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Xiao Chai Hu Tang, a Chinese herbal medicine formula, for chronic hepatitis B (Protocol)

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Xiao Chai Hu Tang, a Chinese herbal medicine formula, for chronic hepatitis B.
Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD013090.
DOI: 10.1002/14651858.CD013090.

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[Intervention Protocol]

Xiao Chai Hu Tang, a Chinese herbal medicine formula, for chronic hepatitis B

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Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New, published in Issue 8, 2018.

Citation: Kong DZ, Liang N, Liu JP, Nikolova D, Jakobsen JC, Gluud C. Xiao Chai Hu Tang, a Chinese herbal medicine formula, for chronic hepatitis B. *Cochrane Database of Systematic Reviews* 2018, Issue 8. Art. No.: CD013090. DOI: 10.1002/14651858.CD013090.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of Xiao Chai Hu Tang formula versus placebo or no intervention in people with chronic hepatitis B.

BACKGROUND

Description of the condition

Approximately 257 million people around the world, or 3.5% of the world's population, are infected with hepatitis B virus (WHO 2017). The estimated prevalence of hepatitis B virus infection is highest in the Western Pacific region (6.2%) and Africa (6.1%) (WHO 2017). Annually, more than 780,000 people may die because of complications, such as cirrhosis, liver failure, or hepatocellular carcinoma, due to chronic hepatitis B (WHO 2017). Chronic hepatitis B infection imposes substantial economic, psychological, and life burden on people with chronic hepatitis B and their families (Alizadeh 2008; Lu 2013; Keshavarz 2015; Ezbarami 2017).

Hepatitis B virus is commonly spread through blood, body fluids, mother-to-child transmission, sexual contact, or induced unintentionally through medical procedures (WHO 2017). Hepatitis B infection can either be acute or chronic, ranging in severity from asymptomatic to a symptomatic progressive disease (WHO 2015). Hepatitis B virus DNA (HBV-DNA), the core of the hepatitis B virus particle, is the most sensitive marker for replication of hepatitis B virus. Covalently closed circular DNA (cccDNA) acts as a template for new viral RNAs (Peng 2000; Nassal 2008) and is responsible for the persistence of hepatitis B virus infection and reactivation (Moraleda 1997; Delmas 2002; Gripon 2002; Zoulim 2005). The initial evaluation of people with chronic hepatitis B virus infection includes a thorough history, physical examination, assessment of liver disease activity and severity, and markers of hepatitis B virus infection (AASLD 2016; EASL 2017). Reducing

the risk of hepatocellular inflammatory necrosis, liver fibrosis, decompensated liver cirrhosis, liver failure, and liver cancer, improving quality of life, and prolonging survival is the aim of the long-term treatment of chronic hepatitis B (WHO 2015; EASL 2017).

