The effect of acupuncture on people with hepatitis C virus: A randomised controlled pilot study.

Christine Anne Berle

A thesis submitted as partial requirement for the degree of
Master of Science (Research)

Faculty of Science

University of Technology Sydney
29th August 2008

CERTIFICATE OF AUTHORSHIP/ORIGINALITY

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Signature of Candidate

Production Note:
Signature removed prior to publication.

Acknowledgements

There are many people for whom I will always feel grateful for their support and encouragement along this journey. Without their contribution, encouragement and advice this project may never have happened. There are many others without whose help in a thousand ways the quality of the project would have been severely compromised.

From the University of Technology, Sydney (UTS)

My principal supervisor, Dr Christopher Zaslawski, had the confidence to encourage me to make an application for admission for a higher degree by research. Lecturer, Mr Cong Xing Yang, endorsed my application as a referee. These people showed a leap in faith as I was applying for a higher degree without an undergraduate qualification, which I believe is uncommon. Thirty two years ago when I entered my profession there was no accredited course available.

Dr Zaslawski enthusiastically supervised the project making himself regularly available to offer guidance, support and encouragement. His knowledge and expertise will forever be greatly appreciated.

My sincere thanks go also to my co-supervisor, Dr Deirdre Cobbin who always has, and I guess, always will, astound me with her infinite knowledge, dedication and wisdom. Her critical observation, recommendations, support and editing contributed enormously to every aspect that she was engaged in with this project.

The most enthusiastic Dr Narelle Smith amazingly transposed vast amounts of data into something meaningful. Other UTS staff who deserve a special mention and thanks are; from the media team Terry Burton, Sue McInerny from U, the official UTS publication and Ms Rochelle Seneviratne from the Science Research Office, who assisted with all sorts of administrative issues in a very pleasant manner.

I have had probably more then my fair share of funds from the Vice-Chancellor's Conference Fund to attend conferences and seminars. My thanks to the University for the privilege and I hope, and fervently believe, that I have and, more importantly will, put that learning to good use.

To all the staff of the UTS Library thank you for your dedication to duty and patience with students still on training wheels such as I was, and too often feel, still am. I can't embellish these people enough for the job, not just the formal training, that they do.

Project support form outside the University of Technology (UTS)

Professor Jacob George is Professor of Gastroenterology and Hepatic Medicine, Faculty of Medicine, University of Sydney was co-investigator and has provided direction and support to me and this project. His guidance is appreciated.

The Australian Acupuncture and Chinese Medicine Association which supported and provided the project with very necessary research funding. This funding went towards pathology tests for three separate years with a total amount of $7,200.

Hepatitis C Council of NSW helped enormously with recruitment, especially Paul Harvey the editor of the Hep C Review, Grant Malpas, the help desk man and CEO Stuart Loveday.

Tony Chianese, Director Helio Supply Co. Pty. Ltd. (Chippendale), kindly donated all the acupuncture needles for the clinical trial. My thanks Tony.

To the participants, my real heroes

What a wonderful group of people. Each and every one of them donated not just their time, but themselves to this project, in the full knowledge that there was a 50% chance that they were in the control group and therefore had only a 50% prospect of receiving any potential relief for the first five and a half months of their participation. It takes

special people to give as they have and each and every one of them are very exceptional people.

Personal Support

Finally to my dear partner, Mr Ross Keys who earned the acronym PBR (Poor Bloody Ross), for his continual encouragement, help and support which without, this undertaking and thesis certainly would not have been possible.

I very respectfully offer my sincere appreciation and gratitude to all these people.

List of conference presentations and posters arising from the research

Conference presentations

Berle C, Cobbin D, George J, Zaslawski C (2006) The Effect Of Acupuncture On People Who Are Hepatitis C Antibody Positive: The Study Protocol Of An Ongoing Randomised Controlled Pilot Study. 2006 *AACMA Australasian Acupuncture and Chinese Medicine Annual Conference, Adelaide.*

Berle C, Cobbin D, Zaslawski C (2007) A Methodological Approach to Convert A Western Disease To TCM Patterns Of Disharmony – An Assessment And Re-evaluation/Outcome Tool. 2007 *AACMA Australasian Acupuncture and Chinese Medicine Annual Conference, Brisbane.* The presentation won the Helio Supply Co. Award for "Best Research/Scientific Paper AACMAC Brisbane 2007.

Berle C, Cobbin D, Smith N, Zaslawski C (2008) An Acupuncture Pilot Study Using Pattern Differentiation In The Treatment Of Hepatitis C Virus. 2008 *AACMA Australasian Acupuncture and Chinese Medicine Annual Conference, Sydney.*

Berle C, Cobbin D, Smith N, Zaslawski C (2008) A Novel Outcome Measure for Acupuncture and Herbal Medicine Clinical Trials. *4th Symposium on Acupuncture and Meridian Studies 2008, Korea.*

Poster

Berle C, Cobbin D, George J, Zaslawski C (2006) The Effect of Acupuncture on People who are Hepatitis C Antibody Positive: The Study Protocol of an ongoing Randomised Controlled Pilot Study. *5th Australasian Conference on Viral Hepatitis, Sydney.*

Contents

Page Number

Appendices

Figures

Tables

Abbreviations - Acronyms

ANOVA	Analysis of Variance
ALT	Alanine Aminotransferase
AGDHA	Australian Government Department of Health and Ageing
AST	Aspartate Aminotransferase Tests
CAM	Complementary and Alternative Medicine
CHC	Chronic Hepatitis C
CHM	Chinese Herbal Medicine
CONSORT	Consolidated Standards of Reporting Trials
EIA	Enzyme immunoassays
ELISA	Enzyme linked immunosorbent assay
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCCNSW	Hepatitis C Council of NSW
HCV	Hepatitis C virus
HCVPWG	Hepatitis C Virus Projections Working Group
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
ID	Identification Number
IDU/s	Injecting drug user/s
IFN	Interferon alpha
IU	International Unit (measurement)
LFT	Liver Function Test
m/L	Millilitre
NCHECR	National Centre in HIV Epidemiology and Clinical Research
NSP	Needle and syringe program
PCR	Polymerase Chain Reaction
PBS	Pharmaceutical Benefits Scheme
QoL	Quality of Life questionnaire
RCT	Randomised Controlled Trial

RNA	Ribonucleic acid
SF36	Short Form 36 Health Survey Questionnaire
SF-36v2	Short form 36 version 2 Questionnaire
TCM	Traditional Chinese Medicine
U/L	Units per Litre
UTS	University of Technology, Sydney

Abstract

Background

The use of Complementary and Alternative Medicine (CAM) in Australia has been steadily increasing. This has resulted in many people infected with Hepatitis C Virus (HCV) consulting CAM practitioners in the hope of alleviating some of the debilitating symptoms associated with this viral infection. Chronic symptoms often lead to a reduction in everyday functional health producing a lower quality of life compared with healthy population norms or patients with other forms of liver disease. Current recommended pharmaceutical treatment has a sustained virological response in approximately 50-60% of patients. Also large numbers of people are either not suitable candidates or intolerant to treatment or do not choose this option.

In the mid 1990s, HCV residents in a Sydney alcohol and drug rehabilitation centre who were also receiving auricular (ear) acupuncture as part of their rehabilitation program, verbally reported decrease in their alanine aminotransferase (ALT) blood levels after approximately 16 acupuncture treatments administered over a three month period (Berle 1997).

Objective

To investigate whether 24 acupuncture treatments over a twelve week period has an effect on the health outcomes of people with HCV.

Design

A randomised single blind controlled pilot study with two parallel arms.

Participants

Sixteen applicants who met the eligibility criteria and agreed to participate in the study were randomised into either treatment or control group.

Outcome measures

The primary outcome measure was ALT blood levels at the completion of treatment (week 12), weeks 16 and 20. The secondary outcomes were HCV PCR quantitative (viral load test) and hepatitis quality of life (QoL) questionnaire. In addition a HCV Traditional Chinese Medicine (TCM) pattern questionnaire, acupuncture treatment credibility questionnaire and acupuncture needling sensation questionnaire were administered.

Setting

Participants were offered treatment at two clinic locations; a private clinic at Guildford and at the University of Technology, Sydney (UTS) city campus. Blinded serum pathology/testing was conducted through independent Douglass Hanly Moir Pathology clinics.

Treatment

Sixteen HCV participants were randomly allocated to two groups; one group receiving verum acupuncture treatment and the other receiving invasive sham acupuncture treatment. The treatment methodology involved the development of a TCM pattern differentiation diagnostic/outcome measure which identified 17 TCM/HCV patterns.

One participant (treatment group) left the study after eight treatments due to work commitments.

Results

No significant change was found between the two groups for ALTs, viral load or any domains of the QoL measure.

The TCM pattern questionnaire identified the primary, secondary and tertiary TCM pattern expressions for HCV within the study group. On completion of the treatment phase there was a significant reduction in the secondary and tertiary TCM pattern expression for the treatment group ($p=0.045$ and 0.037 respectively). No significant change was found for the control group.

The acupuncture credibility questionnaire identified that neither the treatment nor control group identified the type of treatment they had received; however the treatment group did perceive their treatment as more credible than the control group at week 12. There was no significant difference found between or within the two groups for the acupuncture needling sensation questionnaire.

Conclusions

Despite the small number of participants and no significant changes for ALTs, viral load or any domains of the QoL there was a significant difference in the secondary and tertiary TCM patterns.

Chapter 1: Introduction

1.1 Rationale for the study

During the mid 1990s a group of acupuncturists reported on a clinical project which compared retention rates of 263 residents over a 74 week period following introduction of acupuncture at a Sydney inpatient alcohol and other drugs rehabilitation centre. As part of facilities treatment program, residents could decide on any given day whether to receive auricular acupuncture (National Acupuncture Detoxification Association protocol), (offered three times per week) or participate in a meditation class. During the 74 week period two groups evolved; an auricular acupuncture/meditation group and a meditation only group. The study reported a statistically significant higher retention rate for the acupuncture/meditation group compared with the meditation only group (77% cf 21%). Anecdotally, the residents who received acupuncture reported less stress, anxiety and craving. This may explain why retention rates were higher when receiving acupuncture than for retention rates prior to the introduction of acupuncture (21% cf 16%).

One unexpected outcome of the study was that some acupuncture participants who identified that they had Hepatitis C Virus (HCV) verbally reported decreases in their alanine aminotransferase (ALT) serum levels (a biochemical measure of damage to the liver), following approximately 16 acupuncture treatments (three months) (Berle 1997). Although this observation could have been due to a variety of reasons (for example decrease in alcohol intake, improvement in nutritional status, natural clearance of the virus), the observation prompted the development of this research project.

1.2 Aim of the study

The aim of the study was to determine whether 12 weeks (24 sessions) of acupuncture affected the health outcome of people with HCV.

The primary outcome measure in the study was ALT blood levels. Other measures used to evaluate change from baseline were;

- HCV polymerase chain reaction (PCR) quantitative (viral load)
- Quality of Life (QoL) questionnaire
- Hepatitis C Virus/Traditional Chinese Medicine history and examination questionnaire

In addition two questionnaires were used to evaluate acupuncture treatment;

- Acupuncture Needling Sensation Questionnaire (ANSQ) and
- participant blinding, Acupuncture Treatment Credibility Questionnaire (ATCQ)

To replicate TCM practice within the framework of rigorous evidence based medical research, a standardised and replicable TCM/HCV framework needed to be developed which remained true to both Western medical science and TCM theory paradigms. As most Western defined diseases are represented by several TCM patterns, this study needed to incorporate individualised TCM treatment protocols for each identified TCM/HCV diagnostic pattern which could be objectively measured and analysed.

This is the first acupuncture pilot study for HCV using rigorous objective outcome measures and a novel protocol that uses TCM patterns to direct individualised treatment and has potential for use as a clinical outcome.

1.3 Format of the thesis

Chapters

Chapter 1. Introduction

This chapter outlines rationale and aims and format of the thesis.

Chapter 2. Background

This chapter presents important definitions and information crucial to understanding HCV. It involves the epidemiology, diagnosis and the current treatment of hepatitis C. In addition, the concept of TCM pattern identification is outlined.

Chapter 3. Literature Review

A critical evaluation of available TCM research studies on hepatitis and critically evaluates the design adequacy of treatment and outcome measures. Clinical trials and cohort studies are examined for their strengths and weaknesses.

Chapter 4. Methods

The presentation of study design and methods, includes details relating to the participant profile, randomisation procedures, inclusion and exclusion criteria, participant flow, treatment protocols for each identified TCM hepatitis pattern identification and control intervention, the outcome measures and statistical procedures used to analyse the data.

Chapter 5. Results

This chapter presents the results from the primary and secondary measures employed in the study. This chapter also reports on medical history, common and significant health findings and information on the participants perception related to needling sensation, group allocation, and TCM pattern changes for the two groups.

Chapter 6. Discussion

Discusses the results, identifies strengths and limitations of the study and raises implications for future acupuncture research.

Chapter 7. Conclusion, Recommendations

Summarises the findings with recommendations from the findings for design of acupuncture clinical trials and future research directions.

References

Appendices

Appendix 1: Comprehensive report on HCV transmission, the current Australian profile, global and Australian snapshot and epidemiology

Appendix 2: Activity Sequencing and Gantt chart

Chapter 2: Background

2.1 What is HCV?

HCV is a single-stranded, enveloped ribonucleic acid (RNA) virus belonging to the flavivirus family (ASHM 2004; Simmonds 2001) which was first identified in 1989. Prior to 1990 HCV was called non-A non-B hepatitis. Hepatitis C is a blood borne viral disease which can be slowly progressive, resulting in serious liver disease such as cirrhosis, liver failure and liver cancer (Bayliss et al 1998; Bonkovsky et al 1999). The origin and spread of HCV in the human population have been the subject of extensive investigation however, knowledge of the virus and its effects are poor. Therefore predicting clinical outcomes and controlling its spread is difficult. Chronic Hepatitis C (CHC) infection is the major infectious cause of chronic liver disease in Western countries (Bonkovsky et al 1999). Contributing to the difficulty in understanding the epidemiology of HCV is the lack of symptoms associated with both initial infection and slow progression over a prolonged period of chronic infection (Kenny-Walsh 1999; Seeff et al 2000; Wiese et al 2000).

