Therapien bei therapienaiven Patienten mit
chronischer Hepatitis C im Kontext des deutschen Gesundheitswesens.
Methoden: Es wurde eine systematische Literaturrecherche zur Identifi-
fikation von randomisierten klinischen Studien (RCT), Metaanalysen
und HTAs zur initialen antiviralen Therapie bei chronischer Hepatitis C
durchgeführt. Mit einer modifizierten Version des German Hepatitis C
Model (GEHMO), einem entscheidungsanalytischen Markov-Modell,
waren Langzeitmorbidity, Lebenserwartung, qualitätskorrigierte Le-
bensjahre (QALY), Lebenszeitkosten und das inkrementelle Kosten-
Nutzwert-Verhältnis (IKNV) für verschiedene Therapiestrategien ermittelt.

Ergebnisse: Insgesamt erfüllten 9 RCTs, 2 HTA-Berichte, 1 Cochrane
Review und 2 Metaanalysen zur medizinischen Effektivität sowie 7
ekonомische Evaluation die Einschlusskriterien dieses HTA. Die Sustain-
ed Virological Response Raten (SVR) waren am höchsten für Peginter-
feron plus Ribavirin mit 54-61%, gefolgt von Interferon plus Ribavirin
mit 38-54% der Interferon-Monotherapie mit 11-21%. In internatio-
nalen Kosten-Effektivitäts-Studien wurde die Kombinationstherapie mit
Interferon und Ribavirin im Vergleich zur Interferon-Monotherapie als
costenefektiv eingeschätzt. Publizierte Studien zur Kosteneffektivität
der Kombinationstherapie mit Peginterferon und Ribavirin wurden im
Recherchezeitraum nicht identifiziert. Die Ergebnisse dieses Reviews
wurden in unserer entscheidungsanalytischen Modellierung bestätigt.

Schlussfolgerung: Basierend auf den Ergebnissen dieses HTAs ist
davon auszugehen, dass antivirale Kombinationstherapien bei therapienaiven
Patienten die Lebenserwartung erhöhen, die Langzeit-Lebensqualität
verbessern und als kosteneffektiv einzustufen sind. Die Kombinations-
therapie mit Peginterferon und Ribavirin besitzt unter den untersuchten
Therapien die höchste Effektivität und ist im Vergleich zu anderen
im deutschen Gesundheitswesen akzeptierten medizinischen Verfahren
als kosteneffektiv zu bewerten.

Introduction

Chronic hepatitis C (CHC) is an emerging problem in
city public health. Hepatitis C virus (HCV) infects an estimated
170 million persons worldwide, with 5 million in Western
Europe [1]. In Germany, the prevalence of HCV has been
estimated to be 0.5% and the incidence to be 5000 new
infected persons per year, resulting in more than 400,000
prevalent cases of chronic hepatitis C [2, 3].
The virus imposes significant personal and social burdens
on infected individuals, as well as substantial costs to
society. Progression to chronic disease occurs in the
majority of HCV-infected persons [4]. Approximately 20%
of patients with CHC develop compensated liver cirrhosis
within 20 - 30 years [5], [6], [7], [8], [9], [10], [11], [12],
which is associated with high mortality risk due to liver
failure.
Antiviral combination therapy with interferon alpha and
ribavirin has been considered the standard of care for
treatment-naive patients with chronic hepatitis C infection
and elevated alanine amino transferase (ALT) levels [5],
[13], [14], but recent multinational randomised controlled
clinical trials [15], [16] showed that combination therapy
with peginterferon alpha and ribavirin yielded higher
sustained virological response rates.

However, antiviral combination therapy is relatively ex-
pensive, raising the question of whether its clinical benefit
supports the costs. With rising medical costs and limited
health care budgets, attention is increasingly being fo-
cused not only on the clinical benefits of new drugs but
also on their economic impact. To date no systematic
evaluation of the medical benefits and economic effects
of antiviral therapy for patients with CHC has been under-
taken in Germany.

Therefore, the German Agency for Health Technology As-
sessment at DIMDI and the German Federal Ministry of
Health and Social Security commissioned this health
technology assessment (HTA). Its objectives were (1) to
systematically review the evidence on effectiveness and
cost-effectiveness of initial antiviral combination therapy
in patients with CHC, (2) to develop a decision-analytic
Markov model for treatment-naive patients with CHC for
the context of the German health care system and (3) to
analyse the effectiveness and cost-effectiveness of initial
antiviral therapy in patients with CHC and elevated ALTs
in Germany.

Research Questions

All research questions of this study were based on a
population of treatment naïve patients with chronic hepatica
C and elevated ALT levels. The following specific re-
search questions were examined.
1. How does the effectiveness regarding sustained virolo-
gical response rate (SVR) compare between the evaluated
antiviral treatment strategies?
2. How does the effectiveness compare between the
evaluated antiviral treatment strategies regarding the
following long-term outcomes?
   • Compensated liver cirrhosis
   • Decompensated liver cirrhosis
   • Hepatocellular carcinoma
   • Liver transplantation
   • CHC-related mortality
   • Total mortality
   • Quality-adjusted life expectancy
3. What is the incremental cost-effectiveness of each
antiviral therapy in comparison to the next best strategy?
4. Which antiviral therapy can be recommended as
standard therapy for the German health care context ac-
cording to effectiveness and cost-effectiveness?

Methods

Systematic Review

Electronic databases, HTA-information networks, and
bibliographic sources were systematically searched to
identify randomised controlled trials (RCT), meta-analyses,
or HTA reports that evaluated initial antiviral combination
therapy in patients with CHC (see appendix for search
code in Notes). The time horizon of the literature search
was limited from 1990 to 2002. Study quality and trans-
ferability to the German context were assessed using in-
struments developed by the German Scientific Working
Group Technology Assessment for Health Care [17], [18],
[19]. The information was qualitatively summarised in
evidence tables [20]. Results are reported in country-
specific currencies. To facilitate comparison across
countries, all results were additionally converted to US
dollars (US$) of the index year of each study. As currency
conversion methods in the individual studies were poorly
described, we used exchange rates expressed as national
currency units per US$ instead of applying Purchasing
Power Parities (PPPs) [21].