Description of the intervention

Xiao Chai Hu Tang (also called XCHT, sho-sai-ko-to, or Minor Bupleurum Decoction), a herbal formula, was first recorded in the *Treatise on Febrile Disease* (*Shang Han Lun*) (Zhang 2005a) in about 280 AD. The ingredients of Xiao Chai Hu Tang formula are Chai Hu (Bupleuri Radix, *Bupleurum falcatum Linne*; approximately 26%), Ban Xia (Pinelliae Tuber,*Pinellia ternata breitenbach*; approximately 26%), Sheng Jiang (Zingiberis Rhizoma, *Zingiber officinale roscoe*; approximately 10%), Da Zao (Zizyphi Fructus, *Zizyphus jujuba Miller var. inermis Rehder*; approximately 10%), Ren Shen (Ginseng Radix Rubra, *Panax ginseng Carl Anton von Meyer*; approximately 10%), Huang Qin (Scutellariae Radix, *Scutellaria baicalensis Georgi*; approximately 10%), and Gan Cao (Glycyrrhizae Radix, *Glycyrrhiza uralensis Fisher*, or *Glycyrrhiza glabra Linneá*; approximately 10%) (Zhang 2005a; MHLW 2016) (Note: percentages are authors' calculations). In ancient times, this formula was used to treat people with symptoms, such as loss of appetite, nausea, and mild right upper quadrant discomfort, which are similar to the symptoms that characterise chronic hepatitis B. Nowadays, this formula, with either traditional ingredients (Li 2001; Xiong 2003), or modified ingredients (Yu 2000), is administered in China (Zhang 1998; Yu 2000; Li 2001; Xiong 2003; Wu 2009), and Japan (Tajiri 1991; Yamashiki 1992), especially when individuals are unable to take antiviral therapies because of adverse events (e.g. myelosuppression (Ton 2015), autoimmune manifestations (Ubiña-Aznar 2005; Nadeem 2010; Orságová 2016), neuropsychiatric symptoms (Cattie 2014), drug resistance (Yuen 2001; Papatheodoridis 2002; Liaw 2004; Hongthanakorn 2011; Miyauchi 2013; Zhang 2017), or high cost (WHO 2000; Zheng 2014). This formula is administered by different formulations, such as water decoction, tablets, capsules, granules, and injections (Zhang 1998; Li 2001; Xiong 2003; Wu 2009). Treatment duration ranges from 1 month to 13 months (Li 2001; Chen 2008b). Adverse events, such as pneumonia (Takada 1993; Hatakeyama 1997; Sato 1997), pseudoaldosteronism (Tsumura 2014), acute liver damage (Itoh 1995; Stickel 2000), acute hepatitis (Hsu 2006), acute thrombocytopenic purpura (Kiguchi 2000), and acute respiratory distress syndrome (Sakamoto 2003) are reported to be associated with Xiao Chai Hu Tang treatment.

How the intervention might work

According to Traditional Chinese Medicine, the Xiao Chai Hu Tang formula can complement the healthy qi (a vital force or energy that can control the human body), dispel the unhealthy qi, and mediate the qi and blood circulation in and around the liver and gallbladder. Possible mechanisms of action of Xiao Chai Hu Tang have been studied in animals (ducks, mice, and rats) and animal or human cells (dendritic cells, hepatic stellate cells, and hepatoma cells), and include: inhibition of hepatitis B virus replication (Wen 2000), improvement of the immune function (Gai 2007; Liu 2010), inhibition of the hepatic inflammatory response and amelioration of hepatic fibrosis (Baehem 1993; Ma 1997; Ono 2000; Zhang 2005b; Liu 2010; Chen 2017), protection of hepatocytes (Zhang 2006), and an antitumour effect (Yano 1994; Cao 2003; Wang 2004; Mao 2005).

Why it is important to do this review

We found three meta-analyses on the Xiao Chai Hu Tang formula for chronic hepatitis B. Qin 2010 assessed Xiao Chai Hu Tang formula alone or in combination with antiviral drugs versus placebo, a non-specific treatment (e.g. vitamin C), or antiviral drugs. Qin 2010 showed that the combination therapy compared with the antiviral drugs (interferon-α-2b, adefovir dipivoxil, lamivudine, and ribavirin) reduced the surface antigen of the hepatitis B virus (HBsAg), the hepatitis B e-antigen (HBeAg), HBV-DNA, and alanine aminotransferase levels. Hu 2011 compared Xiao Chai Hu Tang formula plus pegylated interferon-α (peg-IFNα) versus peg-IFNα alone; the combination therapy had higher rates of alanine transaminase improvement, HBeAg seroconversion, and reduction of flu-like symptoms caused by peg-IFNα. However, the meta-analysis included only seven randomised clinical trials with 668 participants. Yang 2015 assessed Xiao Chai Hu Tang formula plus lamivudine versus lamivudine alone; the combination therapy reduced the alanine aminotransferase levels and HBeAg seroconversion rate. All three meta-analyses assessed surrogate outcomes (Qin 2010; Hu 2011; Yang 2015). Whether surrogate outcome results do indeed lead to improvement in clinically important outcomes is still questionable (Gluud 2007; Flemming 2012; Ciani 2017; Jakobsen 2017; Kemp 2017; Jakobsen 2018). Furthermore, none of these meta-analyses took account of random errors, nor did they grade the evidence (Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Mustafa 2013; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; Guyatt 2017). Therefore, we still need to answer the question of the benefits and harms of Xiao Chai Hu Tang formula for people with chronic hepatitis B, in terms of patient-relevant outcomes. The current review, however, will only assess the benefits and harms of Xiao Chai Hu Tang formula versus placebo or no intervention in people with chronic hepatitis B. The question on the benefits and harms of Xiao Chai Hu Tang formula versus other interventions in people with chronic hepatitis B should be the subject of another review (Jakobsen 2013).