HCV is usually discovered incidentally, with most patients initially presenting with general complaints of fatigue, irritability, nausea, weight loss, muscle ache, headache, joint pain, abdominal discomfort or right upper quadrant pain (Bayliss et al 1998; Farrell 2002; HCCNSW 2007). HCV is transmitted from person to person by blood to blood contact. The majority of HCV infections in Australia are due to either illicit drug users sharing injecting equipment (over 75 percent) or transfusion of blood products (prior to 1990) (five to ten percent). Currently there is no HCV vaccine with little expectation of developing one in the near future.

2.1.1 Pathology testing

Diagnosis of HCV is obtained by identifying pathology "blood markers" which indicate the presence of HCV. These markers include antibodies to the virus and evidence of the

presence of HCV viral RNA. These markers provide evidence of active viral replication and may be found in the liver and/or serum of HCV infected persons.

Blood tests are used to detect antibodies produced by the immune system specifically in response to the HCV virus. These antibodies will form between one and three months after initial exposure to the virus. Although the presence of anti-HCV antibodies is a measure of prior exposure to HCV infection, it cannot be considered a marker for current infection. At present the most common test to detect anti-hepatitis C virus antibodies (anti-HCV) is enzyme-linked immunosorbent assay (ELISA) (ACMERC 1995; Farrell 2002).

Additional blood screening tests can detect elevated ALT levels while a liver biopsy is able to determine the degree of injury to the liver cells. ALT is an enzyme involved in liver metabolism which is released with tissue damage and increases during active liver disease. This occurs with hepatitis, some other liver conditions and the intake of certain drugs. ALT measurement is considered to be a surrogate indicator of HCV infection, but is not a direct measure of viremia. The degree of ALT elevation cannot be directly correlated with the level of HCV infection. The normal range of ALT is 6-<40 U/L (units per litre). Twice the normal range is considered clinically significant (80 U/L). Chronic viral hepatitis caused by infection with HCV may cause a benign infection with normal serum aminotransferase activity (Foster et al 1998).

Viral load is the amount of virus in the body or in tissues such as the liver or lymph nodes. A sample of liver is needed to measure the hepatic content of HCV RNA. Commercial assays allow the level of HCV RNA to be determined in blood which is generally referred to as "viral load". Determination of the HCV viral load is performed using the COBAS Ampliprep/COBAS TaqMan HCV assay. Viral load is used to assess patients for treatment and response to combination therapy. Viral loads are considered high if greater than HCV RNA800,000 IU/mL. A better response to combination therapy is obtained with a lower viral load, particularly for the less responsive genotypes 1 and 4. Persons with genotype 1 and high viral load receive combination treatment for 12

months, whereas those with low HCV RNA titre need only six months of treatment. A Log_2 reduction in viral load is considered favourable following 12 weeks of combination treatment. Patients who have higher levels of viremia (above two million copies/m/L) are less likely to respond to combination therapy.

2.1.2 HCV prognosis and progression

There is some disagreement as to the prognosis of patients with CHC infection. Most people who develop HCV antibodies following exposure to HCV do not experience any ill effects at the time of infection (Van Der Poel et al 1994). Approximately 10 to 25 percent of people who develop HCV antibodies experience an acute illness. Some research suggests that most patients with CHC will have a normal life span and not suffer severe consequences of this disease (Alter et al 1997). Some CHC individuals remain asymptomatic for long periods of time and never develop progressive or symptomatic liver disease. Other infected individuals only become aware of the development of liver failure or liver cancer several decades after initial infection. Approximately 20 percent of patients at the time of their first liver biopsy have cirrhosis (Bonkovsky et al 1999). Other studies show that patients with CHC have a reduced QoL (Bayliss et al 1998; Carithers et al 1996; Davis et al 1994; Foster et al 1998; Ware et al 1994).

The long term sequelae following exposure to the HCV are products of the outcome of the two phases of the infection; first, whether or not the acute hepatitis spontaneously resolves; and second, if the viral infection persists, whether or not the established chronic hepatitis remains stable or progresses. A characteristic of acute HCV infection is its low rate of viral loss, presumable a consequence of a blunted innate immune response to the virus through multiple mechanisms (Wieland et al 2005). This has prompted researchers to identify features associated with, or predictive of, viral persistence. Of several identified features, age at initial infection plays a crucial role. While 75% to 85% of older infected persons (usually considered to be over 40 years of age) do not lose the virus, spontaneous resolution occurs in almost 50% of younger infected person (Alter et al 1992; Kenny-Walsh 1999; Vogt et al 1999). Other factors that correlate with failure to recover include male gender, African-American heritage, specific human leukocyte

antigen subtypes and polymorphisms, and intrinsic or induced immunosuppression (Thomas et al 2005). There is insufficient evidence that either viral load or genotype affect spontaneous resolution of the disease. The disease shifts from acute to CHC when the HCV infection persists for six months or longer (Heller et al 2005) (see Figure 2.1).

Among people who develop HCV antibodies following exposure to HCV, around 25% will clear the HCV infection without any long-term effect (Dore et al 1997; Micallef et al 2006; Van Der Poel et al 1994). For the other 75% the resultant chronic liver disease is of variable severity and runs a protracted course. Some patients remain asymptomatic for long periods of time and may never develop progressive or symptomatic liver disease. It is estimated approximately 45% will not develop serious liver damage. Approximately 44% will develop progressive liver damage which may be only mild or moderate. A small proportion however will develop long-term sequelae, in particular compensated cirrhosis, liver failure and hepatocellular carcinoma (HCC). Recent data suggest that the progression to cirrhosis is accelerated with the increased duration of the infection (Poynard et al 2001). Limited surveillance (20 years) leaves progression rates uncertain.

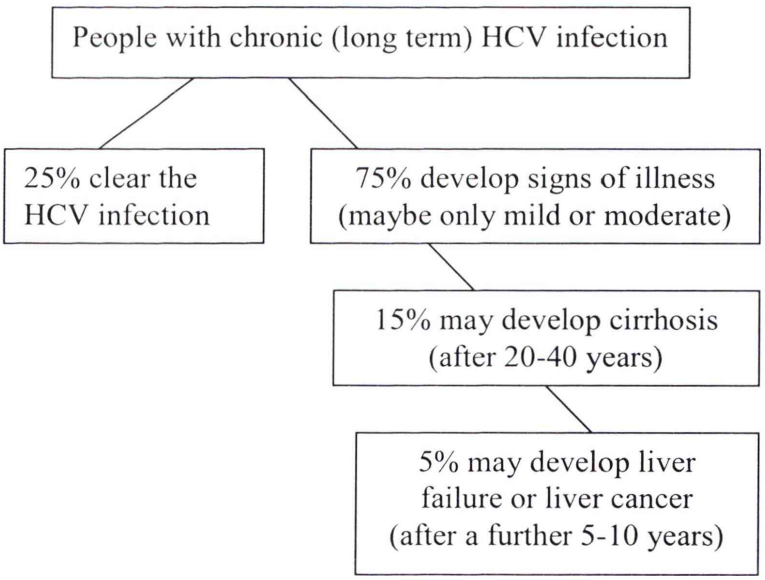


Figure 2.1: HCV prognosis and progression.

HCV infection is now the most common reason for liver transplantation in Australia. The new liver will, however, always become infected, with liver damage progressing at a greatly increased rate.

2.1.3 HCV genotypes

The HCV can be classified into a number of distinct genotypes and subtypes. Distribution varies both geographically and between risk groups.

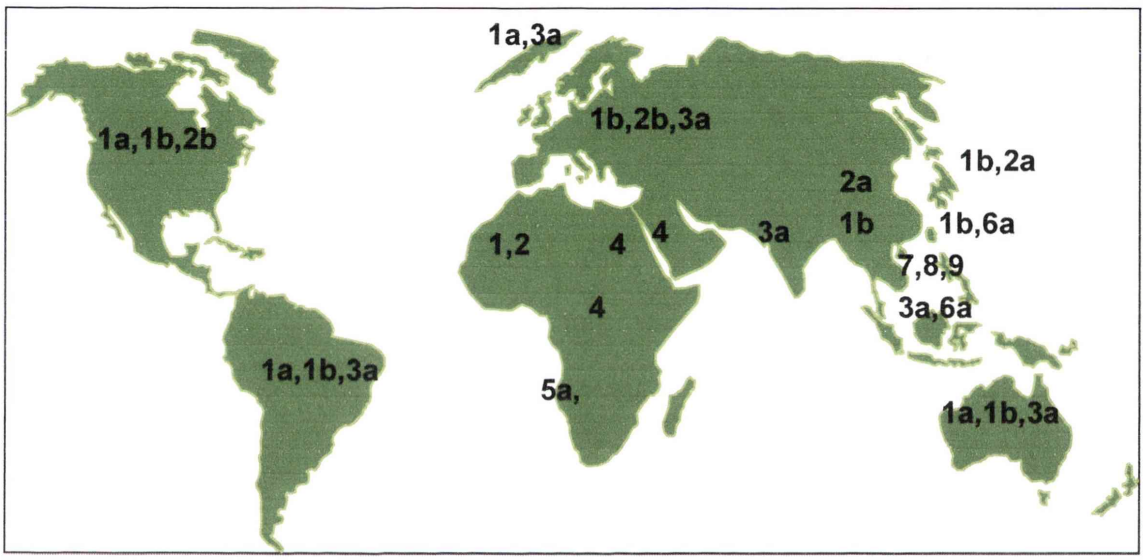


Figure 2.2: Global genotype/subtype distribution pattern (Dore 2006).

There are six major genotypes numbered 1 to 6 (HCV 1 – 6) (Simmonds 2001). Genotypes are identifiable "families" which differ slightly from each other in their DNA sequencing. Within each genotype, small but significant differences exist but are not sufficiently different to be classified as a new genotype. These are called subtypes and are classified by subtypes: a, b, and c. Duration and success rates of current medical treatment, pegylated combination therapy (interferon and ribavirin) are dependent upon an individual's genotype and subtype factors. While additional genotypes have been proposed (HCV 7-11), these can be accommodated in the existing six genotypes with genotypes 7, 8, 9 and 11 being recognised as subtypes of genotype 6 and the type 10 as a subtype of genotype 3.

In Europe types 1b and type 2 are widely distributed, particularly in older age groups, while those infected through drug use are more likely to be infected with genotypes 3a and 1a (Simmonds et al 1996; Tisminetzky et al 1994). This observation suggests a geographically large injecting drug users (IDUs) transmission network distinct from other HCV-infected individuals (Holmes 1995; Leigh Brown 1997) (see Figure 2.2).

The Australian genotype profile consists of genotype 1a (35%), genotype 1b (15%), genotype 2 (7%), genotype 3 (35%) and others (8%) (see Figure 2.3).

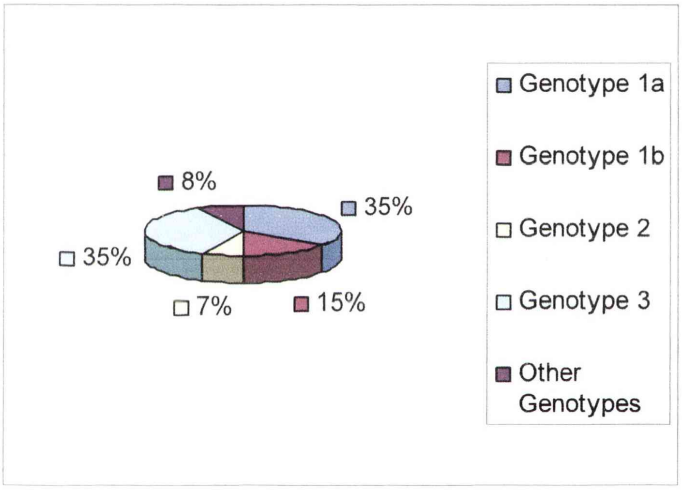


Figure 2.3: Australian genotype profile (percent).

2.1.4 Signs and symptoms of HCV

Few people will show any overt signs of illness soon after infection, as acute symptoms are rare. Typical chronic symptoms include debilitating fatigue, nausea and abdominal pain. HCV infected people may report joint and muscle pain, general malaise, weight loss, hormonal irregularities in women, flu-like symptoms and depression (Poynard et al 2002). People with significant symptomatic illness are often unable to carry out ordinary, everyday activities.

It has been shown that patients with hepatitis C infection have a reduced QoL (Davis et al 1994; Ware et al 1994). Patients without cirrhosis have demonstrated a decrease in both mental and physical QoL (Foster et al 1998). These reductions have been judged to be clinically and socially relevant and are comparable with, or more severe than, those for a representative sample of type II diabetics (Bayliss et al 1998; Carithers et al 1996; Ware et al 1994).

2.1.5 Risk factors/transmission

HCV is transmitted primarily through blood-to-blood contact. The sharing of equipment during injecting drug use is the most common mode of transmission in Australia. Other modes of HCV transmission include; non-sterile medical, dental, tattooing or body piercing procedures, needle-stick injuries and accidental exposure to infected blood or blood products, blood-to-blood contact due to physical assault, mother-to-child transmission during pregnancy and delivery, sharing personal toiletries such as toothbrushes and razors.

See Appendix 1 for a more comprehensive report on HCV risk factors/transmission, the current Australian profile, snapshot, epidemiology and current medical treatment.

2.1.6 Global snapshot

The World Health Organisation has estimated that 170 million people worldwide are infected with the HCV.

2.1.7 Australian snapshot

HCV is one of the most commonly reported notifiable infectious diseases in Australia with over 225,000 diagnoses reported (HCVPWG 2006; NCHECR 2006). It is estimated that approximately 80 per cent of people with HCV in Australia have been diagnosed (Australian Government 2005).

2.1.8 Epidemiology

Within the general community there is a one percent HCV prevalence rate. Of the estimated 264,000 people living with HCV antibodies in Australia at the end of 2005, it was estimated that; 25% had cleared their HCV infection, 58% had chronic HCV infection and stage F0/1 liver disease, 15% had chronic HCV infection and stage F2/3 liver disease and 2% were living with HCV related cirrhosis (Australian Government 2005).