A meta-analysis of randomised clinical trials on the
medical effectiveness of antiviral combination therapy with
peginterferon plus ribavirin was performed using
random and fixed effects models (REM, FEM). Based on
the standards of the Cochrane Collaboration [22], the
pooled relative risk (RR) for the outcome "No Sustained
Virological Response" with its 95% confidence interval
(CI) was reported. Results were presented as forest plot.

Collaboration and HTA Expert Panel on
Hepatitis C

During this HTA, collaboration was established with the
following institutions:
• Cochrane Hepato-Biliary Group, Copenhagen Trial Unit,
  Centre for Clinical Intervention Research, Copenhagen,
  Denmark
• Canadian Coordinating Office for Health Technology
  Assessment (CCOHTA)
• Robert Koch-Institute, Berlin, Germany
• Federal Institute for Drugs and Medical Devices, Bonn,
  Germany
• National Association of Statutory Health Insurance
  Physicians, Cologne, Germany
• Hep-Net - German Network of Excellence for Viral Hepa-
titis

Furthermore, the HTA Expert Panel on Hepatitis C was
established for this HTA. This interdisciplinary panel in-
cluded members of the German Hepatitis C Model
(GEHMO) Group and further experts from different areas
who consulted information concerning actual unpublished
data and studies and methodological issues. The list "HTA
Expert Panel on Hepatitis C" (see Notes at the end of the
article) gives the names, affiliations, and assigned areas
of the expert panel members.

Decision Analysis

A modified version of the German Hepatitis C Model
(GEHMO) was used. This model was designed to include
pooled effectiveness data from meta-analyses, as well
as benefits and costs, for employing different antiviral
therapy strategies for patients with chronic hepatitis
C. Pooled effectiveness data were derived from meta-
analyses performed by the Hepato-Biliary Cochrane Group
[23], [24] and additional meta-analyses were performed
by the authors. GEHMO is a decision-analytic Markov
model based on a previously published and validated
Markov model for the natural history of disease [25], [26]
and modified for the German health-care system and
German hepatitis C-specific practice patterns.

The model was used to determine long-term morbidity,
life expectancy, quality-adjusted life expectancy, lifetime
costs, and discounted incremental cost-utility ratios (ICUR)
of the following strategies: (1) no antiviral therapy, (2)
interferon monotherapy (3x3 MU/week) for 48 weeks,
(3) combination therapy with interferon (3x3 MU/week)
and ribavirin (1000-1200 mg/day) for 48 weeks, and (4)
combination therapy with peginterferon (180 μg/week
for peginterferon alpha 2a; 1.5 μg/kg for peginterferon
alpha 2b) plus ribavirin (800-1200 mg/day) for 48 weeks.
According to the European guidelines [5], interferon
monotherapy was stopped after 12 weeks and combina-
tion therapies were stopped after 24 weeks if no virolo-
gical response was observed at this time. Dosing was based on European recommendations for patients with chronic hepatitis C and European drug approved labelling [5].

Natural history data were estimated from several published studies and have been described elsewhere [25], [26]. Histological classification as mild or moderate chronic hepatitis or compensated cirrhosis was defined by the modified histology activity index of Knodell [27], [28]. For the German context, demographic and clinical parameters as well as utilities were based on original data from a quality-of-life survey in CHC patients (n=428) [29], [30]. Utility data included empirically estimated relative reductions in short-term quality-of-life due to positive HCV status (2%) and adverse events during antiviral treatment (5% for interferon plus ribavirin and 10% for peginterferon plus ribavirin).

Our model included pooled short-term outcomes (overall sustained virological response rates and respective relative risks) from recently published RCTs and meta-analyses. Relative virological response rates of interferon monotherapy and combination therapy with interferon alpha plus ribavirin were based on a recently published meta-analysis [23] and a Cochrane Review [24]. We performed a meta-analysis to derive pooled virological response rates of combination therapy with peginterferon plus ribavirin published in two randomised clinical multi-centre trials [15], [16] (see Table 1).

Direct annual costs were calculated based on frequencies of inpatient and outpatient visits, diagnostic and laboratory testing, medication, and procedures related to the specific health states (Table 2). Health resource utilisation frequencies were derived from a German expert panel (n = 10) and an economic survey in chronic hepatitis C patients (n = 196). Costs were derived from healthcare databases and currently applicable pharmaceutical prices of interferon alpha, peginterferon alpha, and ribavirin in Germany (Table 3). A 5% deduction from pharmaceutical prices for the proportion of persons insured by the social health insurance in Germany was performed. For modelling the costs of liver transplantation, a study [31] based on German patient data for the year 1993 was used. All costs were converted to year 2002 Euros (1 Euro = 1.95583 DM) by using the medical care component of the Consumer Price Index for Germany [32]. An annual discount rate of 3% was applied to costs and effectiveness based on international recommendations [33], [34] and varied in sensitivity analyses between 0% and 10% regarding German recommendations [35].