OBJECTIVES

To assess the benefits and harms of Xiao Chai Hu Tang formula versus placebo or no intervention in people with chronic hepatitis B.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of blinding, language, year, publication format, and publication status. We will also consider quasi-randomised studies, controlled clinical studies, and other observational studies for data on harms if retrieved with our searches for randomised clinical trials. This is because adverse events are rarely reported in randomised clinical trials. Moreover, observational studies may provide information on rare or late occurring adverse events (Storebø 2018). We are aware that the decision not to search for all observational studies may bias our review towards assessment of benefits and may overlook certain harms such as very late or very rare harms.

Types of participants

Inclusion criteria

Trial participants of any sex and age, diagnosed with chronic hepatitis B, defined by the trialists, or according to guidelines (HBsAg positivity for more than six months, serum HBV-DNA positivity more than 2000 IU/mL (i.e. 10^4 copies/mL), persistent or intermittent elevation in levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT), and liver biopsy findings that show chronic hepatitis B with moderate or severe necro-inflammation) (AASLD 2016; EASL 2017).

In addition to chronic hepatitis B, trial participants may also have cirrhosis, hepatocellular carcinoma, concomitant human immunodeficiency virus infection (HIV) or acquired immune deficiency syndrome (AIDS), hepatitis C, hepatitis D, or other concomitant diseases.

Exclusion criteria

None.

Types of interventions

We will include trials of Xiao Chai Hu Tang formula in any dose, formulation, and regimen compared with placebo or no intervention.

We will also allow include trials assessing the Xiao Chai Hu Tang formula if the herbal components of the formula are obtained from different sources, or if the content of the formula is modified but still contains the following four main herbs: Chai Hu, Ban Xia, Ren Shen, and Huang Qin.

We will allow co-interventions in the experimental and control intervention groups, provided that the co-interventions are administered equally to all the intervention groups of a trial.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Proportion of participants with one or more serious adverse events; that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect (ICH-GCP 1997)
- Health-related quality of life: any scale used by trialists to assess the participants' reporting of their quality of life

Secondary outcomes

- Hepatitis B-related mortality
- Hepatitis B-related morbidity (proportion of participants with one or more of the following events: cirrhosis, ascites, variceal bleeding, hepatorenal syndrome, hepatocellular carcinoma, hepatic encephalopathy, or liver transplantation, and who have not died)
- Propotion of participants with one or more non-serious adverse events: any untoward medical occurrence in a participant that does not meet the above criteria for a serious adverse event is defined as a non-serious adverse event (ICH-GCP 1997)

Exploratory outcomes

- Proportion of participants with detectable HBV-DNA in serum, plasma, or HBV-DNA viral load
- Proportion of participants with detectable hepatitis B e-antigen (HBeAg) in serum or plasma
- Separately reported serious adverse events
- Separately reported non-serious adverse events
- Separately reported hepatitis B-related morbidity

We will assess all outcomes at maximum follow-up.

Search methods for identification of studies

Electronic searches

We will search the The Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2018), Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS Bireme (Latin American and Caribbean Health Science Information database), Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index-Science (Web of Science) (Royle 2003). We will also search the China National Knowledge Infrastructure (CNKI) Database, Chongqing VIP (CQVIP) Database, Wanfang Database (WF), and SinoMed (CBM) Database.

Appendix 1 provides the preliminary search strategies with the expected time spans for the searches.