2.2 Current medical treatment

The current medical treatment for HCV is a combination of two drugs, pegylated interferon and ribavirin, commonly known as pegylated combination therapy. Treatment duration and success rate is dependent upon the HCV genotype. Genotypes 2 and 3 require six months of treatment (80% clearance success rate) and genotype 1 (the dominant Australian genotype) requires from 12 to 24 months treatment with only a 35% clearance success rate. There is a much lower response rate in individuals with more advanced disease, such as cirrhosis (HCCNSW 2007).

Side effects of combination therapy vary for each person and often decrease as treatment continues. A potential side effect of Ribavirin is anaemia caused by the destruction of red blood cells. Ribavirin has been linked to birth defects in trial animals and therefore is not prescribed to pregnant women, those currently breast feeding, nor any person (male or female) not taking contraceptive precautions during and for several months following treatment. Interferon (IFN) alfa has been associated with depression and suicide and therefore all users are monitored carefully. Due to treatment side effects and the mandatory pre-treatment liver biopsy examination (until 31st March 2006) only 2,000 people underwent combination therapy treatment per annum. It is now expected that this number will increase.

2.3 Traditional Chinese Medicine

TCM differentiates Western diseases into TCM patterns *(Bian Zheng)*, which are symptom clusters each with their own unique treatment protocol. Chinese classical

medical texts recognised jaundice, a symptom often associated with hepatitis, over two thousand years ago. In the *Huang Di Nei Jing Su Wen,* an important foundation medical text thought to be written in 200 BC, jaundice was termed *"dan"*, meaning yellow disease (Unschuld 2003).

Most modern TCM research has used fixed formula treatments for Western defined diseases/illnesses. In addition clinical trial outcomes are often measured using recognised objective biomedical markers. More recently a number of research designs have attempted to accommodate TCM clinical practice within the framework of rigorous evidence based medical research (Schnyer et al 2006). Participants in clinical trials were diagnosed according to established TCM patterns (manualisation) and acupuncture administered based on each of the participant's TCM pattern status.

Whilst the use of fixed treatment protocols is appropriate for some types of TCM research (eg knee pain) complex clinical conditions may need individualised but reproducible treatment protocols. Homogeneous populations of patients which share the same Western medical diagnosis and the same TCM diagnosis are conducive to formulaic acupuncture whereas heterogeneous populations with multiple symptoms and signs require individualised treatments (Stux and Hammerschlag 2001). TCM pattern differentiation is an integral aspect of the clinical practice of traditional Chinese acupuncture. It is defined as "the process of overall analysis of clinical data to determine the location, cause and nature of a patient's disease" (WHO 2007). In addition to being used for diagnostic reasons it also guides the practitioner towards a treatment principle (*lun fa*) whereby specific acupoints or herbal formula are selected for treatment. In clinical practice a primary TCM pattern is often discerned, but occasionally secondary and tertiary patterns are also identified. Subsequent treatment focusing on the primary TCM pattern but may also include additional acupoints or herbal substances which address secondary or tertiary TCM patterns. Furthermore these TCM patterns may change over the course of the disease and different or modified treatment strategies may be administered (Deng 1999).

In an attempt to align research design with clinical practice a number of studies have used TCM pattern identification to direct both acupuncture and herbal treatment within the constraints of a clinical trial (Allen et al 1998; Bensoussan et al 1998; Sung et al 2004). First documented by Schnyer, participants who were initially recruited according to a Western biomedical diagnosis were then further diagnosed according to the TCM pattern (Schnyer et al 2001). Schnyer termed this approach manualisation whereby each TCM pattern for the condition of depression was linked to a defined treatment protocol with each subject receiving acupuncture at a set of acupoints dependent on their TCM pattern. This was thought to improve the external and face validity of the trial with the treatment designed to align with clinical practice.

The method used in this HCV pilot study extended Schnyer's work. TCM pattern differentiation was used not only to guide acupuncture treatment but also as a tertiary outcome measure. TCM patterns were quantified on initial recruitment of participants and then reassessed at the completion of the trial to evaluate possible change in the TCM patterns.

Chapter 3: Literature review

The review was undertaken to identify and critically examine HCV published literature including clinical trials and cohort studies.

Literature searches were conducted using the following electronic databases: Alternative and Allied Medicine Database (AMED), Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane multifile EBM reviews, Medline, and PubMed (last searched 14th July, 2008). The initial electronic search using the key words acupuncture with hepatitis or hepatitis C failed to identify any English randomised clinical trials. A hand search identified only one paper involving five single case studies (Campbell 1995). When the electronic search terms were extended to include Chinese herbal/ or medicine, traditional Chinese medicine (which shares the same theoretical framework as acupuncture) a total of 235 references were generated. Upon closer assessment replicated studies (n=29), non English references (n=51) and no abstract availability (n=11) were removed leaving 144 papers.

3.1 Types of studies

Studies were categorised into the classifications listed below with 17 studies being represented in more than one classification:

- acupuncture (n=68);
- CHM (n=69);
- TCM (n=13);
- complementary and alternative medicine (CAM) (n=32) and;
- various non relevant references (n=13) which included unrelated diseases/conditions (n=7), reviews of articles/conferences (n=3), software program (n=1), TCM material medica (n=1),) and an article on the sexual transmission of HCV (n=1).

3.2 Exclusion of studies

Of the 144 references 26 references were non acupuncture, CHM or TCM references. A further 43 papers were excluded which reported acupuncture (n=42) and CHM (n=1) as the mode of transmission for hepatitis. Another four papers reported on adverse events from acupuncture (n=2) and CHM (n=2) and eight papers were animal studies. A further 19 studies were non clinical references. Twenty six studies were pharmaceutical, physiological or used laboratory parameters and 15 studies were eliminated for not providing any clinically relevant outcome measures.

This left four CHM studies plus the acupuncture case study which are included in the following review. The first two studies reviewed are case studies (Campbell 1995; Stern 1997) and the following three are randomised clinical trials (RCT). The following flowchart illustrates the process of identifying the four studies (Figure 3.1). A summary of the main features of the five clinical studies are presented in Table 3.1.

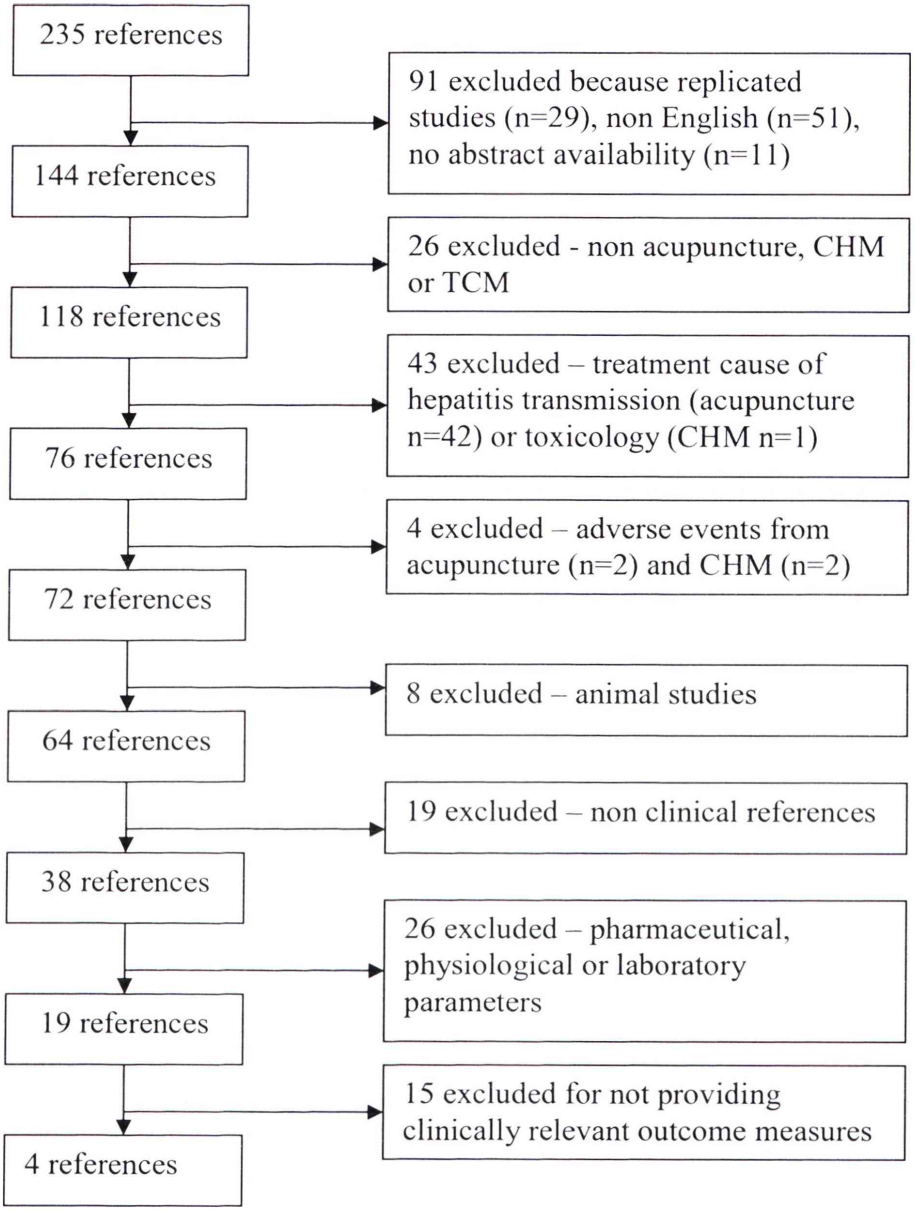


Figure 3.1: A flowchart illustrating the process of reference exclusion.

Author/s name and type of study	Name of study	Sample	Intervention	Outcome measures
(Campbell 1995) Case studies.	Hepatitis without jaundice	5 female patients, mean age 57.8 years with abnormal LFTs for past 2 years.	Individualised acupuncture treatments.	ALT and AST
(Stern 1997) Case studies.	Two Cases of Hepatitis C Treated with Herbs and Supplements	2 HCV case studies.	Various Chinese herbs specific for each patient dependent on pattern differentiation.	ALT and AST
(Batey et al 1998) Randomised, double-blind placebo-controlled clinical trial.	Preliminary report of a randomized, double-blind placebo controlled trial of a Chinese herbal medicine preparation CH-100 in the treatment of chronic hepatitis C	40 HCV patients randomised into two groups (20 each group). Groups matched for age, sex, duration of illness, previous IFN therapy and alcohol intake.	CHM (CH-100) for treatment group (19 different herbs) with placebo (not nominated).	LFT (which includes ALT and AST), creatinine and full blood count (monthly).
(Jakkula et al 2004) Randomised, double-blind placebo-controlled pilot study.	A Randomized Trial of Chinese Herbal Medicines for the Treatment of Symptomatic Hepatitis C	45 HCV participants randomised to two treatment arms and stratified by sex.	10 traditional Chinese medicinal herbs with placebo (not nominated).	QoL ALT PCR genotype, limited PCR viral load
(Mollison et al 2006) Randomised, double-blind placebo-controlled clinical trial.	Randomized double blind placebo-controlled trial of a Chinese herbal therapy (CH100) in chronic hepatitis C	91 HCV participants randomised into two groups (61 treatment group, 30 placebo group).	CHM (CH-100) for treatment group (19 different herbs) with placebo (not nominated).	ALT, viral load QoL

Table 3.1: Summary of five studies in the review.

3.3 Acupuncture

In 1992, Campbell evaluated the effectiveness of acupuncture treatment for non specific liver dysfunction in a small uncontrolled and unblinded pilot study (n=5). All patients had previously had abnormal liver function tests (LFTs) for a minimum of two years prior to commencing acupuncture treatment. LFTs were monitored monthly while abnormal. Based upon examination of the patient's symptom/signs, pulse and tongue

three TCM patterns were identified (*liver qi stagnation*, *spleen deficiency* and *spleen kidney yang deficiency*). "Suggested points" were nominated for each TCM pattern. Treatment points were individualised at each visit. Diagnosis was based upon practitioner interpretation rather than a documented objective protocol which could have allowed study replication. Eight to 15 acupuncture treatments were administered twice weekly. Once LFTs returned to normal (different timeframes for each patient - between 1-12 months), patients reported they were symptom free. LFT results were within the normal range at 12 months and at a three year follow-up (1995). This study was a case series, had no control and was unblinded. In addition it did not control for time tied factors and no valid measure for symptom reporting was used. There was no literature review or reference to textbook TCM pattern differentiation. The author failed to identify whether acupoints were needled unilateral or bilaterally, depth of needle insertion, needle type, needle manipulation or retention time. Thus the results of this case study provide little evidence to support the assertion that acupuncture can reduce ALTs.

3.4 Chinese Herbal Medicine (CHM)

Four papers where found on the use of CHM for HCV. The first paper involved two case studies using individual CHM formulae and nutritional supplements (Stern 1997). CHM was selected according to patient TCM pattern differentiation and nutritional supplements were prescribed consistent with information derived from unsourced biomedical research for HCV. The first case study was a 53 year old male who was diagnosed with multiple TCM patterns (*excess heat in the liver and blood, liver and kidney yin deficiency, qi and blood deficiency*). This patient was treated for four months, observed for a 13 month period, with a blood test taken before commencement of treatment and thereafter every three months. The second case study was a 61 year old woman who again was diagnosed with multiple TCM patterns (*kidney and liver yin deficiency, kidney yang deficiency, excess heat in liver and blood with some blood stasis, qi and blood deficiency*). The patient was treated for three months, with blood tests taken prior to commencement of treatment, nine months later and a final follow-up at eight months. Both patients improved during the course of treatment; outcome measures included subjective signs and symptoms as well as liver enzymes. ALTs and Aspartate Aminotransferase tests

(ASTs) (normal range 0-37U/L) were monitored and results showed a reduction in both liver enzymes. Both patients were reported to have continued a modified CHM and supplement treatment program. Again this study was a case study which used TCM pattern differentiation without literature review or references. A description of the herbal preparations and quantity was presented but the characteristics (part of plant, fresh or dry) and quality was not. There was no valid measure for symptom reporting or re-evaluation and no adverse event or side effects reported. Again this unblinded, uncontrolled case study failed to provide rigorous evidence that the interventions were responsible for the improvement observed over the time period.