Table 1: Efficacy data used in the Markov model

<table>
<thead>
<tr>
<th>Antiviral treatment</th>
<th>VRStop</th>
<th>RR_{noVRStop}</th>
<th>VRETR</th>
<th>RR_{noVRETR}</th>
<th>SVR</th>
<th>RR_{noSVR}</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon monotherapy</td>
<td>0.68*</td>
<td>0.72*</td>
<td>37%</td>
<td>0.74*</td>
<td>[24; 25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon plus ribavirin</td>
<td>55%</td>
<td>54%</td>
<td>37%</td>
<td>0.74*</td>
<td>[24; 25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peginterferon plus ribavirin</td>
<td>72%**</td>
<td>69%</td>
<td>58%</td>
<td></td>
<td>[18; 32]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VRStop: Virological response rate after 12 (Interferon mono-therapy) or 24 weeks of therapy  
VRETR: Virological response rate at end of treatment  
RR_{noVRStop}: Relative risk for not having a virological response until 12th or 24th week  
RR_{noVRETR}: Relative risk for not having a virological response until end of therapy  
RR_{noSVR}: Relative risk for not having a sustained virological response  
* efficacy for interferon mono-therapy: relative risk for not having a sustained virological response (RR_{noSVR}) or not having a virological response until end of therapy (RR_{noVRETR}) compared to combination therapy with interferon plus ribavirin  
** calculated based on breakthrough rate between 24th and 48th week

Model Validation

The decision model was validated on three levels:
• Technical validation: ‘clean up’ of the software program from potential programming bugs  
• Internal validation: comparison of model predictions with epidemiological and clinical data used in the model  
• External validation: comparison of model predictions with published epidemiological data not used in the model

The technical validation using different routine tests (e.g. setting SVR equal for all strategies, eliminating antiviral treatment costs, eliminating CHC-related mortality, etc.) yielded the expected results. In the internal validation, all data values used were reproduced exactly by the decision model (e.g. SVR rates, progression incidences, background mortality).

In the external validation, the incidence of developing compensated liver cirrhosis in patients with mild chronic hepatitis C was adjusted for the spontaneous HCV-remission rate of 31% in patients with acute HCV-infection [36]. The model predicted a 20-year incidence of developing
compensated liver cirrhosis of 19% in patients with initial HCV-infection. This result is consistent with published data from prospective studies [4], [37]. As the spontaneous HCV remission rate and the incidence of liver cirrhosis have been extracted from different sources, using different values for spontaneous HCV remission could lead to a proportional deviation from the cirrhosis incidence used in the validation. However, different rates for spontaneous HCV remission would not influence results from this model because the target cohort of our analysis are patients with chronic hepatitis C.

Sensitivity Analyses

To assess the robustness of base-case results, univariate sensitivity analyses were performed for all model parameters based either on 95% confidence intervals or on ranges used in the literature. Costs were halved and doubled to obtain lower and upper limits. In addition to univariate sensitivity analyses, multivariate sensitivity analyses were performed on the entire set of disease progression rates. As it has been shown that the progression of hepatitis C observed in epidemiologic studies varies and strongly depends on the study design [8], we performed conservative sensitivity analyses with extremely low progression rates. Furthermore, we analysed a worst-case scenario using extremely conservative estimates for benefits and costs for the combination therapy with peginterferon and ribavirin.

Software

Decision analytic calculations were performed with DATA Pro for Health Care (TreeAge Software Inc., Williamstown, MA), SAS 8.1 (SAS Institute Inc., Cary, NC). Systat 10 (SPSS, Inc., Chicago, IL) was used for statistical analyses of primary data.

### Table 2: Annual treatment costs for HCV-related health states

<table>
<thead>
<tr>
<th>Health state</th>
<th>Annual costs (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild chronic hepatitis C</td>
<td>125</td>
</tr>
<tr>
<td>Moderate chronic hepatitis C</td>
<td>128</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>634</td>
</tr>
<tr>
<td>Diuretic-sensitive ascites</td>
<td>1,872</td>
</tr>
<tr>
<td>Diuretic-refractory ascites</td>
<td>12,714</td>
</tr>
<tr>
<td>Hepatic encephalopathy (first year)</td>
<td>7,856</td>
</tr>
<tr>
<td>Hepatic encephalopathy (subsequent years)</td>
<td>2,703</td>
</tr>
<tr>
<td>Variceal haemorrhage (first year)</td>
<td>12,653</td>
</tr>
<tr>
<td>Variceal haemorrhage (subsequent years)</td>
<td>3,380</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>19,700</td>
</tr>
<tr>
<td>Liver transplantation (first year)</td>
<td>134,851</td>
</tr>
<tr>
<td>Liver transplantation (subsequent years)</td>
<td>19,503</td>
</tr>
</tbody>
</table>

Costs were based on frequencies of inpatient and outpatient visits, diagnostic and laboratory testing, medication, and medical procedures associated with the specific health states. All costs were converted to year 2002 Euros by using the medical care component of the Consumer Price Index of Germany [32].

### Table 3: Medication prices for antiviral treatment [60]

<table>
<thead>
<tr>
<th>Medication</th>
<th>Application and Dosage</th>
<th>Price (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon α-2a</td>
<td>12 injectors x 3 MU</td>
<td>595.75</td>
</tr>
<tr>
<td>Interferon α-2b</td>
<td>2 pens x 18 MU</td>
<td>647.42</td>
</tr>
<tr>
<td>Alfacon-1</td>
<td>12 injectors x 9μg</td>
<td>569.93</td>
</tr>
<tr>
<td>Peginterferon α-2a</td>
<td>4 injectors x 180μg</td>
<td>1,321.82</td>
</tr>
<tr>
<td>Peginterferon α-2b</td>
<td>4 injectors x 100 μg</td>
<td>1,305.31</td>
</tr>
<tr>
<td>Ribavirin (Copegus)</td>
<td>168 capsules x 200mg</td>
<td>1,214.54</td>
</tr>
<tr>
<td>Ribavirin (Rebetol)</td>
<td>168 capsules x 200mg</td>
<td>1,146.82</td>
</tr>
</tbody>
</table>
Table 4: Sustained virological response rates (SVR) for interferon plus ribavirin versus interferon monotherapy - primary studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment duration [Weeks]</th>
<th>SVR [%] (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interferon + Ribavirin</td>
</tr>
<tr>
<td>Lai et al. 1996</td>
<td>40</td>
<td>48</td>
<td>48 (26-70)*</td>
</tr>
<tr>
<td>Mchutchison et al. 1998</td>
<td>912</td>
<td>48</td>
<td>38 (32-45)</td>
</tr>
<tr>
<td>Poynard et al. 1998</td>
<td>832</td>
<td>48</td>
<td>43 (37-49)</td>
</tr>
<tr>
<td>Mangia et al. 2001</td>
<td>192</td>
<td>48</td>
<td>54 (44-64)</td>
</tr>
<tr>
<td>Chemello et al. 1995</td>
<td>45</td>
<td>24</td>
<td>47 (22-73)*</td>
</tr>
<tr>
<td>Mchutchison et al. 1998</td>
<td>912</td>
<td>24</td>
<td>31 (25-37)</td>
</tr>
<tr>
<td>Poynard et al. 1998</td>
<td>832</td>
<td>24</td>
<td>35 (29-41)</td>
</tr>
<tr>
<td>Reichard et al. 1998</td>
<td>100</td>
<td>24</td>
<td>36 (23-51)*</td>
</tr>
<tr>
<td>Barbaro et al. 2000</td>
<td>428</td>
<td>24</td>
<td>43 (36-50)*</td>
</tr>
</tbody>
</table>