Searching other resources

We will search reference lists of systematic reviews and meta-analyses on this topic, and of the retrieved studies. We will also search the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp), ClinicalTrial.gov (www.clinicaltrials.gov/), and the Chinese Clinical Trial Registry (ChiCTR) for ongoing or unpublished trials.

Data collection and analysis

We will conduct our review according to the guidelines of *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and the Cochrane Hepato-Biliary Group Module (Gluud 2018).

We will perform analyses using Review Manager 5.3 (RevMan 2014) and Trial Sequential Analysis version 0.9.5.10 Beta software (Thorlund 2011a; TSA 2011).

Selection of studies

Two review authors will independently screen titles and abstracts to identify potentially eligible trials. We will list multiple reports of the same trial under their main reference. We will list ineligible studies with reasons for exclusion in the 'Characteristics of excluded studies' table. We will resolve any disagreements through discussion, or we will ask JPL to arbitrate. We will record the selection process in a PRISMA flow diagram (PRISMA 2009).

Data extraction and management

Two review authors will independently extract data using a pre-piloted electronic data collection form created in Microsoft Excel. In case of discrepancies, we will recheck the extracted data. If disagreements persist, we will try to resolve any disagreements through discussion. We will contact JPL to arbitrate if disagreements still exist, before proceeding with the analyses.

The two review authors will independently extract the following information: publication data (i.e. year, country, authors); study characteristics and design; characteristics of trial participants; trial inclusion and exclusion criteria; interventions; outcomes; follow-up; types of data analyses (i.e. intention-to-treat, modified intention-to-treat, per protocol). If data are missing in the reports, we will contact trial authors for the missing information. We will extract data at maximum follow-up.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in the included trials. We will assess risk of bias according to the Cochrane 'Risk of bias' tool (Higgins 2011), the Cochrane Hepato-Biliary Group Module (Gluud 2018), and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017; Savović 2018), using the following definitions.

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person, not otherwise involved in the study, performed them.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We will only include such studies for assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation, so the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We will only include such studies for assessment of harms.

Blinding of participants and personnel

- Low risk of bias: any of the following: blinding of participants and key study personnel ensured, and it was unlikely

that the blinding could have been broken; no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding, such as mortality.

- Unclear risk of bias: any of the following: insufficient information to permit judgement of low risk or high risk; or the study did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessment

- Low risk of bias: any of the following: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding, such as mortality.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of low risk or high risk; or the study did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data, in combination with the method used to handle missing data, were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: all pre-defined, or clinically relevant and reasonably expected, outcomes were reported. If the original study protocol is available, the outcomes should be those called for in that protocol. (Note: If the study protocol is obtained from a study registry (e.g. www.clinicaltrials.gov), the outcomes sought are those enumerated in the original protocol, if the study protocol was registered before, or at the time that the study began; if the study protocol was registered after the study began, those outcomes will not be considered to be reliable in representing the outcomes initially being sought.) If the study protocol is not available (or if the protocol was registered after the study began), then we will assess for reports of all-cause mortality, serious adverse events, and health-related quality of life outcomes, as we deem these to be the most clinically relevant and reasonably expected outcomes.
- Unclear risk of bias: the study authors did not report all predefined outcomes fully, or it was unclear whether the study authors recorded data on these outcomes or not.
- High risk of bias: the study authors did not report one or more predefined outcomes.

For-profit bias

- Low risk of bias: the study appeared to be free of industry sponsorship or other type of for-profit support that could manipulate the study design, conductance, or results of the study (industry-sponsored studies overestimate the efficacy by about 25%) (Lundh 2017).
- Unclear risk of bias: the study may or may not have been free of for-profit bias, as the study did not provide any information on clinical study support or sponsorship.
- High risk of bias: the study was sponsored by industry or received another type of for-profit support (Lundh 2017).

Other bias

- Low risk of bias: the study appeared to be free of other factors that could put it at risk of bias.
- Unclear risk of bias: the study may or may not have been free of other factors that could put it at risk of bias.
- High risk of bias: there were other factors in the study that could put it at risk of bias.

