Hepatobiliary clinical trials and their inclusion in the Cochrane Hepato-Biliary Group register and reviews

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Introduction

Hepatobiliary diseases present important clinical problems to the practitioner. Interventions to increase survival, relieve symptoms and improve quality of life of patients with hepatobiliary diseases exist. The benefits and harms of the interventions should be assessed in as unbiased a manner as possible. Randomized clinical trials (RCT) are the “gold standard” for such assessments.1–3 Synthesising evidence from RCT is highly important for directing local guidelines, clinical practice and future research. RCT might be subjected to systematic errors (“bias”), random errors (“play of chance”) and design errors.1–3 Therefore, to obtain a valid assessment of benefits and harms, it is necessary to carry out systematic reviews with meta-analyses and trial sequential analyses of the identified randomized trials.1–3

The Cochrane Hepato-Biliary Group (the CHBG) is one of the 52 collaborative review groups within The Cochrane Collaboration. The activities of the CHBG focus on collecting hepatobiliary randomized clinical trials (RCT) and controlled clinical trials (CCT), and including them in systematic reviews with meta-analyses of the trials. In this overview, we present the growth of The CHBG Controlled Trials Register, as well as the systematic reviews that have been produced since March 1996.

Results: The CHBG register includes almost 11 000 RCT and 700 CCT publications. The earliest RCT in the register were published in 1955, and the earliest CCT in 1945. From 1945 to 1980, there were less than 100 publications each year. From 1981 to 1997, their number increased from over 100 to 600 a year. After 1997, the number of publications seems to have been decreasing. The CHBG has published 199 protocols for systematic reviews and 107 systematic reviews through to August 2009 in which 21% of the RCT and CCT were included. The CHBG reviews have been cited approximately 1200 times.

Conclusions: A large amount of work has been carried out since 1996. However, there is still much to do, as the CHBG register contains a great number of RCT and CCT on topics that have not yet been systematically reviewed.
CHBG’s formation in March 1996, we have been searching medical literature and databases for RCT and CCT, and at the same time we have been compiling the selected trials in a CHBG Controlled Trials Register. This register is part of The Cochrane Central Register of Controlled Trials (CENTRAL).

Here, we give an overview of the RCT and CCT in The CHBG Controlled Trials Register, and their inclusion in the CHBG systematic reviews, published by August 2009. In addition, we give an estimate of the number of trials not yet included in the CHBG systematic reviews and state the foreseeable demand for systematic reviews.

Materials and methods

To build The CHBG Controlled Trials Register, we searched the MEDLINE (WinSPIRS) database in 1996, 1997 and 1999 by using an earlier version of The Cochrane Collaboration MEDLINE search strategy for RCT and CCT in combination with a hepatobiliary search strategy, developed in collaboration with The Danish National Library of Science and Medicine, Copenhagen. All identified citations were downloaded; the full text of the publications was obtained if a reference title or reference abstract was found to be of relevance to the scope of the Group. Depending on the publication report of the study design, the papers were given a code. The RCT code was given if the trial was defined as “randomized” or if the sequence generation was achieved using computer random number generation or a random number table. When the allocation of patients to the groups was not strictly random, for example, when the patients were allocated using dates, names or admittance numbers, the publications were given the CCT code. We use ProCite, a bibliographic database, to store information on the identified publications. This ProCite file—The CHBG Controlled Trials Register—is regularly expanded with searches in CENTRAL. In turn, staff at Wiley identify trials from MEDLINE quarterly and add EMBASE citations provided by the UK Cochrane Centre annually as well as add trials submitted by Cochrane entities, identified through manual or electronic searching activities. We also search Science Citation Index Expanded, Latin American and Caribbean Health Sciences (LILACS), The National Cancer Institute’s (NCI’s) PDQ Cancer Clinical Trials Registry, and The Chinese Biomedical Literature Database for clinical trials. Trials identified through hand searching of specialist journals and conference proceedings are also added. As Cochrane entities replicate the described methods for identification and compiling of trials in their own registers, CENTRAL is considered one of the most comprehensive trials registers (Clarke M and Clarke T, unpublished work 2009). The searches are carried out when a protocol is developed into a review or when a review is updated.

In order to gain insight into how many reviews remain to be carried out by the CHBG, we made an extrapolation from the work done to August 2009. From March 1996 to August 2009, we counted the number of the published CHBG protocols for systematic reviews and systematic reviews in The Cochrane Library for each year. We also counted the number of included RCT and CCT as well as the number of references to these trials in the CHBG systematic reviews in order to find the average number of publications per trial. Furthermore, we calculated the proportion of included trial references in each review out of the total number of RCT and CCT publications included in the CHBG register for each year. The average number of trials per review and the total number of publications that have been reviewed until August 2009 enables us to estimate how many systematic reviews still need to be completed. To gain insight into the development of the different hepatobiliary disease areas, we subsequently divided the reviews and the references in the CHBG register into 13 different categories based on topic. These numbers gave us a rough estimate of how well the different disease areas are covered based on the number of reviews published, and the number of references included in the reviews out of the approximate number of references in the CHBG register on that specific topic.