SVR: Sustained virological response rate  
* Calculations based on data in publication  
n.a.: not available

Table 5: Sustained virological response rates (SVR) for peginterferon plus ribavirin versus interferon plus ribavirin.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment duration [Weeks]</th>
<th>SVR [%] (95% confidence interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peginterferon + Ribavirin</td>
<td>Interferon+ Ribavirin</td>
</tr>
<tr>
<td>Manns et al. 2001</td>
<td>1016</td>
<td>48</td>
<td>54 (49-58)*</td>
<td>47 (42-51)*</td>
</tr>
<tr>
<td>Fried et al. 2002</td>
<td>897</td>
<td>48</td>
<td>56 (51-61)*</td>
<td>44 (39-49)*</td>
</tr>
</tbody>
</table>

SVR: Sustained virological response rate  
* Calculations based on data in publication

Results

Systematic Review

Twelve studies regarding the medical efficacy of combination therapy with interferon plus ribavirin compared to interferon monotherapy were included; herein 2 HTA reports [38], [39] 1 systematic Cochrane review [24], 2 meta-analyses [23], [40] and 7 controlled randomised clinical trials [41], [42], [43], [44], [13], [14], [45]. Two controlled randomised multicentre studies [15], [16] regarding medical efficacy of combination therapy with peginterferon and ribavirin compared to interferon plus ribavirin were identified and included.

All included studies reported significantly higher SVR for combination therapy with interferon and ribavirin compared with interferon monotherapy (38-54% vs. 11-21%) (Table 4). Meta-analyses reported SVRs of 32-41% for interferon in combination with ribavirin compared to 8-16% for interferon monotherapy.

For peginterferon combined with ribavirin, multicentre clinical trials reported SVRs of 54% vs. 47% (p-value 0.01) [16] and 56% vs. 44% (p-value < 0.001) [15] compared to standard combination therapy, respectively (Table 5). In a subgroup data analysis, one multicentre study [16] showed that patients treated with a dosage of 10.6 mg or more ribavirin per kg body weight had higher SVRs. Sixty-one percent of patients treated with peginterferon plus ribavirin compared to 48% patients treated with interferon plus ribavirin achieved a sustained virological response. The pooled relative risk for the outcome ‘no sustained virological response’ for the combination therapy with peginterferon plus ribavirin versus interferon plus ribavirin was 0.83 (95% CI 0.76-0.91 for fixed effects model and 0.75-0.91 for random effects model). Figure 1 shows the forest plot for the fixed effects model.
Seven studies including one HTA report [46], [47], [48], [39], [49], [50], [51] regarding cost-effectiveness of antiviral combination therapy with interferon and ribavirin in patients with chronic hepatitis C were identified in the search period of this HTA (January 1990 - December 2002), but no publications were found examining cost-effectiveness of antiviral combination therapy with peginterferon and ribavirin.

Incremental cost-effectiveness ratios varied over a wide range depending on discount rate, treatment duration, and population characteristics (Table 6). All studies considered antiviral therapy with interferon plus ribavirin seemed to be reasonably cost-effective.

For full evidence tables and results on study quality and transferability see the online HTA, the full text of which is available at www.dimdi.de [52].

German Decision Analysis

Based on our decision analysis, initial antiviral therapy compared to no treatment in patients with chronic hepatitis C saved 1.1 life years for interferon monotherapy, 2.9 life years for interferon plus ribavirin, and 4.6 life years for peginterferon plus ribavirin (Table 7), and reduced the 20-year-risk of dying from liver failure by 12% for interferon alone, 29% for interferon plus ribavirin, and 46% for peginterferon plus ribavirin (Table 8). Compared to no antiviral therapy, interferon monotherapy saved 1.2 quality-adjusted life years (QALY), while combination therapy with interferon and ribavirin saved 3.0 QALYs and peginterferon plus ribavirin saved 4.8 QALYs.

After discounting for future benefits, interferon monotherapy gained 0.53 QALYs with additional costs of €2,800 resulting in an ICUR of €5,300 per QALY compared to no antiviral therapy (Table 9). Moving from interferon monotherapy to interferon plus ribavirin was associated with 0.78 QALYs gained, additional costs of €9,000, and an ICUR of 11,600 €/QALY. Compared to interferon monotherapy (as the next best non-dominated strategy), peginterferon plus ribavirin gained 1.53 QALYs and increased costs by €14,900 yielding an ICUR of 9,800 €/QALY. Therefore, combination therapy with peginterferon plus ribavirin was the most effective treatment strategy and was more efficient than interferon plus ribavirin. To facilitate comparison with ICURs presented in Table 6, we converted the model-based ICURs for Germany to 2002 US dollars using the currency exchange rate (US$1 equals €1.07) [21]. When compared to interferon monotherapy, the ICURs of interferon plus ribavirin and peginterferon plus ribavirin were 10,800 US$/QALY and 9,200 US$/QALY, respectively.