Overall risk of bias

- Low risk of bias: the outcome result will be classified as at overall low risk of bias only if all of the risk of bias sources described above are classified as at low risk of bias.
- High risk of bias: the outcome result will be classified as at high risk of bias if any of the risk of bias sources described above are classified as at unclear risk of bias or high risk of bias.

We will try to reach consensus through discussion. If disagreements still exist, we will contact JPL to arbitrate.
Our primary conclusions will be based on the results of all our primary and secondary outcome results with overall low risk of bias.

Measures of treatment effect

We will use the risk ratio (RR) for measuring dichotomous outcomes and mean difference (MD) for continuous data with 95% confidence intervals (CI) for head-to-head comparison meta-analysis. When different instruments are used to measure the same continuous outcome, we will calculate the standardised mean difference (SMD) with 95% CI.

Unit of analysis issues

We will follow the guidelines set in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The unit of analysis will be the participants randomised into the trial intervention groups. For trials with multiple intervention groups, we will only include the groups in which our experimental and control interventions are compared. If the control intervention group is a common comparator for two or more experimental intervention groups, then we will divide the control group into two in order to avoid double-counting.

For cluster-randomised trials, we will directly extract data from the analysis that properly accounts for the cluster design. If control of clustering has not been performed, we will determine the inflated standard errors, which account for clustering, entering them into Review Manager 5 under a generic inverse-variance outcome (RevMan 2014).

For cross-over trials, we will extract only data from the first period in order to avoid residual treatment effects (Higgins 2011).

Dealing with missing data

We will attempt to contact trial authors for missing data or information that is not clearly presented.

We will perform our analysis using the intention-to-treat method whenever possible. If not possible, we will use the data that are available to us. For all primary and secondary outcomes, we will include participants with incomplete or missing data in the sensitivity analyses by imputing them as follows:

For dichotomous outcomes

- Best- and worst-case scenario: assumes that all participants lost to follow-up in the experimental group have survived, have improvement in clinical symptoms, have no serious adverse event, and have no morbidity (for all dichotomous variables); and that all participants lost to follow-up in the control group have not survived, have no improvement in clinical symptoms, have a serious adverse event, and have morbidities (for all dichotomous variables).
- Worst- and best-case scenario: assumes that all participants lost to follow-up in the experimental group have not survived, have no improvement in clinical symptoms, have a serious adverse event, and have morbidities (for all dichotomous variables); and that all participants lost to follow-up in control group have survived, have improvement in clinical symptoms, have no serious adverse event, and have no morbidity (for all dichotomous variables).

For continuous outcomes

- We will base the 'beneficial' outcome on the group mean plus 2 standard deviations (SDs), or 1 SD, and the 'harmful' outcome on the group mean minus 2 SDs, or 1 SD (Jakobsen 2014).

If SDs are not reported, we will request the information from trial authors, or we will calculate them using data from the trial, if possible.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the trial participant characteristics and design of included trials. We will assess the presence of clinical heterogeneity by comparing effect estimates (please see Subgroup analysis and investigation of heterogeneity) in trial reports in terms of participants with different diagnostic criteria, participants diagnosed with only chronic hepatitis B and participants diagnosed with concomitant diseases, formula types, formula forms, different duration and dosages of the intervention, co-interventions, different control interventions, and follow-up. Different study designs and risk of bias can contribute to methodological heterogeneity. We will assess statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis. We will start by looking at the forest plots for signs of statistical heterogeneity. Next, we will use the Chi² test with significance threshold set as $P < 0.10$, and measure the amount of heterogeneity using the I^2 statistic to assess to what extent heterogeneity is present (Higgins 2002; Higgins 2003; Higgins 2011). A rough guide of I^2 is as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity (Higgins 2011).

For the heterogeneity adjustment of the required information size (RIS) in the Trial Sequential Analysis, we will use diversity (D^2) because the I^2 statistic used for this purpose may underestimate the required information size (Wetterslev 2009).