The third paper was a preliminary report of a randomised, double-blind placebo-controlled trial using a specific Chinese herbal formula CH-100 (Batey et al 1998). Forty-four patients were randomised to receive either an active herbal or placebo tablet. Four patients failed to complete the six month study (two in the treatment group and two in the control group). Although there was no TCM patterns reported in the paper a preliminary summary prior to the report identified common diagnostic categories (Batey et al 1998). A full blood count, LFT (which includes ALT and AST), serum urea, creatinine and electrolyte determinations were obtained from the subjects every month. HCV RNA was assessed at completion in a proportion of patients (10 treatment group, 3 control group). There was a statistically significant ($p<0.03$) fall in ALT levels over the six months in the treatment group. Four participants in the treatment group normalised ALT levels which were maintained throughout the study period. One participant in this group retained a normal liver function 18 months later. No patient cleared the virus. A single CHM formulation was given for all patients which is not regarded as normal TCM prescribing practise. Neither the characteristics or the quality of the herbal product were identified, nor the content of the placebo tablet formula. Evaluation of whether participants remained blinded to their group allocation was not undertaken.

The second randomised, double-blind placebo-controlled CHM pilot study tested a defined combination of ten Chinese medicinal herbs on HCV patients with fatigue (Jakkula et al 2004). Eligibility and exclusion criteria were reported. Forty five subjects

were stratified by sex and randomised to receive either a Chinese herbal medicine formula or a matched placebo for 12 weeks. The main outcome measures were changes in QoL using the role physical and vitality scale scores and ALT levels. In addition other QoL variables, HCV viral load and adverse effects were monitored. All analyses were conducted using the principle of intention to treat; all participants randomised were included in the final analysis. Of the 45 participants randomised 37 completed week 12 of the study. Thirty-one participants finished both post-treatment follow-up visits (weeks 16 and 20). ALT values did not significantly change and there was no difference between the two groups at any time. Three participants discontinued treatment due to elevated ALT levels (>350 U/L). No significant differences in QoL scores were observed in either group. Of the 31 participants who completed the exit interview, 21 (68%) incorrectly guessed their treatment arm. The authors claimed that the regimen in this study was similar to that used in an Australian trial (Batey et al 1998) which reported improved ALT levels in treated patients. The Batey (1998) trial used 20 herbs and was over a six month period. Criticisms of the study include the small herbal formula dosage (equivalent to only a tenth normal dosage), and failure to identify the herbal characteristics of the product. In addition the content of the placebo tablet formula remained unidentified, 33 participants of the 45 were genotype 1 which has a poor response rate when using combination therapy and not all QoL domains were reported.

The fifth paper concerned a randomised, double-blind placebo-controlled trial using the Chinese herbal formula CH-100, (same formulae used in the Batey (1998) trial) (Mollison et al 2006). Ninety-seven patients were randomised into two groups with two stratifications; prior IFNα use and concomitant HBV infection. One group received active herbal capsules and the other identically packaged placebo capsules over 24 weeks. The ALT levels, QoL using short form 36 (SF-36), HCV genotype and side effects were reported. HCV viral load was measured in a subgroup of 30 (22 CH100 and 8 placebo). There were no TCM patterns identified or reported in the paper. Six patients suffered at lease a two week interruption in supply of CH100/placebo thereby being excluded from the analysis. Of the remaining 91 patients, four participants' (two from each group) data for QoL, side-effects and blood pressure were not available for analysis as they lived

outside the metropolitan area. There was no significant difference between the two groups at baseline.

No significant differences were detected between the two groups during or after therapy on an intention-to-treat analysis. Patients receiving CH100 had an improvement in ALT over baseline at 4 weeks (p=0.05), no significant improvement at week 12 (p=0.26) and significant improvement at week 24 (p=0.04) compared to baseline. By week 48, levels had reverted to no significant difference to baseline (p=0.66). No significant changes were seen at any time point in the placebo group compared with baseline. No patient became HCV-RNA negative during therapy. Compared to baseline there was no difference in HCV viral load within or between groups. Deviation in blood pressure and side-effects due to herbal medications were reported. QoL analyses indicated no significant differences between groups. However, within the treatment group the only improvement over time was in the domain of bodily pain at week 24 (p=0.02). Again neither the characteristics or the quality of the herbal product were identified, nor the content of the placebo tablet formula.

3.5 Summary of study findings

The single acupuncture study was a case study involving five subjects, the other four were herbal studies, one, a small case study (n=2) and the other three being randomised controlled double blind clinical trials. While of limited research value the acupuncture case study did provide useful information about possible acupoints based upon pattern differentiation and the endorsement of the use of objective Western medical outcome measures (ALTs and ASTs). The herbal studies were relevant to the present research in view of the potential value of the study designs including inclusion and exclusion criteria, the combination of a range of common objective biochemical tests (ALT and viral load) and subjective participant questionnaires (QoL), administration and outcome measurers, treatment duration and follow-up period.

In view of the extensive literature search which was undertaken for this project and considering the global prevalence of HCV there is a lack of TCM HCV research

generally and acupuncture specifically. Whilst this suggests a need for the present study there was no real foundation nor assistance in the way of guidelines to build the proposed work. The present research represents the first/initial study that attempts to evaluate acupuncture's efficacy in relation to HCV in a rigorous, randomised, controlled clinical study.

All of the reviewed studies suffered from significant methodological problems, for example; the one acupuncture study failed to adequately describe needling procedures and the case studies did not provide a control intervention meaning that the treatment effect could not be assessed. The RCTs did not attempt to individualise herbal treatment according to TCM pattern differentiation as would occur in clinical practice and there was no practitioner description given in reference to TCM training and practise experience. All studies had small sample size which may have reduced the statistical power and contributed to type II errors. That is, an actual intervention effect may have been erroneously rejected because it was not of sufficient magnitude to be differentiated from either the baseline levels or control group effects with the sample size employed.

3.6 Monitoring and outcome measures

The combination of objective biochemical tests and subjective patient questionnaires used in this research were drawn from the RCTs reported in this literature review. Common liver function tests (which include ALT and AST) and QoL questionnaires are widely reported in established Western medical research and clinical literature. A subjective outcome measure was sought to evaluate/measure the participant's perception of their health and quality of life.

3.6.1 Health related Quality of Life assessment (QoL) measures

To assess quality of life in CHC patients it was necessary to extend the literature search to verify reliable QoL measures and identify healthy population norms for these instruments to allow comparison. Two studies reported QoL population norms in large community samples (Bonkovsky et al 1999; Jenkinson et al 1993) and another clinical

trial evaluated the questionnaire to assess the generic and disease specific health outcomes of HCV (Bayliss et al 1998).

The first study was a postal survey response (n=9,332) drawn from a computerised sample of randomly selected subjects aged 18-64 years from selected family health service authorities in England (Jenkinson et al 1993). The results showed that there were significant differences on all questionnaire variables between gender. The discussion made two recommendations; that it is necessary to use both a generic questionnaire and a questionnaire which identifies disease specific variables and that not all questionnaires are suitable for all age groups.

The second study evaluated QoL of 642 CHC patients at baseline and at the end of a 24-week post-treatment observation period after 24 weeks of IFN treatment. These patients were compared with healthy control subjects (the Well-Norm sample, n=750) which was taken from the US National Survey of Functional Health Status, which provided a representative sample of non institutionalised adults without chronic diseases (Bonkovsky et al 1999). Trial results showed that QoL scores were significantly lower in patients with CHC compared with healthy controls in the presence or absence of cirrhosis and hepatic decompensation. The decrease is at least as large as that of some other chronic diseases. Results showed improvements in QoL scores for those patients who experienced sustained virological and/or biochemical responses.

Another study evaluated a questionnaire to assess the generic and disease specific health outcomes of patients with CHC (Bayliss et al 1998). The cross-sectional sample consisted of 157 patients with CHC who were randomised into two trials of recombinant IFNα-2b. Patients completed the functional health and well-being questionnaire which included all eight scales from the SF-36 and measures of nine other generic and disease specific health concepts baseline and at additional points during the clinical trial. The general population data used in the empirical validation came from the National Survey of Functional Health Status, a representative national sample of non-institutionalised US adults. The ratios of the ALT levels to the high normal value were calculated and

classified into three groups, (<3, 3-5 and >5 times normal). The generic and disease specific scale scores were lower in the presence of physical findings of CHC. Only physical functioning and bodily pain domains were linked to cirrhosis or extreme ALT ratios. Statistical analysis allowed comparisons between age and sex distributions of the CHC sample. The CHC patients scored significantly lower than the well norm, particularly in measures of general health (general health and vitality scales). These findings are consistent with the clinical picture of the disease and comparatively worse in some health domains in representative sample groups of type II diabetics, clinical depression and hypertension patients.

QoL is a valid measure which is widely used in clinical trials for various diseases. The two CHC studies demonstrated that QoL questionnaires detected health changes in people with HCV.

Chapter 4: Methods

All details reported conform to the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher et al 2005). The study is a randomised, controlled, single blind (with blind evaluator) design.

The activity sequencing and Gantt chart for this project is attached as Appendix 2.

4.1 Recruitment

Recruitment commenced in October, 2005 and was concluded on 30th April 2007. The CONSORT flow diagram detailing recruitment, enrolment and randomisation is shown in Figure 4.1.

4.1.1 Recruitment strategies

The aim of the recruitment campaign was to enroll 40 eligible participants for the pilot study. In an endeavor to reach the HCV population information brochures (Appendix 3), advertisements, press releases and a radio advertisement were developed and sent to various organisations, institutions and groups which could reach the HCV community. Limited financial support was available for advertising and trial exposure was predominantly based on a good will and for community awareness. A trial announcement was published in the Hep C Review, the major resource publication of the HCCNSW. In addition information was circulated by the HCV Helpline, healthcare workers, support and drug and alcohol groups, methadone clinics and the media (newspapers and radio). See Appendix 4 for a more comprehensive report on the recruitment campaign and copies of documentation.

4.1.2 Enrolment

In total 130 people expressed an interest in entering the trial. Those who believed they fulfilled entry requirements attended an hour interview. An extensive explanation of the trial was given and participants were allowed to ask questions. Applicant eligibility was assessed and if suitable for inclusion, written consent was either obtained at the time of

interview or the participant could return post the consent form (Appendix 5) to the researcher. Sixteen eligible participants were recruited and block randomised (block of four) into either the treatment or control group (see Figure 4.1). One participant in the treatment group left the trial after eight treatments (one month) due to work commitments.

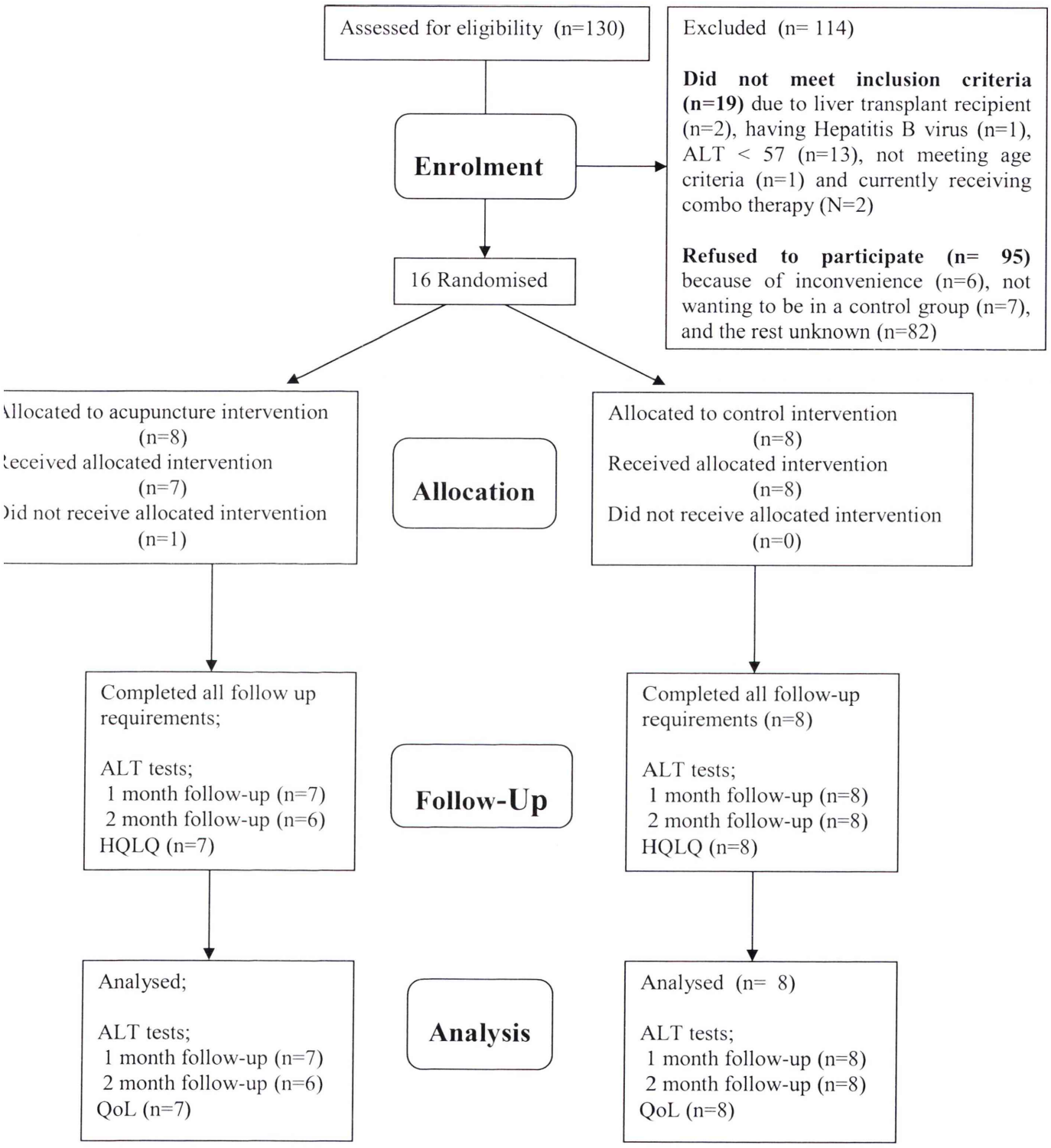


Figure 4.1: CONSORT flow diagram showing recruitment, enrolment and randomisation.