The number of citations per CHBG review published either in The Cochrane Library or in any paper journal as a co-publication, was obtained from Web of Science (http://apps.isiknowledge.com).

The charts were produced with Microsoft Office Excel 2003.

Results

In total, we have given the RCT code to almost 11 000 publications and the CCT code to almost 700 publications. Figure 1 shows the cumulative numbers of publications on RCT and CCT that were added to The CHBG Controlled Trials Register from March 1996 to August 2009.

Figure 2 shows the number of RCT or CCT according to their year of publication in the CHBG register. The earliest two CCT were published in 1945, and the earliest report on three RCT was published in 1955. From 1955 to 1980, the number of publications on RCT and CCT rose slowly (Fig. 2). From 1980 to 1997, there was a steep increase in the number of publications published each year (Fig. 2). However, after 1997 the number of the identified publications has fallen from more than 600 to less than 250 by the end of 2008 (Fig. 2).

Figure 3 shows the cumulative numbers of CHBG protocols for systematic reviews and CHBG systematic reviews published in The Cochrane Library per year since Issue 2, 1996 (March) to Issue 3, 2009 (August). For this period, the CHBG has published 199 protocols for CHBG systematic reviews of which 107 have been developed into systematic reviews (the topics plus review abstracts are available at http://www.mrw.interscience.wiley.com/cochrane/cochrane_clsysrev_crglist_fs.html).

In order to examine how many of the identified publications in the CHBG register were used in the systematic reviews produced by August 2009, we counted the cumulative numbers of included publications in all CHBG reviews published in The Cochrane Library each year from March 1996 to August 2009 and compared it with the cumulative numbers of publications on RCT and CCT included in the CHBG register each year (Fig. 4). Our first two reviews were published in 1997; the reviews included less than 2% of the publications in the CHBG register at that time, whereas the presently published 107 systematic reviews include 21% of the identified publications by August 2009. The 107 reviews include 1106 trials, giving an average of approximately 10 trials per review (median of 7 trials) and an average of approximately two publications per trial.

In order to examine the development of the different hepatobiliary disease areas, we divided both the reviews and the references in the CHBG register into 13 different categories based on...
Figure 1  Cumulative numbers of publications coded as randomized clinical trials or controlled clinical trials from March 1996 to August 2009, registered in The Cochrane Hepato-Biliary Group Controlled Trials Register. *Note: 1996 and 2009 are not complete years. RCT; CCT.

Figure 2  Number of publications coded as randomized clinical trials and controlled clinical trials according to their year of publication in The Cochrane Hepato-Biliary Group Controlled Trials Register. RCT; CCT.
topic (Table 1). The miscellaneous category covers topics that do not fall within any of the other categories. Based on number of reviews published, the top three most productive areas are bile duct surgery (21 reviews, including 274/1369 [20%] references in the CHBG register), viral hepatitis (20 reviews, including 662/4166 [16%] references in the CHBG register), and liver surgery (15 reviews, including 147/802 [18%] references in the CHBG register). In contrast, we have only one published review on medical treatment of liver failure (including 34/134 [25%] references in the CHBG register), one review on medical treatment of gall/bile duct stones (including 8/10 [80%] references in the CHBG register), and three reviews on medical treatment of sclerosing cholangitis (including 15/64 [23%] references in the CHBG register).

The 107 systematic reviews and their 39 co-publications in paper journals have been cited approximately 1200 times. Divided by category, the reviews in the miscellaneous category have been cited the most (322 citations), followed by reviews on liver cancers (175 citations) and on gastric or esophageal varices (149 citations; Table 1).

**Discussion**

During the past 14 years, the CHBG has collected more than 11 000 publications on trials within the hepato-biliary specialty. From 1945 to 1997, the number of published hepato-biliary trials increased, more slowly initially and then much more dramatically. However, after 1997, the annual number of RCT and CCT have fallen.

We can only speculate on possible reasons for this fall-off in the annual numbers of publications. There might simply have been a decline in the number of hepato-biliary studies carried out, there might have been a less frequent publication of randomized trials or controlled trials, or there could have been less active hand searching of trials. With the establishment of The Cochrane Collaboration in 1993, there has also been an increasing focus on the issues regarding risks of biases in clinical trials focusing on trial methodological quality (http://www.cochrane.org). Subsequently, the CONSORT Statement initiatives in 1996 used stricter rules regarding clinical trials reporting. There have also been a number of studies pointing out the weaknesses of published hepato-biliary and gastroenterology trials and trials within the other specialties. These collective studies and activities might have led to the subsequent changes in investigator attitudes and editorial policies. In this regard, the quality of trial reporting has improved significantly during the recent years, so the fall in the numbers of trial publications might be less concerning. Regardless of the cause, similar trends in trial publications have been observed in other specialties, indicating that it is neither an isolated problem for hepato-biliary publications nor a coincidence.