In sensitivity analyses, results were robust when varying most relevant model parameters. Even when reducing SVR to 50%, combination therapy with peginterferon plus ribavirin was still the most effective strategy. Peginterferon plus ribavirin remained the most effective and cost-effective strategy when varying the proportion of patients with compensated cirrhosis from 0% to 52%, the propor-
### Table 6: Discounted incremental cost-effectiveness-ratios (ICER) and discounted incremental cost-utility-ratios (ICUR) for combination therapy with interferon plus ribavirin (24 or 48 weeks) vs. interferon monotherapy (48 weeks) in treatment-naïve patients with chronic hepatitis C

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al. 2000a</td>
<td>USA</td>
<td>US$ 1999</td>
<td>3</td>
<td>24</td>
<td>40</td>
<td>Mild</td>
<td>n.a.</td>
<td>7,000</td>
<td>n.a.</td>
<td>7,000</td>
</tr>
<tr>
<td>Buti et al. 2000</td>
<td>Spain</td>
<td>€ 1998</td>
<td>3</td>
<td>48</td>
<td>30</td>
<td>Mild</td>
<td>2,984</td>
<td>1,325</td>
<td>3,316</td>
<td>1,472</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>48</td>
<td>45</td>
<td>Mild</td>
<td>8,515</td>
<td>2,558</td>
<td>9,461</td>
<td>2,842</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>48</td>
<td>60</td>
<td>Mild</td>
<td>36,171</td>
<td>5,581</td>
<td>40,190</td>
<td>6,201</td>
</tr>
<tr>
<td>Stein et al. 2002</td>
<td>UK</td>
<td>£ 1998</td>
<td>6</td>
<td>48*</td>
<td>n.a.</td>
<td>Mild</td>
<td>n.a.</td>
<td>5,900</td>
<td>n.a.</td>
<td>9,833</td>
</tr>
<tr>
<td>Wong et al. 2000</td>
<td>USA</td>
<td>US$ 1999</td>
<td>3</td>
<td>24</td>
<td>40</td>
<td>Mod</td>
<td>n.a.</td>
<td>2,600</td>
<td>n.a.</td>
<td>2,600</td>
</tr>
<tr>
<td>Buti et al. 2000</td>
<td>Spain</td>
<td>€ 1998</td>
<td>3</td>
<td>48</td>
<td>30</td>
<td>Mod</td>
<td>880</td>
<td>678</td>
<td>978</td>
<td>642</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>48</td>
<td>45</td>
<td>Mod</td>
<td>2,172</td>
<td>1,172</td>
<td>2,413</td>
<td>1,302</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>48</td>
<td>60</td>
<td>Mod</td>
<td>7,575</td>
<td>2,885</td>
<td>8,417</td>
<td>3,206</td>
</tr>
<tr>
<td>Stein et al. 2002</td>
<td>UK</td>
<td>£ 1998/9</td>
<td>6</td>
<td>48*</td>
<td>n.a.</td>
<td>Mod</td>
<td>n.a.</td>
<td>2,735</td>
<td>n.a.</td>
<td>4,558</td>
</tr>
<tr>
<td>Wong et al. 2000</td>
<td>USA</td>
<td>US$ 1999</td>
<td>3</td>
<td>24</td>
<td>40</td>
<td>Cirr</td>
<td>n.a.</td>
<td>2,600</td>
<td>n.a.</td>
<td>2,600</td>
</tr>
<tr>
<td>Younossi et al. 1999</td>
<td>USA</td>
<td>US$ 1998</td>
<td>3</td>
<td>24</td>
<td>45</td>
<td>Mild+Mod</td>
<td>n.a.</td>
<td>cs</td>
<td>n.a.</td>
<td>cs</td>
</tr>
<tr>
<td>Sagmeister et al. 2001</td>
<td>Switzerland</td>
<td>€ 1998</td>
<td>3</td>
<td>48</td>
<td>42</td>
<td>Mild+Mod+G1</td>
<td>n.a.</td>
<td>7,135</td>
<td>n.a.</td>
<td>7,928</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>48</td>
<td>42</td>
<td>Mild+Mod+G-non-1</td>
<td>n.a.</td>
<td>3,565</td>
<td>n.a.</td>
<td>3,961</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>24</td>
<td>42</td>
<td>Mild+Mod+G1</td>
<td>n.a.</td>
<td>13,464</td>
<td>n.a.</td>
<td>14,900</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>24</td>
<td>42</td>
<td>Mild+Mod+G-non-1</td>
<td>n.a.</td>
<td>cs</td>
<td>n.a.</td>
<td>cs</td>
</tr>
<tr>
<td>Wong et al. 2000</td>
<td>USA</td>
<td>US$ 1999</td>
<td>3</td>
<td>24</td>
<td>40</td>
<td>Mild+Mod+Cirr</td>
<td>n.a.</td>
<td>5,400</td>
<td>n.a.</td>
<td>5,400</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>48</td>
<td>40</td>
<td>Mild+Mod+Cirr</td>
<td>n.a.</td>
<td>7,700</td>
<td>n.a.</td>
<td>7,700</td>
</tr>
</tbody>
</table>
Table 6: Discounted incremental cost-effectiveness-ratios (ICER) and discounted incremental cost-utility-ratios (ICUR) for combination therapy with interferon plus ribavirin (24 or 48 weeks) vs. interferon monotherapy (48 weeks) in treatment-naïve patients with chronic hepatitis C