4.1.3 Inclusion criteria

Potential participants were eligible to enter the trial if;

- they had a documented positive serum hepatitis C virus PCR (polymerase chain reaction) viral detection test;
- were aged between 18 to 70 years;
- had an elevated ALT, (≥57 and ≤350 U/L) during the last six months prior to entering the study.

4.1.4 Exclusion factors

Potential participant applicants were excluded if;

- they had recently (within the last three months prior to screening), currently or were about to undertake combination therapy;
- their current alcohol consumption was greater than two standard drinks daily (42 g [1.5 oz], 80 proof; 336 g [12 oz], 5% beer; or 150 g [5 oz], 12%-17% wine);
- they had been a liver transplant recipient;
- were currently participating in another clinical trial (including herbal medicine trials).

4.2 Randomisation

Upon receipt of the consent form an identification number (ID) was allocated to the participant and three pathology referral forms were given to participants at two week intervals prior to commencement of treatment.

Pathology sampling/tests were organised through Douglass Hanly Moir Pathology clinics at locations convenient for each participant. The ID number was placed on the medical history questionnaire, pathology referrals/reports, questionnaires and treatment diary during the study period to preserve confidentiality. Only the principal researcher, (Christine Berle) was aware of the name of the participants and their ID numbers. The participants' identity features such as name, addresses, consent forms and ID code numbers were kept separate from the data.

Once IDs were allocated, the participants went on a wait list until four participants were listed. The four ID numbers were then emailed to an external person who then randomised the block of four IDs to either a treatment group (2 participants) or control group (2 participants). Randomisation was achieved by using a random number generator and at no time did the external person know who was allocated the ID number. All study participants were blinded to their group allocation.

Following allocation a second appointment was made with each participant immediately following their second pathology test and two weeks prior to treatment commencement. This session was to collect the relevant medical history (Appendix 6) needed to determine their TCM pattern and establish a date for commencement of treatment.

4.3 Design

The design of this pilot study was a randomised controlled single blind (and blinded evaluator) clinical trial with repeated measures.

4.4 Interventions

The treatment group (verum) received acupuncture at specifically designated acupoints (ear and body) with needle manipulation. The control group received shallow needle insertion at designated non acupoint sites without needle manipulation. Twenty-four treatments were administered over a 12 week period (two treatments per week).

Verum acupuncture involved perpendicular insertion of single-use, stainless steel, sterile filiform 25mm long (0.20mm gauge with guide tubes) acupuncture needles (Helio Medical Supplies Inc - San Jose). These were inserted at body acupoints. For the auricular acupuncture 13mm long (0.20 gauge) Vinco (10 needles per pack for detox protocol) were used. Needle insertion followed cleansing of the skin using an alcohol swab.

4.4.1 Verum acupuncture

Acupoint location were used as illustrated and described in A Manual of Acupuncture (Deadman et al 2001). Following insertion the needle was manipulated using either a supplementation method (bidirectional needle rotation with small amplitude, 90° - 180° slowly, two rotations per second) or reduction, (bidirectional needle rotation with increased force, 360° - 720° quickly, four rotations per second) as described in Acupuncture and Moxibustion: A guide to Clinical Practice (Auteroche et al 1992). Needling sensation was sought. Body needles remained in situ for 20 minutes with three periods of needle manipulation, following insertion and at 10 and 20 minutes post insertion. Ear points were located according to the text Auriculotherapy Manual, Chinese and Western Systems of Ear Acupuncture (Oleson 2003). Needling of the auricular points were alternated for each ear every treatment and left in situ for 40 minutes (20 minutes longer than the body points). Following insertion no needle manipulation was applied.

The acupoints needled related to the TCM patterns expressed by the participant. The TCM patterns are documented in section 4.5.6 and lists of the acupoint prescriptions for each TCM pattern are listed in Appendix 7.

4.4.2 The control intervention

The sham acupuncture protocol was formulated for the control group using nonacupoints (needling sites considered to produce a minimal physiological response). This involved the shallow insertion of the needle in an off-channel area with no needle manipulation while the needle was insitu. The points were based on a previous study undertaken at the UTS and reported by Zaslawski et al (1997). Needle insertion depth was approximately 0.5cm to ensure that the needle stood upright after insertion. It was intended that the sham intervention provide as "real" a treatment as possible as several participants in the control group had previously received acupuncture.

The sham acupoints included, one ear point and seven bilateral body points (Table 4.1 and Figure 4.2).

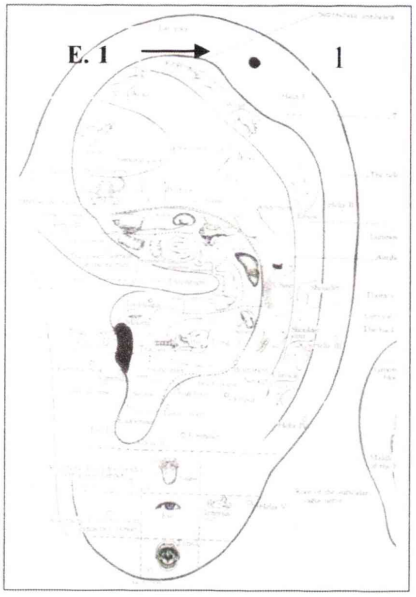
Points	Location description
E. 1	On the tubera helices of the ear mid-way between the points Tonsil#1 and Liver Yang #1
A. 1	On the palmar surface of the arm 4 cun distal to the elbow crease, 2 fen lateral to the tendon flexor carpi radialis
H. 1	1 cun lateral to the anterior midline, and 1 cun superior to the umbilicus
A. 2	On the posterior surface of the forearm 4 cun inferior to the olecranon
F. 1	1 cun lateral to the midline above the second rib
F. 2	1 cun lateral to the midline above the second rib
L. 1	On the lateral aspect of the leg, 4 cun inferior to the knee crease
T. 1	Between the 3rd and 4th metatarsals, 1.5 cun superior to the web between the toes

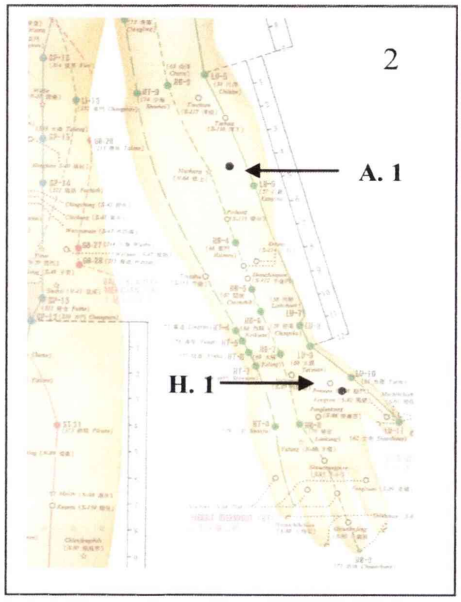
Table 4.1: Location description of nonacupoints.

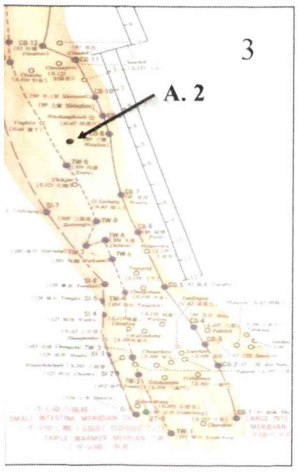
The body points were divided into two consecutive treatments which were repeated over the 12 week period. The ear point was alternated from left to right for each treatment (Table 4.2).

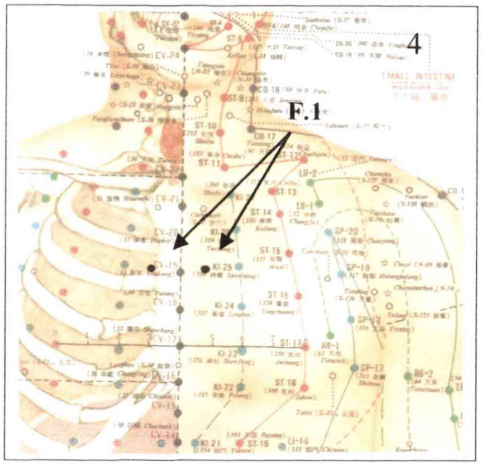
First treatment in week	Second treatment in week
Bilaterally body points; Hand 1 (H.1) Arm 1 (A.1) Foot 2 (F.2) Toe 1 (T.1)	Bilaterally body points; Arm 2 (A.2) Foot 1 (F.1) Leg 1 (L.1)
Left Ear 1 (E.1)	Right Ear 1 (E.1)

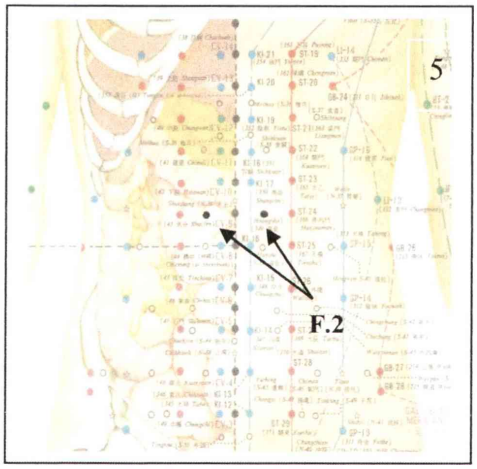
Table 4.2: Sham point selection schedule.

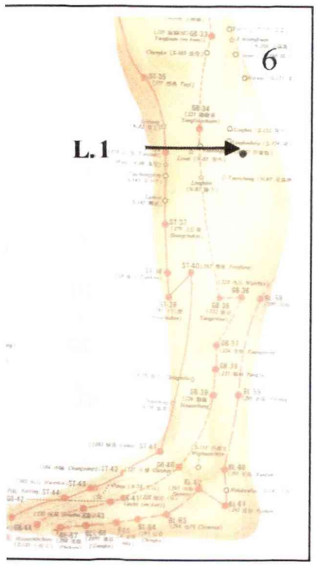












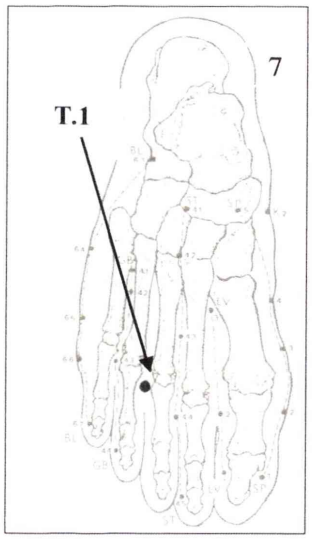


Figure 4.2: Nonacupoint locations.

1: From "An Outline of Chinese Acupuncture", The Academy of Traditional Chinese Medicine, 1975, page 272.

2-6: From China Cultural Corporation, Hong Kong, 1985 wall charts.

7: From Point Location and Point Dynamics Manual, Rogers and Rogers, 1989 page 220.

4.5 Outcome measures

To evaluate the outcomes of the acupuncture intervention three outcome measures were recorded to detect and monitor change. These were ALT levels, viral load and the QoL Questionnaire. In addition an acupuncture needling sensation questionnaire and acupuncture treatment credibility questionnaire were administered. Outcome measure collection points are summarised in Figure 4.3 and Table 4.3.

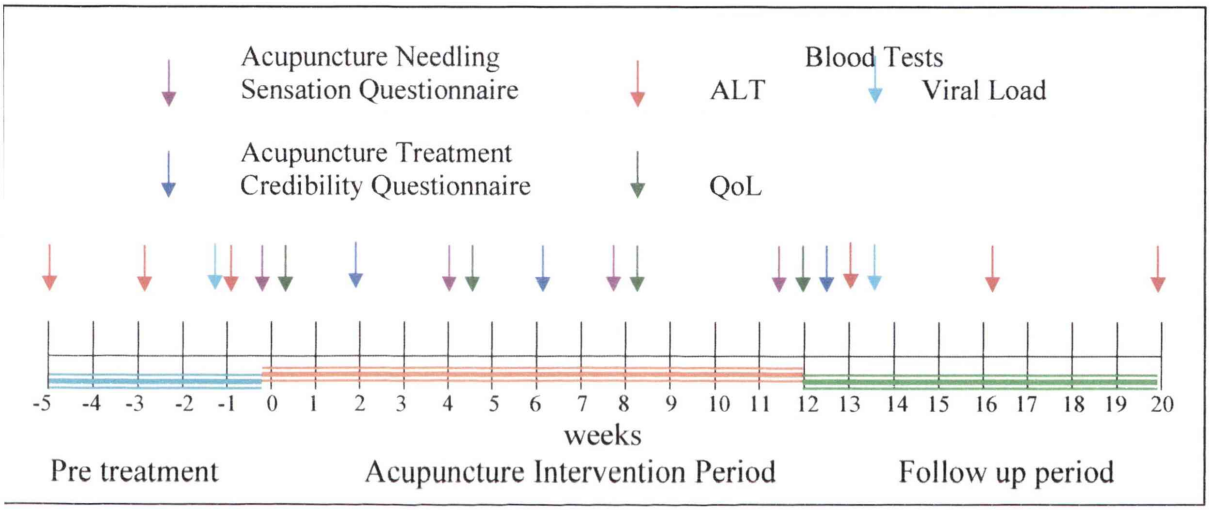


Figure 4.3: Outcome measure collection points.

4.5.1 Primary - ALT levels

The primary quantitative measure in the study was ALT levels. For each participant six serum ALT pathology tests were collected and analysed by an independent blinded pathology laboratory (Douglass Hanly Moir Pathology). Participants attended their local Douglass, Hanly Moir pathology collection centre and a blood serum sample was obtained. The laboratory was blind to the allocation status for each participant. Results were posted to the researcher. Three blood samples were obtained (at two week intervals) during the five week period prior to commencement of treatment, one on completion of treatment and a further two at the one month and two months period after the last treatment.