Assessment of reporting biases

We will assess reporting bias using funnel plots if we have data from at least ten trials per comparison. To assess bias risk, we will look for symmetry or asymmetry of each funnel plot. For dichotomous outcomes, we will assess asymmetry using the Harbord test (Harbord 2006). For continuous outcomes, we will apply the regression asymmetry test (Egger 1997).

Data synthesis

Meta-analysis

We will perform meta-analyses following the instructions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and The Cochrane Hepato-Billiary Group Module (Gluud 2018). We will analyse data with Review Manager 5 software (RevMan 2014).

We will assess our intervention effects with both fixed-effect model and random-effects model meta-analysis, and we will report both results if results differ (e.g. one giving a significant intervention effect, the other no significant intervention effect). We will use the more conservative point estimate of the two. We will consider the more conservative point estimate as the estimate closer to 1.00 (for dichotomous outcomes with RR) or 0.00 (for continuous outcomes). Where the two estimates are equal, we will use the estimate with the wider CI (Jakobsen 2014).

We will assess the three primary outcomes with a P value of 0.025 or less as statistically significant, and three secondary outcomes with a P value of 0.025 or less as statistically significant, to secure a family-wise error rate below 0.05 (Jakobsen 2014). For exploratory outcomes, we will consider a P value less than 0.05 as statistically significant, because we view these outcomes as only hypothesis-generating outcomes. Whether we present our data synthesis as a meta-analysis or in a narrative way, will depend on our assessment of the statistical and clinical heterogeneity of the meta-analysed trial data per comparison.

We will not impute any missing data in our primary analysis; however, we will impute missing values in our sensitivity analysis of continuous and dichotomous data (see Sensitivity analysis; Jakobsen 2014).

If data are available from only one trial, we will use Fisher's exact test for dichotomous data (Fisher 1922), and Student's t-test for continuous data (Student 1908).

Trial Sequential Analysis

As cumulative meta-analyses contain a risk of producing random errors due to sparse data and repetitive testing, we will perform Trial Sequential Analysis. To minimise random errors, we will calculate the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect; Wetterslev 2008; Thorlund 2011b; TSA 2011). The required information size calculation should also account for the diversity present in the meta-analysis (Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). A more detailed description of Trial Sequential Analysis can be found at www.ctu.dk/tsa (Thorlund 2011a; TSA 2011).

We will control the risks of type I errors and type II errors for both dichotomous and continuous outcomes (Brok 2008; Wetterslev 2008; Brok 2009; Wetterslev 2009; Thorlund 2010; Casetllini 2017; Wetterslev 2017). For dichotomous outcomes, we will estimate the diversity-adjusted required information size (DARIS), based on the event proportion in the control group, a relative risk reduction of 15%, an alpha of 2.5% for primary outcomes, 2.5% for secondary outcomes, 5.0% for exploratory outcomes, a beta of 10% (Casetllini 2017), and diversity suggested by the trials in the meta-analysis (Wetterslev 2009; Jakobsen 2014). For continuous outcomes, we will estimate the DARIS, based on the SD observed in the control group, a minimal relevant difference of 50% of this SD, an alpha of 2.5%, a beta of 10% (Casetllini 2017), and diversity suggested by the trials in the meta-analysis (Wetterslev 2009; Jakobsen 2014).

We will test statistical significance using statistical monitoring boundaries and futility using futility boundaries (Thorlund 2011a). If the Z-curve crosses the statistical monitoring boundaries for benefit or harm before reaching DARIS, the effect of the intervention will be considered superior or inferior to the control intervention, as indicated. If the Z-curve crosses the futility monitorial boundaries before reaching the DARIS, it would mean that the intervention does not possess the postulated effect, and further randomisation of trial participants may be futile. Furthermore, if the sequential monitoring boundaries are not surpassed, and the trial monitoring boundaries for futility are not crossed, it is probably necessary to continue doing trials in order to detect or reject a certain intervention effect (Wetterslev 2008; Thorlund 2011b). In cases where the monitoring boundaries are not reached, we will also display the Trial Sequential Analysis-adjusted CI.