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Currency Year</th>
<th>Discount rate [%]</th>
<th>Therapy duration [weeks]</th>
<th>Age [years]</th>
<th>Histology</th>
<th>Original Currency</th>
<th>Converted to US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shepherd et al. 2000</td>
<td>UK</td>
<td>£ n.a. (1)</td>
<td>6</td>
<td>24</td>
<td>n.a.</td>
<td>CHC</td>
<td>10,086 n.a.</td>
<td>16,810 n.a.</td>
</tr>
<tr>
<td>Stein et al. 2002</td>
<td>UK</td>
<td>£ 1998/9</td>
<td>6</td>
<td>48</td>
<td>n.a.</td>
<td>CHC; G-1</td>
<td>8,626 n.a.</td>
<td>14,377 n.a.</td>
</tr>
<tr>
<td>Wong et al. 2000</td>
<td>USA</td>
<td>US$ 1999</td>
<td>3</td>
<td>24</td>
<td>40</td>
<td>Mild+Mod+Cirr, G-1</td>
<td>11,600 n.a.</td>
<td>11,600 n.a.</td>
</tr>
<tr>
<td>Sennfält et al. 2001</td>
<td>Sweden</td>
<td>US$ n.a. (2)</td>
<td>3</td>
<td>24</td>
<td>43</td>
<td>Mild+Mod+Cirr, G-1</td>
<td>6,800 1,400</td>
<td>6,800 1,400</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild+Mod+Cirr, G-1</td>
<td>6,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild+Mod+Cirr, G-1</td>
<td>21,900</td>
<td>21,900</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild+Mod+Cirr, G-1</td>
<td>6,000</td>
<td>6,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild+Mod+Cirr, G-1</td>
<td>21,900</td>
<td>21,900</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild+Mod+Cirr, G-1</td>
<td>6,000</td>
<td>6,000</td>
</tr>
</tbody>
</table>


(1) therapy duration for genotype 1 (other genotypes 24 weeks).
Exchange rates expressed as national currency units per US$ were used to convert all results to US$ [21].
(2) assumed index year 1998, (3) assumed index year 1999.
Several sensitivity analyses were performed on progression rates. In a conservative scenario, the 20-year incidence of compensated cirrhosis was set to 7% as reported in a meta-analysis of results from community-based studies [8]. This scenario is conservative, because the study population of community-based studies included 38% of patients with normal ALT levels which is associated with a reduced risk of developing liver cirrhosis compared to our target population of CHC-patients with elevated ALT levels [53]. Figure 2 demonstrates the impact of progression on the ICUR of antiviral combination therapy. Even with a 20-year incidence of cirrhosis of only 7%, as reported in community studies [8], peginterferon plus ribavirin was the most effective therapy and, with an ICUR of 21,100 €/QALY, was still reasonably cost-effective. When we further removed the 2% quality-of-life reduction due to HCV-infection in viral-positive CHC patients in this conservative scenario, the ICUR increased to 26,200 €/QALY.

In the worst-case scenario, which was performed to obtain extremely conservative estimates for benefits (e.g., SVR) and costs for the combination therapy with peginterferon and ribavirin, peginterferon plus ribavirin was the most effective treatment strategy and resulted in an ICUR of 27,300 €/QALY compared to the next best non-dominated strategy (i.e., interferon monotherapy).
Table 9: Base-case analysis: absolute and incremental discounted costs and efficacy, discounted incremental cost-effectiveness-ratio and discounted incremental cost-utility-ratio for different treatment strategies at annual 3% discount rate*

<table>
<thead>
<tr>
<th></th>
<th>No antiviral therapy</th>
<th>Interferon (vs. no therapy)</th>
<th>Interferon + Ribavirin (vs. Interferon)</th>
<th>Peginterferon + Ribavirin (vs. Interferon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs (€)</td>
<td>14,800</td>
<td>17,600</td>
<td>26,600</td>
<td>32,500</td>
</tr>
<tr>
<td>Incremental costs (€)</td>
<td>–</td>
<td>2,800</td>
<td>(9,000)</td>
<td>14,900</td>
</tr>
<tr>
<td>Life expectancy (years)</td>
<td>17.97</td>
<td>18.45</td>
<td>19.19</td>
<td>19.90</td>
</tr>
<tr>
<td>Incremental Life expectancy (years)</td>
<td>–</td>
<td>0.48</td>
<td>(0.73)</td>
<td>1.45</td>
</tr>
<tr>
<td>Incremental cost-effectiveness-ratio (€/year)</td>
<td>–</td>
<td>5,800</td>
<td>(12,300)</td>
<td>10,300</td>
</tr>
<tr>
<td>Quality-adjusted life expectancy (QALY)</td>
<td>16.07</td>
<td>16.60</td>
<td>17.38</td>
<td>18.13</td>
</tr>
<tr>
<td>Incremental quality-adjusted life expectancy (QALY)</td>
<td>–</td>
<td>0.53</td>
<td>(0.78)</td>
<td>1.53</td>
</tr>
<tr>
<td>Incremental cost-utility-ratio (€/QALY)</td>
<td>–</td>
<td>5,300</td>
<td>(11,600)</td>
<td>9,800</td>
</tr>
</tbody>
</table>

* Values are rounded. QALY: quality-adjusted life year. Values in parentheses indicate dominated situations.

Figure 2: Influence of disease progression rate on the incremental cost-utility-ratio of antiviral combination therapy. Disease progression is described as 20-year incidence of compensated liver cirrhosis in initial HVC-infected patients (including acute hepatitis C).