4.5.2 Secondary outcome measure - HCV PCR quantitative (viral load) test

One HCV PCR quantitative (viral load) pathology test was undertaken pre and post treatment intervention. Blood collection was at the same time as the third and fourth ALT collection. Analysis was undertaken and reported to Douglass Hanley Moir Pathology by Sullivan and Nicolaides Pathology, a member of the Sonic Healthcare, Brisbane. Douglass Hanley Moir Pathology posted the results to the researcher. At no time was the laboratory aware of the participant's allocation status.

4.5.3 Secondary outcome measure - Quality of Life Questionnaire (QoL)

The QoL measure used for the trial was the Hepatitis Quality of Life version 2 which is a self assessment questionnaire developed and licensed by QualityMetric Incorporated, USA. It is a 51 item questionnaire which includes all items from the short form 36 version 2 (SF-36v2) questionnaire plus 15 items pertinent to the assessment of the health related quality of life of hepatitis patients (see Appendix 8). The SF-36 is a short questionnaire with 36 items which measure eight multi-item variables; physical functioning (10 items), social functioning (two items), role limitations due to physical problems (four items), role limitations due to emotional problems (three items), mental health (five items), energy and vitality (four items), pain (two items), and general perception of health (five items). These domains are scored using a scale of 0 (worst possible score) to 100 (best possible score) eg functioning scales are scored so that a high score indicates better functioning and the pain scale is scored so that a high score indicates freedom from pain. The domains are:

Physical functioning: Relates to general activities such as walking, climbing stairs carrying groceries. This scale is scored so that a high score indicates better physical functioning.

Role – physical: Relates to work related activities. This scale is scored so that a high score indicates better Role-Physical functioning.

Bodily pain: Relates to body pain during the last four weeks and how much that interfered with normal work including both work outside the home and housework. This scale is scored positively so that a high score indicates lack of bodily pain.

General health: Relates how the client perceives their health in comparison with other people and their future expectations. This scale is scored so that a high score indicates better general health perceptions.

Vitality: Relates to feeling; full of pep, amount of energy, feeling worn out and tiredness. This scale is scored so that a high score indicates more vitality.

Social functioning: Relates to the past four weeks, to the extent that physical health or emotional problems have interfered with clients normal social activities with family, friends, neighbours or groups. This scale is scored so that a high score indicates better social functioning.

Role – emotional: Relates to whether depression or anxiety has had an effect on work or other regular daily activities. This scale is scored so that a high score indicates better Role-Emotional functioning.

Mental health: Relates to nervousness, feeling down in the dumps, feeling calm and peaceful, downhearted or happiness. This scale is scored so that a high score indicates better mental health.

There is a further unscaled single item on changes to respondents health over the past year. Proponents of QoL questionnaires argue that quality of life is the most important issue to sick people.

The HQLQv2 uses the core set of SF-36 questions supplemented by additional questions from the larger Medical Outcomes Study Social Functioning Scale (MOS) and a series of disease specific questions. Four SF-36 scales were improved by adding additional

questions to; role-physical and role-emotional domains regarding whether poor health had kept the respondent from working or performing regular activities, two questions were added to social function and a question on fatigue added to vitality subscale. Three other MOS scales were added to describe other effects of CHC including sleep somnolence, positive well-being and health distress. Another three questions were added concerning the limitations of everyday activities due to hepatitis and four questions were included concerning the impact of hepatitis on health distress (Bayliss et al 1998; Carithers et al 1996).

Administration of the QoL questionnaire is recommended every four weeks as some items inquire about events which have occurred within the past four weeks. The questionnaire was administered at weeks 1, 4, 8, 12 and 20.

This instrument has been used by several groups to evaluate quality of life in patients with HCV (Bayliss et al 1998; Jakkula et al 2004; Neary et al 1999; Ware et al 1999).

4.5.4 Acupuncture Treatment Credibility Questionnaire

This questionnaire (Appendix 9) listed four questions and a seven point rating scale with end point descriptors of each question. The four questions were:

1. How confident are you that this treatment can alleviate your complaint?
2. How logical does this treatment seem to you?
3. How confident would you be in recommending this treatment to a friend who suffered the same complaint?
4. How successful do you think this treatment would be in alleviating other complaints?

The questionnaire was administered at weeks 2, 6 and 12 to evaluate the adequacy of the control intervention. The final questionnaire (week 12) also included a question asking which group the participant thought they had been allocated to and the reasons for their decision. This question was to determine whether participants may have detected their group allocation.

4.5.5 Acupuncture Needling Sensation Questionnaire

This questionnaire consisted of two sections (see Appendix 10). The first section consisted of a list of 20 possible needling sensations. Respondents were required to indicate their answer on a four point likert scale ("not at all"; "mild"; "moderate" and "severe"). Figure 4.4 shows an example of the format of the first three sensations.

- **Hurting**

Not at all Mild Moderate Severe

- **Penetrating**

Not at all Mild Moderate Severe

- **Sharp**

Not at all Mild Moderate Severe

Figure 4.4: Example of the first three sensations of the acupuncture needling sensation questionnaire.

The second section of the questionnaire required a "yes" or "no" answer to 10 various feelings during or immediately after the treatment intervention. This questionnaire was administered at weeks 1, 4, 8 and twelve.

	Week												
Questionnaire	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**20**
QoL	X				X				X				X	X
Acupuncture Needling Sensation Questionnaire	X				X				X				X	
Acupuncture Treatment Credibility Questionnaire			X				X						X	

Table 4.3: Questionnaire administration intervals.

4.5.6 Manualisation of HCV disease using TCM patterns

HCV/TCM Pattern Questionnaire

An extensive HCV/TCM history and examination of the trial participant was undertaken by the researcher approximately two weeks prior to the commencement of the treatment intervention and at the conclusion of treatment (see Appendix 6).

Most modern TCM and acupuncture textbooks detail several different TCM patterns associated with a disease. An extensive literature review including journals, textbooks, conference abstracts was undertaken to identify the various TCM patterns and associated acupoint treatment for HCV. The search was extended to include inflammation of the liver (including hepatitis A, B, and C) because the search revealed limited studies or publications specifically for HCV.

Thirty-eight TCM hepatitis patterns were identified from six English language sources (Campbell 1995; Cohen 2001; Flaws et al 2001; Hepatitis C Caring Ambassadors Program 2002; Kaptchuk 1983; Wang et al). Since analysis of the 38 TCM patterns revealed some similarity in both name and symptom cluster the 38 TCM patterns were collapsed to 17 patterns. The second edition of "A Practical Dictionary of Chinese Medicine"(Wiseman et al 1998) was used to reference and standardise the TCM pattern terminology (see Appendix 11).

Manualisation

Manualisation is a systematic procedure where an expert group develop a treatment manual through consensus, identifying TCM diagnostic patterns and appropriate acupoint prescriptions. Manualisation allows individualisation of treatment whilst providing a replicable and standardised protocol. The process of manualisation and its use in acupuncture clinical trials has been described by many authors (Ahn et al 2005; Macpherson et al 2006b; Schnyer et al 2002; Schnyer et al 2005; Schnyer et al 2006; White et al 2001).

An example of the symptom cluster for one TCM pattern associated with HCV, *Liver Yin Vacuity* is listed below:

- slight rib/side flank pain
- dizziness
- irritability/quick temper
- fatigue
- warm palms and soles of feet
- low fever
- dryness of eyes, throat, mouth and brittle nails
- blurry vision
- muscle spasms
- reddish cheeks and eyes
- numb limbs

Similarly, signs and symptoms were identified and collated for the remaining 17 TCM patterns as were the acupoint prescriptions for each TCM pattern. Several sources were reviewed for acupuncture protocols for the TCM patterns (Campbell 1995; Flaws et al 2001; Maciocia; Maclean et al 2000). Two consecutive treatments for each TCM pattern were developed. Because multiple TCM patterns were identified for an individual, the primary treatment was administered in week one, the secondary treatment in week two and the tertiary treatment in week three. This routine was repeated three times over the 12 week treatment period.

Finally, an element of treatment flexibility was included which involved an additional list of acupoints for common symptoms shown in Table 4.4 which could be needled on any given treatment day based on the participant's presentation.

Extra Symptoms	Points
Abdominal distention/pain	CV12
Abdominal distention/pain waist	ST25
Vomiting, nausea belching	PC6, CV13
Lack of appetite	ST21
Body weakness/fatigue	ST36
Jaundice	GV9
Bitter taste in mouth	GB43
Dizziness	GB20
Blurred/dim vision	GB37
Constipation	TE6
Concomitant phlegm	ST40
Accumulation lumps below rib-side	LR13, 14
Diarrhea	ST25
Low back, knee soreness and limpness	SP4, KI7
Aversion greasy/fatty food or lack of appetite due to food stagnation	ST24
Insomnia or fright	PC7
Vexation/agitation	GV24
Anger	LR2
Lingering damp heat	GB40

Table 4.4: Additional acupuncture symptom points.

A questionnaire which incorporated all signs and symptoms for each of the 17 TCM patterns was developed. In addition to obtaining general medical information, participants were asked whether they currently experienced all or any of the symptoms associated with the 17 TCM patterns.

Table 4.5 shows an example of a trial participant's response to two patterns of the TCM Pattern Questionnaire.

I.	**Liver Yin Vacuity**	**6/11**
1.	slight rib/side pain	☐
2.	dizziness	☐
3.	irritability/quick temper	■
4.	fatigue	■
5.	warm palms and soles of feet	☐
6.	low fever	■
7.	dryness of eyes, nails, throat and mouth	■
8.	blurry vision	☐
9.	muscle spasms	■
10.	reddish cheeks and eyes	■
11.	numb limbs	☐
II.	**Binding Depression of Liver Qi**	**3/9**
1.	rib-side distension (swelling with pressure) and pain	☐
2.	a tendency to sigh	☐
3.	irritability/anxiety	■
4.	fatigue	■
5.	no appetite	☐
6.	nausea	☐
7.	burping and belching	■
8.	flatulence/bloating	☐
9.	premenstrual syndrome and/or menstrual irregularities in females	☐

Table 4.5: Example of symptom/signs associated with two TCM patterns of *liver yin vacuity* and *binding depression of liver qi*. Coloured block indicates symptom was present.

Once the symptom/signs of the TCM patterns were tabulated the total symptom frequency score for each TCM pattern was then transformed to a percentage using the following formula.

$$\frac{\text{Number of symptom/signs expressed by individual}}{\text{Total number of signs and symptoms associated with the specific TCM pattern}} \times 100 = \%$$

For example the *liver yin vacuity* pattern (Table 4.5) shows that 6 of the 11 symptom/signs were expressed (6/11) which transforms to 55%. For the *binding depression of liver qi* pattern symptom expression (3/9) transforms to 33%.

The following Table 4.6 shows an example for the same participant, listing both untransformed and the transformed percentage scores for all TCM patterns expressed by this individual. The first 13 TCM patterns represented organ specific patterns whereas the last four TCM patterns represent general dysfunction.

TCM Pattern	**Ratio of expressed symptom/signs to total number of symptom/signs**	**Transformed %**
Liver yin vacuity	6/11	54.5
Binding depression of liver qi	3/9	33.3
Liver qi stagnation and blood stasis	2/8	25.0
Liver gallbladder damp-heat	5/13	38.5
Liver qi invading spleen	3/15	20.0
Liver-kidney yin vacuity	9/14	64.3
Spleen qi vacuity	2/9	22.2
Spleen kidney yang vacuity	1/12	8.3
Damp heat brewing the spleen	4/14	28.6
Damp heat transforming into fire and brewing toxins	4/14	28.6
Phlegm nodulation	2/10	20.0
Blood stasis obstructing the network vessels	2/8	25.0
Cold damp encumber spleen internally	2/15	13.3
Qi vacuity	1/3	33.3
Yin vacuity	4/6	66.7
Blood vacuity	0/3	0.0
Blood stagnation	0/2	0.0

Table 4.6: HCV TCM scores for a trial participant.

The expression of transformed percentages can be clearly seen when using a histogram (Figure 4.5). Disregarding the general TCM patterns the primary TCM pattern was *liver-kidney yin vacuity* (64%),while the secondary pattern was *liver yin vacuity* (55%) and the tertiary pattern was *liver gallbladder damp-heat* (39%).

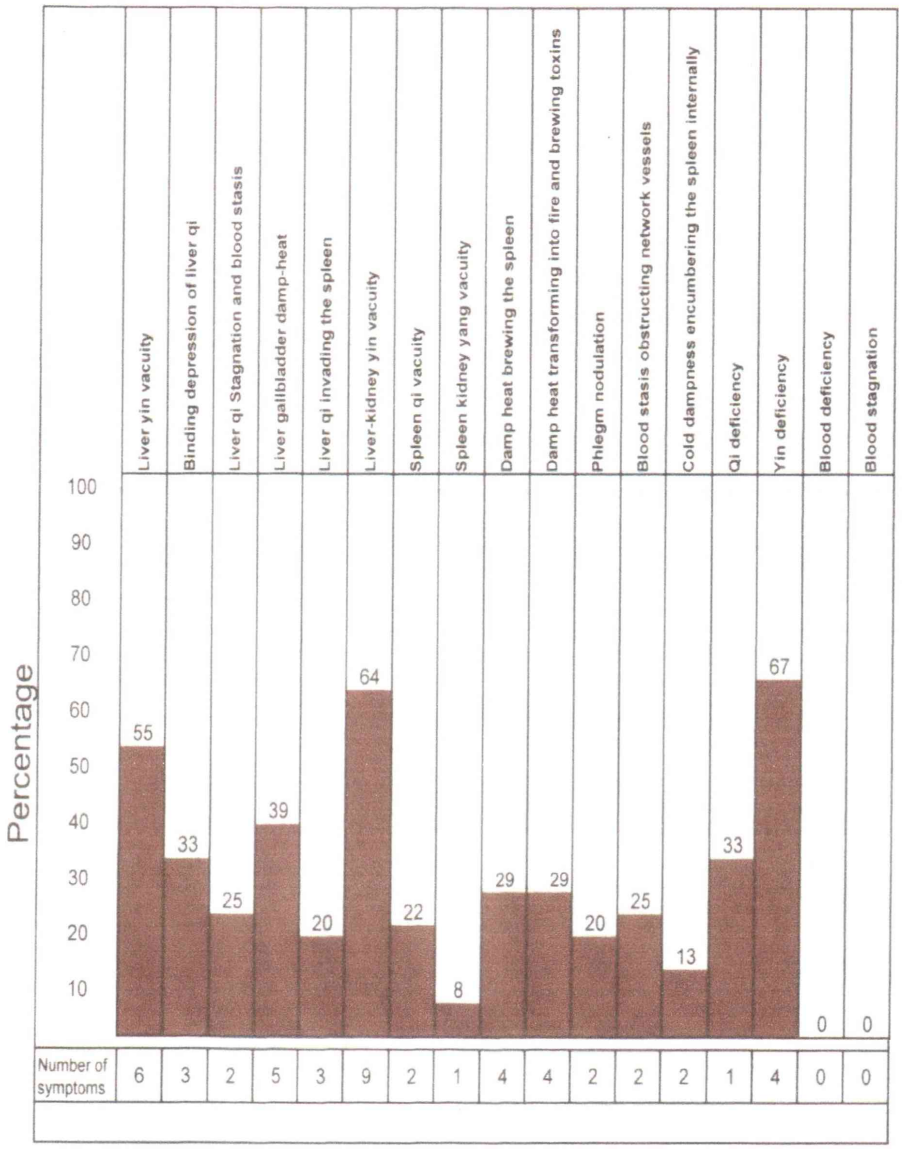


Figure 4.5: Example of a HCV TCM pattern percentage graph for an individual.