In addition to the activities regarding building the CHBG Controlled Trials Register and carrying out systematic reviews, the CHBG has actively been engaged in methodological research regarding risks of systematic errors (“bias”) in clinical trials and meta-analyses of such trials and risks of random errors (“play of chance”) in meta-analyses. These activities are...
ongoing, with a view to continuously improve the internal validity and thereby the external validity of the CHBG systematic reviews. The CHBG reviews co-published in paper journals were published in journals with impact factors above 3.0.38–55

The growth of publications on hepato-biliary RCT and CCT per year seems to follow a general historical pattern of publications of RCT and CCT56 (Gluud C and Nikolova D, unpublished work 2010). The earliest two hepato-biliary CCT seem to have been

Figure 4  Cumulative numbers of publications coded as randomized clinical trials (RCT) and controlled clinical trials (CCT) registered in The Cochrane Hepato-Biliary Group (CHBG) Controlled Trials Register per year compared with the number of included RCT and CCT in all CHBG reviews published in the Cochrane Library from March 1996 to August 2009 (Issue 3, 2009). *Note: 1996 and 2009 are not complete years.  □ Cumulative numbers of randomized clinical trials and controlled clinical trials in The Cochrane Hepato-Biliary Group Specialised Register;  ■ Cumulative numbers of randomized clinical trials and controlled clinical trials included in The Cochrane Hepato-Biliary Group’s systematic reviews.

Table 1  Number of systematic reviews, publications and citations according to 13 different categories within hepato-biliary diseases

<table>
<thead>
<tr>
<th>Category</th>
<th>No. reviews</th>
<th>No. publications included in reviews</th>
<th>Approximate no. publications in the CHBG register</th>
<th>Proportion of publications included in reviews (%)</th>
<th>No. citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric or esophageal varices</td>
<td>10</td>
<td>135</td>
<td>1288</td>
<td>10.5</td>
<td>149</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>20</td>
<td>662</td>
<td>4166</td>
<td>15.9</td>
<td>84</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>5</td>
<td>102</td>
<td>342</td>
<td>29.8</td>
<td>96</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver</td>
<td>4</td>
<td>16</td>
<td>66</td>
<td>24.2</td>
<td>44</td>
</tr>
<tr>
<td>Liver surgery (resection and transplantation)</td>
<td>15</td>
<td>147</td>
<td>802</td>
<td>18.3</td>
<td>33</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>4</td>
<td>110</td>
<td>282</td>
<td>39.0</td>
<td>2</td>
</tr>
<tr>
<td>Liver cancers</td>
<td>7</td>
<td>201</td>
<td>212</td>
<td>94.8</td>
<td>175</td>
</tr>
<tr>
<td>Liver failure (medical treatment)</td>
<td>1</td>
<td>34</td>
<td>134</td>
<td>25.4</td>
<td>109</td>
</tr>
<tr>
<td>Cirrhosis (medical treatment)</td>
<td>8</td>
<td>209</td>
<td>2154</td>
<td>9.7</td>
<td>30</td>
</tr>
<tr>
<td>Sclerosing cholangitis (medical treatment)</td>
<td>3</td>
<td>15</td>
<td>64</td>
<td>23.4</td>
<td>0</td>
</tr>
<tr>
<td>Gall/bile duct stones (medical treatment)</td>
<td>1</td>
<td>8</td>
<td>10</td>
<td>80.0</td>
<td>0</td>
</tr>
<tr>
<td>Bile duct surgery (cholecystectomy, endoscopy, laparoscopy)</td>
<td>21</td>
<td>274</td>
<td>1369</td>
<td>20.0</td>
<td>116</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>8</td>
<td>495</td>
<td>577</td>
<td>85.8</td>
<td>322</td>
</tr>
</tbody>
</table>

CHBG, Cochrane Hepato-Biliary Group.
published at the end of World War II.\textsuperscript{9,10} This represents a noteworthy delay, considering the facts that the first CCT was published in 1898,\textsuperscript{87} the trial methodology and statistics were well described already in the 1800s,\textsuperscript{88} and that many CCT were published before World War II (http://www.jameslindlibrary.org). Likewise, the earliest three hepato-biliary RCT identified by the CHBG were published in 1955,\textsuperscript{11} whereas other RCT were published long before World War II (http://www.jameslindlibrary.org). The Thomas Chalmers et al. RCT from 1955 still stands today as an exemplary trial, not only being likely the first hepato-biliary RCT, but also a RCT using factorial design,\textsuperscript{11} building on previous experiences with a factorial design CCT on “infective hepatitis”\textsuperscript{59,60} and likely introducing the $2 \times 2 \times 2$ factorial design.\textsuperscript{61}