Subgroup analysis and investigation of heterogeneity

If data are available, we will perform the following subgroup analyses:

- trials at low risk of bias compared to trials at high risk of bias;
- trials at low risk of bias compared to trials at high risk of bias on blinding of outcome assessment;
- trials at low risk of bias compared to trials at high risk of bias on incomplete outcome data;
- trials at low risk of bias compared to trials at high risk of bias on selective outcome reporting;
- different control interventions: no intervention compared to placebo intervention;
- traditional Xiao Chai Hu Tang formula compared to modified Xiao Chai Hu Tang formula;
- different forms of Xiao Chai Hu Tang formula;
- different duration and dosages of the intervention, stratified according to the medians observed;
- participants with different diagnostic criteria;
- participants diagnosed with only chronic hepatitis B, compared to participants diagnosed with concomitant diseases (cirrhosis, hepatocellular carcinoma, HIV infection, AIDS, hepatitis C, hepatitis D, or combination of these). We will try to

analyse each concomitant disease separately.

Sensitivity analysis

In addition to the sensitivity analysis described in Dealing with missing data, we will also compare our GRADE imprecision assessments to that conducted with Trial Sequential Analysis (Jakobsen 2014).

We may conduct further sensitivity analyses during the review process if we need to test further the robustness of conclusions. We will report this in the 'Differences between protocol and review' section of the review.

Summary of findings

We will construct 'Summary of findings' tables in order to show our results and confidence in the evidence of the Primary outcomes and Secondary outcomes. We will display information of assumed control group risk, corresponding intervention group risk, relative effect, mean difference, confidence interval, statistical significance of relative effect, number of participants, and quality of the evidence. The corresponding risk (and its 95% confidence interval) is calculated using the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Using GRADEpro GDT software (community.cochrane.org/help/tools-and-software/gradepro-gdt), we will assess five factors of the evidence referring to limitations in the study design and implementation that suggest the quality of evidence: within-study risk of bias, indirectness of the evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of results, and risk of publication bias (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Mustafa 2013; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; GRADEpro GDT; Guyatt 2017).

The evidence grades are defined as follows.

- **High quality:** we are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate quality:** we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low quality:** our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
- **Very low quality:** we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

ACKNOWLEDGEMENTS

We acknowledge the great help of Sarah Klingenberg, the Information Specialist in the Cochrane Hepato-Biliary Group in designing the search strategies. We also acknowledge Dr. L. Susan Wieland of the Cochrane Complementary Medicine Field (USA) who coordinated the peer review process.

Peer reviewers: Lida Teng, Japan; Yasemin Balaban, Turkey.

Contact editor: Goran Hauser, Croatia.

Sign-off editor: Kurinchi S Gurusamy, UK.

Cochrane Review Group funding acknowledgement: The Danish State is the largest single funder of The Cochrane Hepato-Biliary Group through its investment in The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Denmark. Disclaimer: The views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or The Copenhagen Trial Unit.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage.	(Xiao-Chai-Hu or xiaochaihu or XCHT or chai*u or bupleur* or sho-sai-ko* or shosaiko* or minor bupleurum decoction*) AND ((hepatitis B or hep B or hbv) and chronic)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 (Xiao-Chai-Hu or xiaochaihu or XCHT or chai*u or bupleur* or sho-sai-ko* or shosaiko* or minor bupleurum decoction*) #2 MeSH descriptor: [Hepatitis B, Chronic] explode all trees #3 ((hepatitis B or hep B or hbv) and chronic) #4 #2 or #3 #5 #1 and #4
MEDLINE Ovid	1946 to the date of search	1. (Xiao-Chai-Hu or xiaochaihu or XCHT or chai*u or bupleur* or sho-sai-ko* or shosaiko* or minor bupleurum decoction*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 2. exp Hepatitis B, Chronic/ 3. ((hepatitis B or hep B or hbv) and chronic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word,