Each primary, secondary and tertiary TCM pattern was treated successively over three weeks and then repeated three times. Therefore each participant in the verum treatment group received six different treatments four times (first and second treatment for each of three TCM patterns were repeated three times totalling 24 acupuncture treatments). This process is representative of the procedure which occurs in day to day acupuncture practice closely replicating the diagnostic and treatment process which a TCM practitioner undertakes with each patient.

4.5.7 TCM Pattern reassessment

By systematically identifying symptom/signs and TCM pattern pre and post treatment intervention a unique TCM outcome measure was developed. This measure allows statistical analysis of any change in expression of the TCM patterns for an individual over a course of treatment.

The HCV TCM pattern questionnaire was administered prior to the first treatment and after the 24th (final) treatment (week 12). Each participant's symptom/signs were evaluated prior to the first treatment and then re-evaluated at week 12 against the 17 HCV/TCM patterns. Figure 4.6 shows pre and post treatment TCM pattern changes for the previous example (Figure 4.5). Patterns 16 and 17 are not shown as there was no expression of these two patterns for this subject.

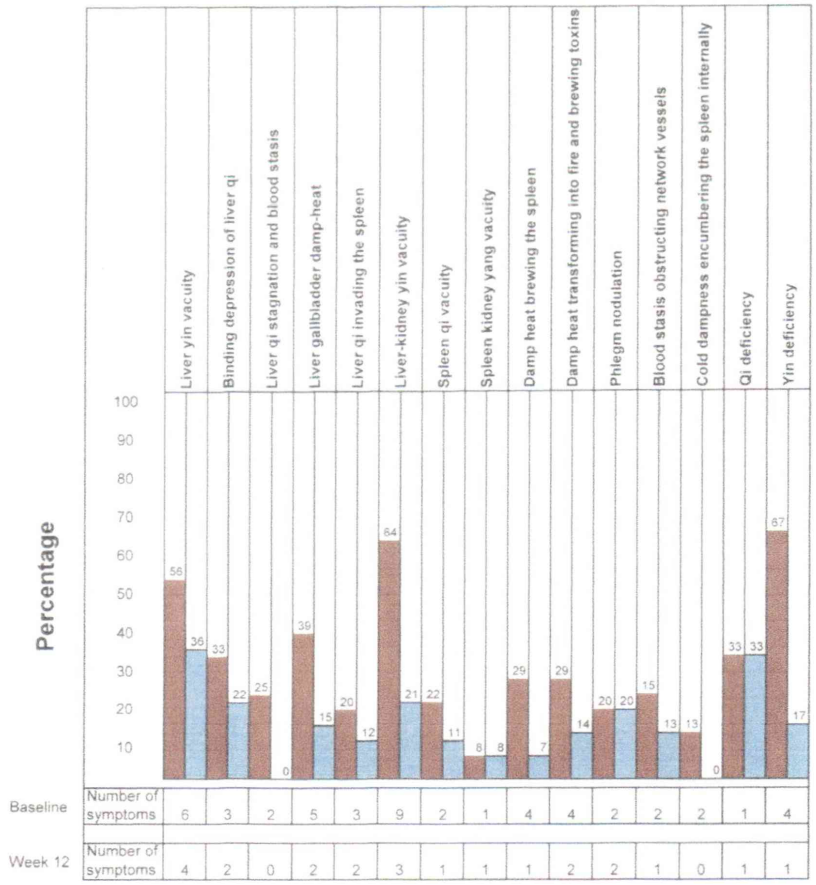


Figure 4.6: HCV TCM pattern expression for an individual, baseline (week 0) and at completion of the treatment (week 12).

4.6 Ethics approval

Prior to commencing the study, ethics approval was obtained from the Human Research Ethics Committee (HREC), University of Technology, Sydney (UTS) in March 2005. All documents related to the study including advertising, information sheets to potential participants, consent forms and questionnaires were approved for use (UTS HREC REF NO 2005-037). Amendments and annual reports were lodged as required.

4.7 Statistical analysis

Data analysis was conducted after all the participants completed the study. Data were tabulated and transferred into an appropriate statistical package (Minitab Release 14 and Statistical Package for Social Sciences (SPSS version 15.0) and an online statistical package (VassarStat http://faculty.vassar.edu/lowry/VassarStats.html.)

Statistical tests involved;

- ANOVA, General Linear Model, Univariate (used for ALT)
- ANOVA, one way (major TCM patterns)
- t-test, independent samples (age, QoL)
- 2 sample t-test (viral load, major TCM patterns)
- Fisher Exact Probability (Acupuncture Treatment Credibility questionnaire, effective blinding of participants, participants who previously had had acupuncture, alcohol consumption, previously had IFN and gender)
- Mann-Whitney U test (Acupuncture Treatment Credibility Questionnaire between groups, Acupuncture Needling Sensation Questionnaire)
- Friedman Test (Acupuncture Treatment Credibility Questionnaire for difference across the three surveys for each question for each group, Acupuncture Needling Sensation Questionnaire)

Chapter 5: Results

5.1 Participants

Of the 130 subjects who participated in the screening process, 16 met the inclusion criteria. All applicants were required to provide documented evidence of a positive serum HCV PCR viral detection test and an elevated ALT level $\geq$ 57 U/L. Reasons for exclusion were: ALT level < 57 (n=13), a liver transplant recipient (n=2), concurrently hepatitis B (n=1), outside age eligibility (n=1), currently or about to receive combination therapy (n=2), unwilling to participate in a trial with a control group (n=7), geographically inconvenient (n=1), time and frequency of treatments inconvenient (n=5) and did not want to be involved for unknown reasons (n=82). Altogether, 16 participants were randomised, with eight allocated to the treatment group where each participant would receive treatment for their three major TCM patterns expressed and the eight subjects in the control group would receive sham acupuncture. One participant withdrew from the clinical trial after the eighth treatment due to work commitments. A total of seven participants in the treatment group and eight in the control group completed the 24 treatment sessions. Following the trial all (n=15) participants completed the two month follow-up QoL. Blood pathology tests were completed by all subjects on completion of treatment (n=15), one month follow-up (n=15) and two month follow-up one participant failed to comply (n=14, treatment group n = 6, control group n = 8).

5.2 Baseline characteristics

Participants' gender, age, whether they had received combination therapy prior to the study and alcohol intake is listed in Table 5.1. There were eight men (56.3%) and seven women (43.7%) with gender representation in both groups similar (p=0.31).

Participants randomised into the treatment and control groups were similar in age (p=0.24). The mean age of the treatment group was 51.3 years (sd $\pm$ 9.7), while for the control group it was 45.6 years (sd $\pm$ 8.3).

Group	Gender		Age		Combination therapy		Alcohol intake	
	Men	Women	Years (sd)	Range	Yes	No	Nil	Yes
Treatment group (n=7)	5	2	51 (9.7)	35-63	5	2	2	5
Control group (n=8)	3	5	46 (8.3)	32-55	2	6	5	3
Total	**8**	**7**			**7**	**8**	**7**	**8**

Table 5.1: Participants' gender, age, whether they had previously received combination therapy and alcohol intake.

Seven participants (47%) had previously unsuccessfully received combination therapy, five were randomised to the treatment group and two to the control group.

Prior to March, 2005 liver biopsy was a mandatory requirement for combination therapy. Five participants (treatment group n=3, control group n=2) identified that they had previously undertaken a liver biopsy and supplied pathology reports. In the treatment group one participant had been clinically diagnosed with cirrhosis; two participants had a fibrosis Scheuer score (a score representing liver damage with three main parameters scored 0-4, where four is the worst scenario - the overall biopsy scored out of 12) of 3 and 7. In the control group two participants similarly reported Scheuer scores of 3 and 5.

Because alcohol intake affects liver disease subjects were questioned about their alcohol intake. The two groups were similar (p=0.31) with seven participants reporting that they were non alcoholic drinkers and eight who reported the following comments at baseline; "only one occasionally", one per day", "two per day", "few at social functions", "don't drink often", "three to four light beers at a function", "two drinks a few times per week", and "four light beers on Saturday".

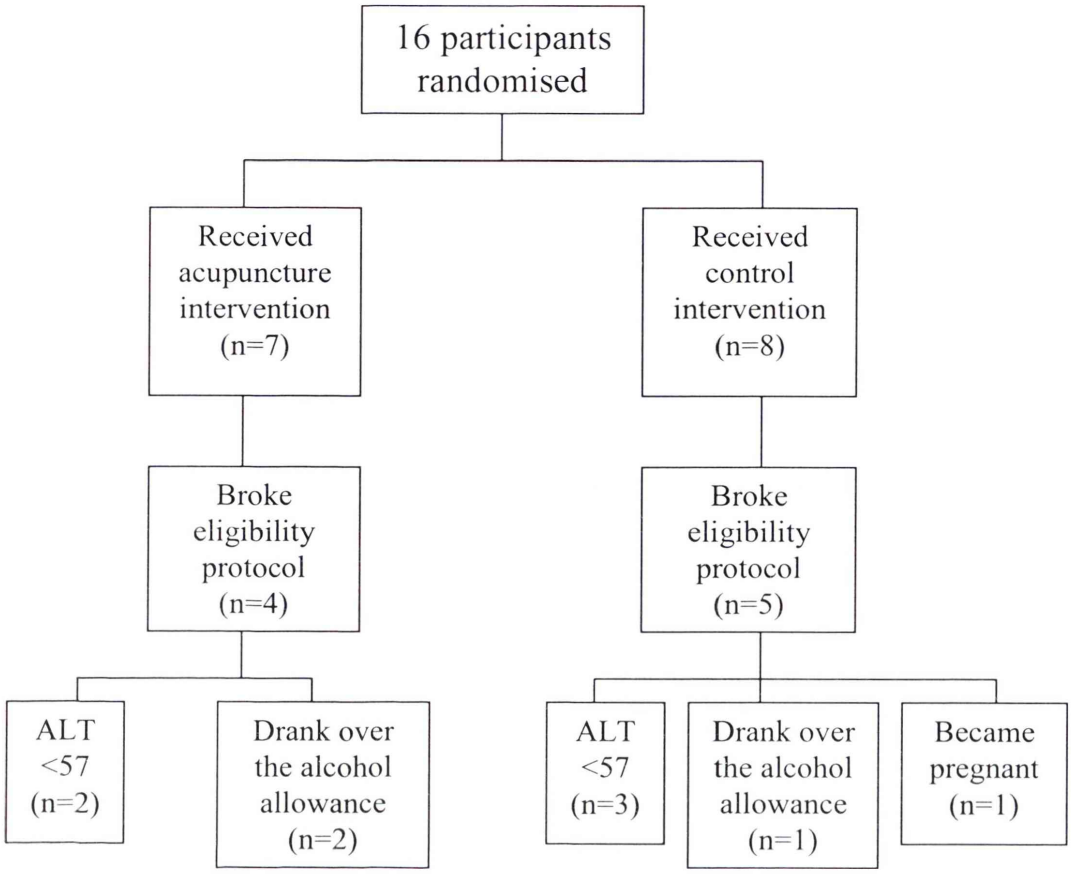


Figure 5.1: Flowchart of participants who did not continue to meet eligibility criteria during the trial.

5.3 Outcome measures

5.3.1 ALT levels

The results for the mean ALT levels for both groups are shown in Table 5.2 and Figure 5.2. At baseline the treatment group reported a higher ALT U/L level (122 U/L) than the control group (99 U/L). There was an increase in mean ALT levels (179 U/L) for the treatment group at week 12 from mean ALT baseline levels (122 U/L) while the control group remained stable. At week 16 (1 month follow up) the mean ALT levels for the treatment group had dropped below baseline to 113 U/L and then increased to a mean of 121 U/L at week 20.

Group	Baseline	Week 12 (completion of treatment)	Week 16 (1 month follow up)	Week 20 (2 months follow up)
Treatment group (n= 7)	122 (sd ± 110.3)	179 (sd ± 186.1)	113 (sd ± 96.1)	121 (sd ± 77.0)
Control group (n= 8)	99 (sd ± 51.9)	100 (sd ± 49.8)	112 (sd ± 63.7)	130 (sd ± 81.8)

Table 5.2: Mean ALT (U/L) levels for the treatment and control groups at week 0 (baseline), week 12 (completion of treatment) and at weeks 16 and 20 (follow up periods).

Interestingly there was a small, but consistent trend for the mean for the control group to increase over time, increasing from 99 U/L at baseline to 130 U/L at week 20. No significant difference was found between the two groups at any measurement point (week 0, 12, 16, 20) ($p = 0.190$).