By August 2009 (i.e. Issue 3, 2009 of The Cochrane Library), the CHBG had published 199 protocols for CHBG systematic reviews and 107 systematic reviews.\textsuperscript{4} These 107 systematic reviews have assessed data from 21% of the total RCT and CCT publications in the CHBG register. Of the 107 reviews, 21 reviews are on bile duct surgery assessing 20% of the references in the CHBG register on this topic. In contrast, only one review has been published on medical treatment of gall/bile duct stones, assessing 80% of the references in the CHBG register on this topic. A potential shortcoming of these calculations is that the CHBG register is not study based, and the references are divided into the selected categories based on simple searches in ProCite using text words only, which might result in a skewed picture of the percentage of references assessed in the different disease areas. It is possible that some references are counted in the wrong category. This might also be the case for the liver surgery category versus the liver cancers category, where 15 reviews assess 18% of the references on liver surgery versus seven reviews assessing 95% of the references on liver cancers. The 20 reviews on viral hepatitis seem to assess just 16% of the references on this topic in the CHBG register. However, there is reason to believe that the total number of references in the CHBG register might be overestimated as a result of the fact that the text word “hepatitis” might appear in references whose primary topic is not on viral hepatitis. As long as the CHBG register is reference-based, we can only give rough estimates for the development of the different disease areas. In addition, it makes it difficult to describe the references not yet included in systematic reviews. For example, were they published many years ago or very recently? Are they abstracts or full text publications? Are they published in English or another language?

From the perspective of a busy clinician, digesting the information of 107 reviews is much easier than looking into 2400 clinical trial publications. However, from the perspective of the CHBG, there are still 79%, or almost 9000 RCT and CCT publications that would seem to be available for systematic reviews. With approximately two publications per trial\textsuperscript{56,62,63} (this study), we have approximately 4500 trials awaiting assessment in CHBG reviews. As each Cochrane review includes a median of six or seven trials (a median of seven in the CHBG reviews),\textsuperscript{62,63} approximately 700 CHBG reviews are waiting to be carried out. This is more than three times as many as previously projected.\textsuperscript{60} The CHBG has published an average of nine reviews per year. If we proceed at the same pace, it will take us almost 78 years to carry out the 700 reviews. At the same time, it is expected that the number of new publications would average 400 per year, which equals to providing material for another 30 new reviews per year. The scientific attractiveness of systematic review preparation is still in its infancy, and more monetary support and intellectual work is needed to help it grow to maturity.

A recent study deals with some critical problems that the CHBG faces.\textsuperscript{64} The study suggests that CHBG reviews seem to be under-valued and underused by physicians. Some of the reviews are “empty reviews”, that is, no or only one RCT is included. Some reviews are “outdated” (the date of search for new trials is more than 2-years-old and hence the results raise uncertainty as data from most recent trials are not included). Some reviews are “difficult to read” and “too lengthy”.\textsuperscript{64} These empty and outdated reviews are issues with which the CHBG Editorial Team continues to tackle. Nevertheless, the CHBG reviews have been cited approximately 1200 times.

The main aim of a Cochrane review is to provide the “best available” and most “up-to-date” evidence on the effects of the interventions under study for patients, physicians and policy makers. Ideally, the evidence should be combined with health economic data to facilitate health decision making. However, evidence is continually evolving and the incorporation of new studies might lead to changes in results of a systematic review.\textsuperscript{3,13,65} Health economic data, if already provided in the review, might also be lacking for the systematic review update. Therefore, a systematic review that is not maintained is at risk of becoming misleading. These observations are also reflected in The Cochrane Collaboration’s policy, requiring that reviews become updated at least every second year.\textsuperscript{7} However, policy is not always easily translated into practice. It is difficult to keep review authors committed to maintaining a review. Some protocols never make it to the review stage and become outdated. To cope with these problems, the CHBG editorial team tries to identify new authors to work with the existing author-teams or to engage new teams of authors to take over the available titles, abandoned or outdated protocols and reviews to deal with the completions or updates. In order to increase quality and productivity, the team of Editors has been recently expanded, and, during the next 2 years, there is a plan to establish other CHBG Editorial Satellites around the world. This overview shows that a large amount of work has already been carried out within the CHBG. However, there are still trials that need to be found and added to our register, so they can be included in CHBG systematic reviews waiting to be prepared or updated. The CHBG Editorial Team provides assistance to healthcare and allied professionals who wish to carry out CHBG reviews. Further information can be found at http://ctu.rh.dk/chbg.

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Hepato-biliary trials in Cochrane reviews


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