Discussion

In this health technology assessment, a systematic evaluation of the medical efficacy and cost-effectiveness of antiviral combination therapy as an initial treatment for patients with chronic hepatitis C was performed. In addition, a modified version of the German Hepatitis C Model (GEHMO) was applied to predict the 20-year risks of CHC-related liver diseases, life expectancy, quality-adjusted life expectancy, lifetime costs, and incremental cost-utility ratio for different antiviral treatment strategies and for the German health care context.
Several randomised trials [41], [42], [43], [44], [13], [14], [45] and meta-analyses [23], [24], [40] reported combination therapy with interferon plus ribavirin to be more efficient than interferon monotherapy (SVR: 32-54% vs. 8-21%). Two randomised multicentre studies [15], [16] reported a higher SVR for peginterferon plus ribavirin compared to combination therapy with interferon plus ribavirin (54-56% vs. 44-47%). In terms of life expectancy and quality-adjusted life expectancy combination therapy with interferon plus ribavirin was more effective and also reasonably cost-effective when compared to interferon monotherapy, based on international cost-effectiveness studies [46], [47], [48], [39], [49], [50], [51].

In our decision analysis for the context of the German health care system, initial antiviral therapy with interferon and ribavirin compared to interferon monotherapy had a discounted ICUR of €11,600/QALY. Compared to interferon monotherapy, peginterferon plus ribavirin cost €14,900 and gained 1.53 QALYs, resulting in an ICUR of €9,800/QALY. Therefore, combination therapy with peginterferon plus ribavirin was the most effective and cost-effective treatment strategy.

As is the case with all model-based cost-effectiveness analyses, ours has several limitations due to the availability of data on the natural history of chronic hepatitis C. The risk of progression to cirrhosis is especially controversially. In a recently published review of 57 studies on the natural history of hepatitis C [8], the authors classified the identified studies into four categories of study design and used regression analysis to derive pooled progression estimates for each category. The estimated 20-year risk of cirrhosis was 24% for post-transfusion cohorts, 22% for liver clinic series, 7% for community-based cohorts, and 4% for blood donors. Adjusting for demographic and clinical characteristics explained only a small part of the heterogeneity. It has been argued that biases such as referral bias and selection bias may explain the high cirrhosis risks in liver series and post-transfusion cohorts as well as the low estimates in blood donors [7]. The fraction of patients with elevated ALT levels varied between these different settings and was as low as 62% in the community-based studies [8].

The target population of our study was a patient cohort with elevated ALT values and a mix of different histological stages as observed in clinical trials and routine clinical practice in the absence of systematic screening. Post-transfusion studies were the only category that required the presence of clinical or biochemical hepatitis, and thus may be the category that best represents the advanced disease stage of the population we studied. However, transfusion may be associated with underlying chronic disease, which itself may influence the progression of hepatitis [7]. In community-based studies, most patients had normal ALT values, and some studies included patients with acute hepatitis C. Thus, these studies do not reflect the decision context and the population we studied. However, even after reducing the progression rates of our model to the extent that 20-year cirrhosis risk was only 7% (i.e., reflecting the community-based estimate), the ICUR for combination therapy with peginterferon plus ribavirin remained below €22,000/QALY. This indicated the robustness regarding the optimal choice among the evaluated strategies even under very conservative assumptions.

However, the results may be different for patients with normal ALT levels, with acute hepatitis C, or in populations in which a systematic screening for HCV was performed and, therefore, most cases were detected in a very early stage of the disease. For an evaluation in these populations, the decision model and its data must be adapted to the specific context. In particular, this means that even if future studies yield good SVRs in screened patients or patients with normal ALT values, long-term effectiveness or cost-effectiveness cannot be automatically inferred from these results without additional decision analyses. For peginterferon plus ribavirin, the estimation of medical efficacy was based on only 2 studies [15], [16], the only published randomised clinical multicentre trials. However, the results of these two trials were similar, and our decision analysis results remained robust when varying the SVR in sensitivity analyses. More evidence should be retrieved from additional randomised clinical trials comparing combination therapy with peginterferon plus ribavirin to standard combination therapy.

Severe adverse events may occur more frequently in patients treated with peginterferon plus ribavirin than in patients treated with interferon plus ribavirin [15], [16]. As the absolute number of adverse events was small, and no utility data were available for each type of adverse event, we were unable to develop a micromodel for severe adverse events. Instead, we empirically estimated the overall relative reduction in quality of life due to different antiviral treatment regimens from the German CHC quality-of-life survey. Our economic analysis likely underestimates disease-related costs for several reasons, and therefore likely underestimates treatment-related savings due to prevented future complications. First, we used variable costs and did not consider fixed costs nor costs due to productivity loss. Second, our model does not include the cost of future liver biopsies and further therapy for non-responders. Third, we did not consider histology normalisation in responders, nor reduced incidence of hepatocellular carcinoma in non-responders.

This analysis applied average age, gender distribution, genotype distribution, and histology to avoid potential biases related to patient-level variation in the different treatment groups of the trials and applied a consistent resource utilisation structure in the model and institutional assignment (where different institutions across Germany may vary in their economic efficiencies and accounting practices).
Country to country differences in sociodemographic structure, distribution of patient’s clinical characteristics, utility profiles, resource utilisation, and prices make it difficult, if not impossible, to transfer the results of our qualitative review of economic evaluations to other healthcare systems and countries [56], [57], [58], [19], [59]. However, the cost-effectiveness patterns for interferon and ribavirin in other industrialised countries were similar to the results derived from the German decision model. As none of the included economic evaluations examined the cost-utility ratio of peginterferon plus ribavirin, the German model results are currently the only data for this new treatment. Future studies should examine the efficacy and the need for antiviral therapy in patients with normal ALT levels, with histological mild hepatitis C, and with certain risk and comorbidity profiles (e.g., HIV infection, intravenous drug users, haemophilia, etc.). All clinical trials used the sustained virological response rate as a surrogate marker for the clinical efficacy. Further epidemiological studies evaluating long-term clinical outcomes (e.g., incidence of cirrhosis, mortality) should be performed to provide more evidence on the long-term benefit of antiviral therapy. Furthermore, further research is needed regarding the natural progression of the disease considering different prognostic factors. More observational long-term studies on the natural history of hepatitis C and the medical effectiveness of different therapeutic strategies should be performed, as well as prospective studies assessing actual cost for treatment and side effects in the routine health care setting.