(*Continued*)

		rare disease supplementary concept word, unique identifier, synonyms] 4. 2 or 3 5. 1 and 4
Embase Ovid	1974 to the date of search	1. (Xiao-Chai-Hu or xiaochaihu or XCHT or chai*u or bupleur* or sho-sai-ko* or shosaiko* or minor bupleurum decoction*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] 2. exp chronic hepatitis B/ 3. ((hepatitis B or hep B or hbv) and chronic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] 4. 2 or 3 5. 1 and 4
LILACS (Latin American and Caribbean Health Science Information database) (Bireme)	1982 to the date of search	(Xiao-Chai-Hu or xiaochaihu or XCHT or chai$u or bupleur$ or sho-sai-ko$ or shosaiko$ or minor bupleurum decoction) [Words] and ((hepatitis B or hep B or hbv) and chronic) [Words]
Science Citation Index Expanded (Web of Science)	1900 to the date of search	#3 #2 AND #1 #2 TS=((hepatitis B or hep B or hbv) and chronic) #1 TS=(Xiao-Chai-Hu or xiaochaihu or XCHT or chai*u or bupleur* or sho-sai-ko* or shosaiko* or minor bupleurum decoction*)
Conference Proceedings Citation Index - Science (Web of Science)	1990 to the date of search	#3 #2 AND #1 #2 TS=((hepatitis B or hep B or hbv) and chronic) #1 TS=(Xiao-Chai-Hu or xiaochaihu or XCHT or chai*u or bupleur* or sho-sai-ko* or shosaiko* or minor bupleurum decoction*)
China Knowledge Resource Integrated Database (CNKI)	1979 to the date of search	#1 hepatitis B in abstract #2 'Xiao-Chai-Hu Tang' or 'Xiao-Chai-Hu granule' or 'Xiao-Chai-Hu capsule' or 'Xiao-Chai-Hu tablet' in abstract #3 random in abstract #4 randomly grouped in abstract #5 #3 OR #4 #6 #1 AND #2 AND #5
Chinese Science Journal Database (VIP)	1989 to the date of search	#1 hepatitis B in abstract #2 'Xiao-Chai-Hu Tang' or 'Xiao-Chai-Hu granule' or 'Xiao-Chai-Hu capsule' or 'Xiao-Chai-Hu

(*Continued*)

		tablet' in abstract #3 random in abstract #4 randomly grouped in abstract #5 #3 OR #4 #6 #1 AND #2 AND #5
Wanfang Database (WF)	1990 to the date of search	#1 hepatitis B in abstract #2 'Xiao-Chai-Hu Tang' or 'Xiao-Chai-Hu granule' or 'Xiao-Chai-Hu capsule' or 'Xiao-Chai-Hu tablet' in abstract #3 random in abstract #4 randomly grouped in abstract #5 #3 OR #4 #6 #1 AND #2 AND #5
Sinomed Database (Sinomed)	1860 to the date of search	#1 hepatitis B in abstract #2 'Xiao-Chai-Hu Tang' or 'Xiao-Chai-Hu granule' or 'Xiao-Chai-Hu capsule' or 'Xiao-Chai-Hu tablet' in abstract #3 random in abstract #4 randomly grouped in abstract #5 #3 OR #4 #6 #1 AND #2 AND #5

CONTRIBUTIONS OF AUTHORS

DZK: developed and drafted the protocol.

NL: developed and co-ordinated the protocol.

DN: developed, co-ordinated, and advised on the protocol.

CG: developed, co-ordinated, and advised on the protocol.

JCJ: developed, co-ordinated, and advised on the protocol.

JPL: initiated the review.

All authors commented and agreed to this final version of the protocol.

DECLARATIONS OF INTEREST

DZK: none known.

NL: none known.

DN: none known.

CG: none known.

JCJ: none known.

JPL: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- 2017 Open-end Fund of Education Ministry Key Laboratory for Research and Application of 'Zang Xiang' Theory in Liaoning University of Traditional Chinese Medicine (zyzx1702), China.
- Science and Technology Research Project of Department of Education of Liaoning Province (L201713), China.

NOTES

Cochrane Reviews can be expected to have a high percentage of overlap in the methods section because of standardised methods. In addition, overlap may be observed across several of our protocols as they share at least three common authors.