Conclusions

This HTA suggests that initial combination therapy for chronic hepatitis C should prolong life, improve quality-adjusted life expectancy, and be cost-effective. The combination of pegylated interferon and ribavirin is currently the most effective and efficient antiviral treatment for CHC. However, because not all chronic hepatitis C patients will develop progressive liver disease, a thorough assessment of the eligibility and appropriateness of treatment with combination therapy requires a careful discussion between patients and physicians. This discussion must consider the demographic and clinical characteristics of the patient and the trade-offs between the expected prognosis, side effects, and the willingness to consider antiviral treatment to prevent potential future liver complications.

Notes

Appendix: Literature Search Strategy

The code in Table 10 represents the OVID search strategy used for identifying clinical and economic studies on antiviral combination therapy for chronic hepatitis C in MEDLINE and PreMEDLINE. Similar searches were performed in EMBASE, Cochrane Library, Best Evidence, NHS HTA databases (DARE, NHS EED, HTA), EconLit, Health Services Research Projects in Progress (HSRPROJ), Health Services/Technology Assessment (HSTAT), International Health Technology Assessment (IHTA), Catalog Online (CATLINE), and Science Citation Index (Science Citation
Table 11: HTA Expert Panel on Hepatitis C

<table>
<thead>
<tr>
<th>Expert</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology, Health Reporting</strong></td>
<td></td>
</tr>
<tr>
<td>Prof. Dr. Bärbel M. Kurth</td>
<td>Abteilung für Epidemiologie und Gesundheitsberichterstattung, Robert Koch-Institut, Berlin</td>
</tr>
<tr>
<td>Dr. Hannelore K. Neuhauser, MPH</td>
<td>Abteilung für Epidemiologie und Gesundheitsberichterstattung, Robert Koch-Institut, Berlin</td>
</tr>
<tr>
<td><strong>Infectious Diseases</strong></td>
<td></td>
</tr>
<tr>
<td>PD Dr. Klaus Stark</td>
<td>Abteilung für Infektionsepidemiologie, Robert Koch-Institut, Berlin</td>
</tr>
<tr>
<td>Dr. Nikolai Mühlberger, MPH</td>
<td>Abteilung für Infektions- und Tropenmedizin der Ludwig-Maximilians-Universität-München</td>
</tr>
<tr>
<td><strong>Gastroenterology/Hepatology</strong></td>
<td></td>
</tr>
<tr>
<td>PD Dr. Siegbert Rossol</td>
<td>Abteilung Innere Medizin - Gastroenterologie, Stadtkrankenhaus Rüsselsheim, Universität Mainz</td>
</tr>
<tr>
<td>Prof. Dr. Michael P. Manns</td>
<td>Abteilung für Gastroenterologie und Hepatologie, Medizinische Hochschule Hannover</td>
</tr>
<tr>
<td>Prof. Dr. Stefan Zeuzem</td>
<td>Klinik für Innere Medizin II, Universitätskliniken des Saarlandes, Homburg/Saar</td>
</tr>
<tr>
<td>Dr. Jürgen K. Rockstroh</td>
<td>Medizinische Klinik und Poliklinik I, Universität Bonn</td>
</tr>
<tr>
<td>PD Dr. Markus Sagmeister</td>
<td>Abteilung für Innere Medizin, Landeskrankenhaus Feldkirch, Österreich</td>
</tr>
<tr>
<td>Dr. Michael Corzilli, MPH</td>
<td>HIV-Ambulanz, II. Medizinische Klinik, Christian-Albrechts-Universität Kiel</td>
</tr>
<tr>
<td><strong>Systematic Reviews, Cochrane Collaboration</strong></td>
<td></td>
</tr>
<tr>
<td>Dr. Lise L. Kjaergard, MD</td>
<td>Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research H:S Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark</td>
</tr>
<tr>
<td>Dr. Christian Gluud, MD</td>
<td>Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research H:S Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark</td>
</tr>
<tr>
<td><strong>Health Economics</strong></td>
<td></td>
</tr>
<tr>
<td>Prof. Dr. Jürgen Wasem</td>
<td>Alfried Krupp von Bohlen und Halbach-Stiftungslehrstuhl für Medizinmanagement, Universität Duisburg-Essen</td>
</tr>
<tr>
<td>Dr. PamelaAidelsburger, MPH</td>
<td>Lehrstuhl für Allgemeine Betriebswirtschaftslehre und Gesundheitsmanagement, Ernst-Moritz-Arndt-Universität Greifswald</td>
</tr>
<tr>
<td>Dr. Franz Hessel, MPH</td>
<td>Alfried Krupp von Bohlen und Halbach-Stiftungslehrstuhl für Medizinmanagement, Universität Duisburg-Essen</td>
</tr>
<tr>
<td>Dr. Florian Buchner, MPH</td>
<td>Lehrstuhl für Allgemeine Betriebswirtschaftslehre und Gesundheitsmanagement, Ernst-Moritz-Arndt-Universität Greifswald</td>
</tr>
<tr>
<td><strong>Pharmacoeconomics</strong></td>
<td></td>
</tr>
<tr>
<td>Dr. rer. nat. Eva-Susanne Dietrich</td>
<td>Referat Arzneimittel, Kassenärztliche Bundesvereinigung, Köln</td>
</tr>
</tbody>
</table>
Index Expanded, Social Science Citation Index and Arts & Humanities Citation Index). The HTA covered documents published between 1990 and December 2002. Line #15 and line #20 represent the final codes for studies on clinical effectiveness and economic studies, respectively.

See Table 11.
Acknowledgements

This work was commissioned and funded by the German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DAHTA@DIMDI), German Federal Ministry of Health and Social Security [Grant No. 05 / 01.2.].

References