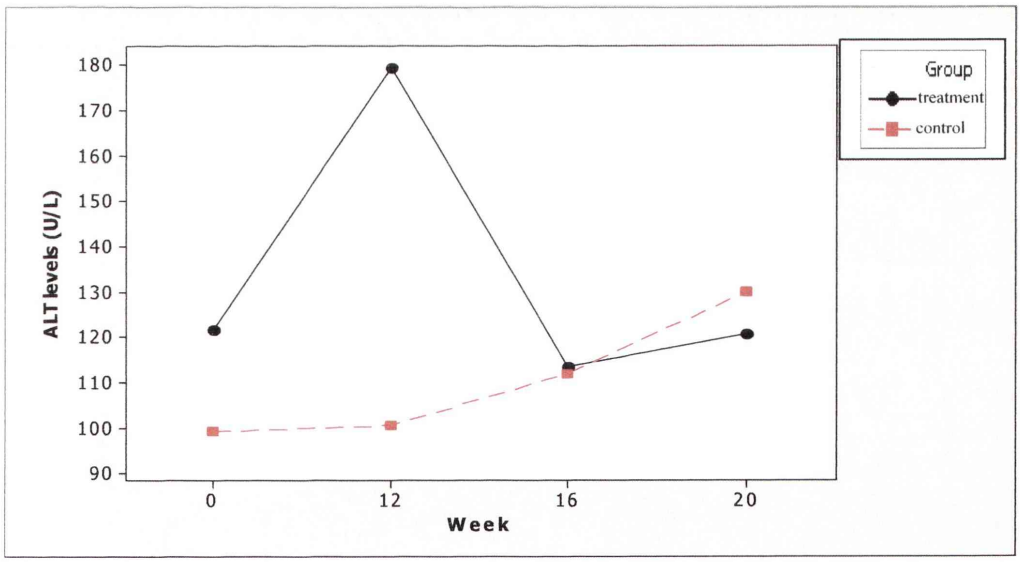


Figure 5.2: Mean ALT levels for treatment and control groups at week 0 (baseline), week 12 (completion of treatment) and at weeks 16 and 20 (follow up periods).

The individual participant ALT U/L results are shown in Figure 5.3 (treatment group) and Figure 5.4 (control group) with the exception of participant 5 (at week 20) who was hospitalised at that time point.

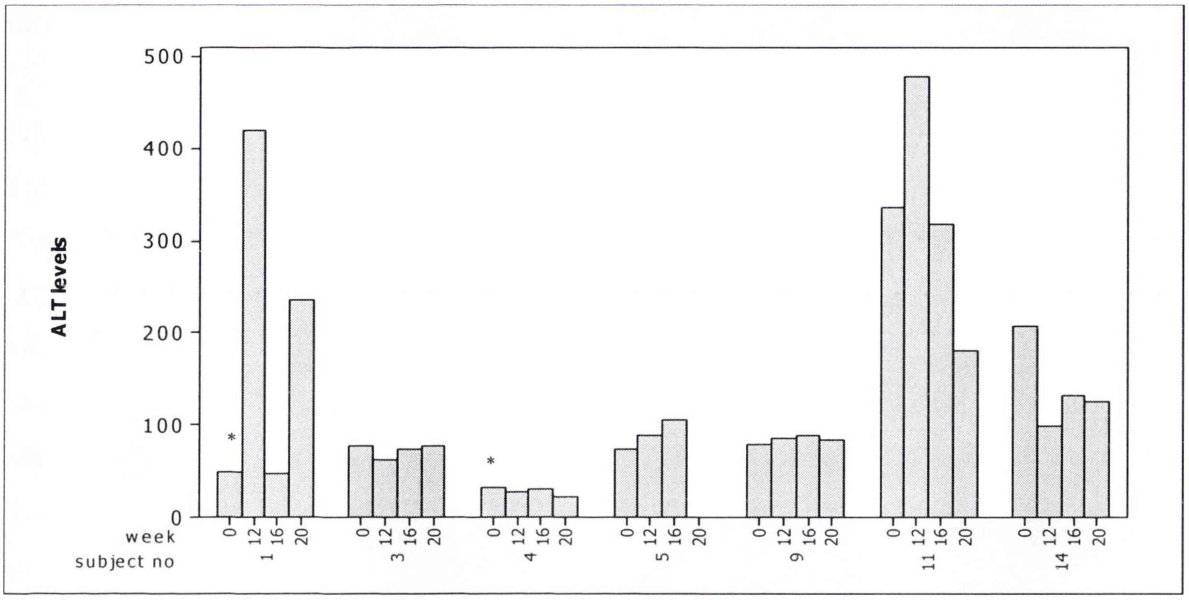


Figure 5.3: ALT levels for each subject in the treatment group at week 0 (baseline), week 12 (completion of treatment) and at weeks 16 and 20 (follow up periods)
* indicates below eligibility ALT requirement at baseline.

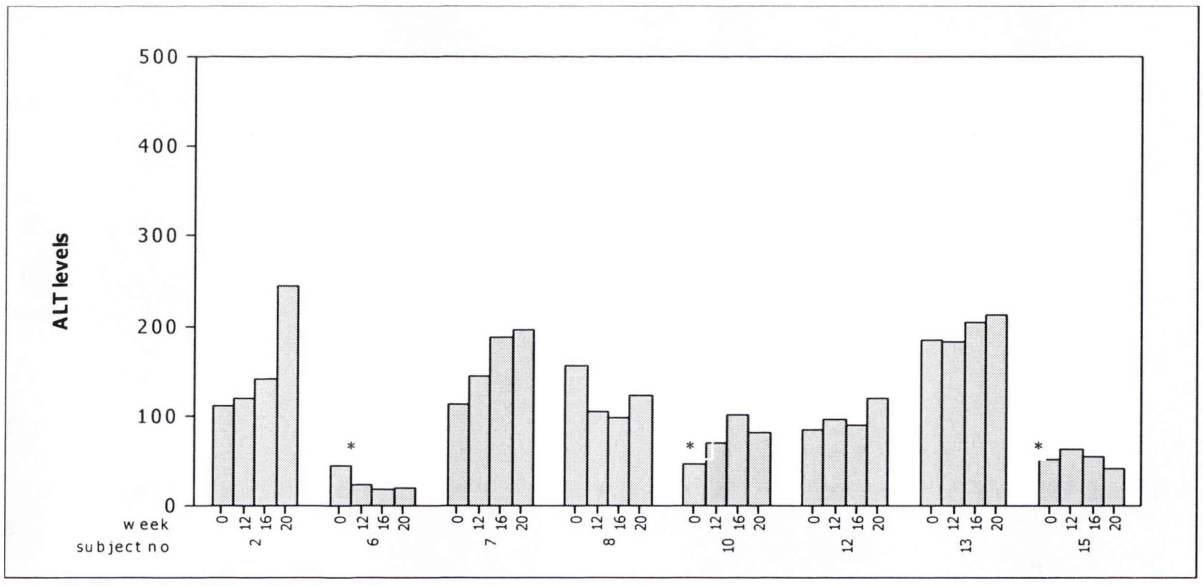


Figure 5.4: ALT levels for each subject in the control group at week 0 (baseline), week 12 (completion of treatment) and at weeks 16 and 20 (follow up periods)
* indicates below eligibility ALT requirement.

Although all trial participants met the eligibility criteria of an elevated ALT ≥57 within the six months period prior to the trial, it should be noted that five participant ALT baseline scores were below this criteria (two in treatment group, participants 1 and 4 and three in the control group, participants 6, 10 and 12).

5.3.2 HCV PCR quantitative (viral load) pathology tests

Table 5.3 shows the mean viral load at week 0 (baseline) and at week 12 for both groups. Note that due to a change in the pathology testing protocol at the pathology laboratory (Douglass Hanly Moir Pathology) viral loads were not all obtained using the same pathology analysis system. The first protocol, the COBAS amplicor HCV monitor assay, reported higher results as an unknown level above >800,000 IU/mL (this involved samples from five participants). The newer test, the COBAS Ampliprep/COBAS TaqMan HCV assay, gave a specific measurement above 800,000 IU/mL. Only those samples for which a specific score was available were analysed.

Although there was a small increase in mean viral load for the treatment group (n=5; $3.5x10^4$) compared with a larger mean increase for the control group (n=6; $3.9x10^4$), this difference between the two groups was not statistically significant (p=0.20).

Group	Week 0 (baseline) mean viral load (IU/mL)	Week 12 (completion of treatment) mean viral load (IU/mL)
Treatment (n=7)	$3.9 x10^6$	$3.9 x10^6$
Control (n=8)	$1.1 x10^6$	$4.9 x10^6$

Table 5.3: Mean HCV PCR (viral load) IU/mL levels for the treatment and control group.

Figure 5.5 (treatment group n=5) and Figure 5.6 (control group n=6) shows the individual viral load for each participant.

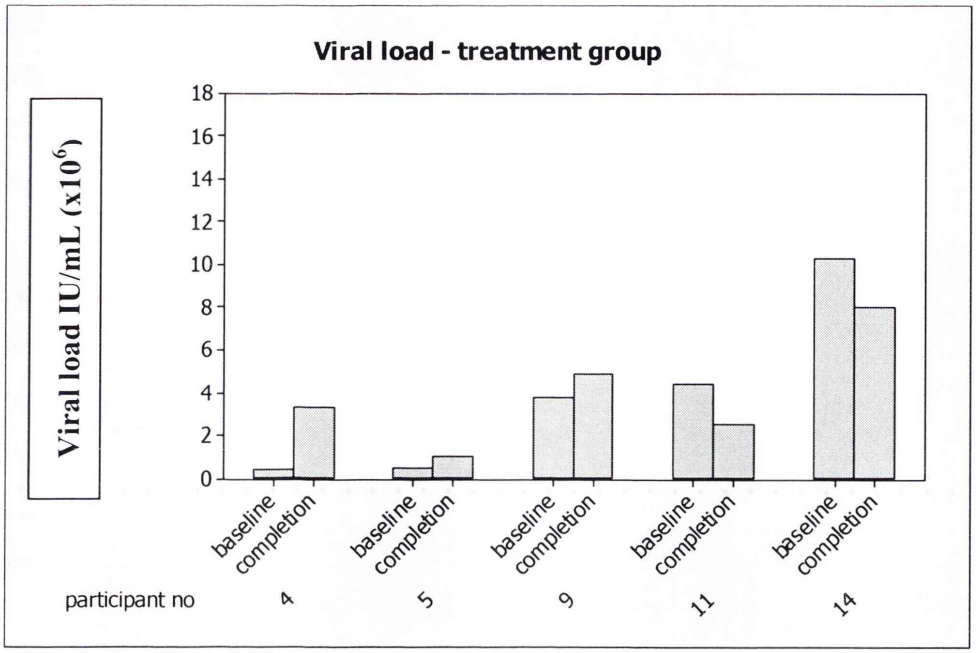


Figure 5.5: Individual participant viral load results at baseline and on completion for the treatment group.

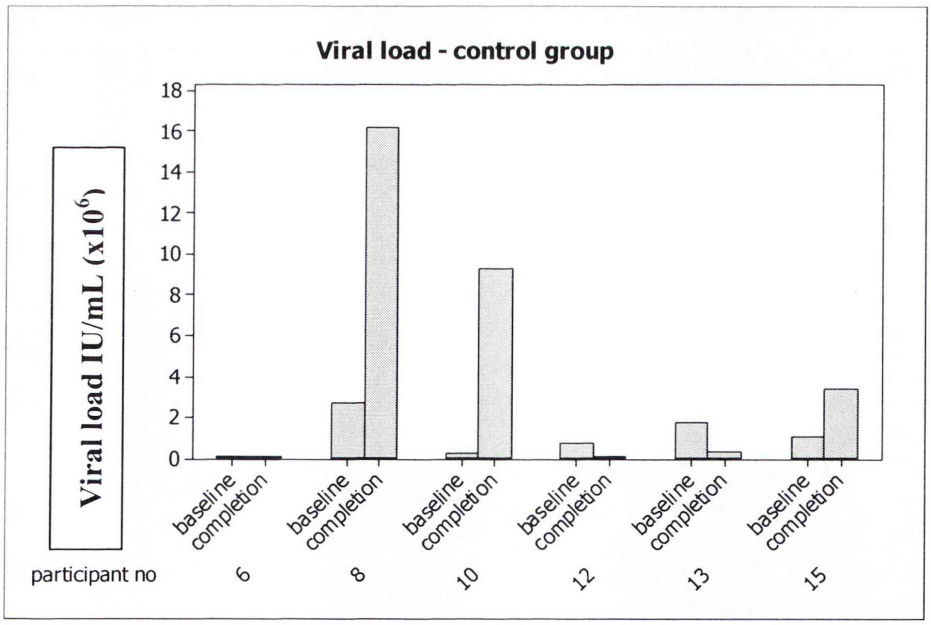


Figure 5.6: Individual participant viral load results at baseline and on completion for the control group.

5.3.3 Quality of Life (QoL) questionnaire

The mean scores of the QoL twelve domains for both groups at weeks 0 (baseline), 4, 8, 12 and 20 are presented in Figure 5.7. A higher score indicates better function for the ten function domains and a high bodily pain domain score indicates less pain.

At baseline the control group showed higher scores in all domains with the exception of health distress (generic) and hepatitis specific health distress. A significant difference between the mean scores for the two groups was found for physical functioning (treatment group 60.0, control group 88.8; p=0.049), role-physical (treatment group 51.8, control group 82.0; p=0.035), general health (treatment group 42.7, control group 66.8; p=0.007) and role-emotional (treatment group 58.3, control group 86.5; p=0.004).

On completion of treatment (week 12) there was an improvement in mean scores for both groups in the domains however there was no significant difference between the groups for: role-physical (p=0.68), bodily pain (p=0.39), general health (p=0.75), vitality (p=0.84), social functioning (p=0.64), role-emotional (p=0.43), mental health (p=0.39), health distress (generic) (p=0.29), hepatitis specific health distress (p=0.61). For physical functioning there was an improvement for the treatment group (+15.7) while the control group deteriorated (-1.7) and both groups showed a decline in positive well-being (treatment group -6.4, control group -1.9; p=0.65). There was no change for the treatment group and an improvement for the control group (+2.5) for hepatitis special limitations (p=0.62). Again no significant difference was found between the two groups for these three domains (p=0.12, p=0.451, p=0.67).

At week 20 (two month follow-up) no significant difference was found between the groups or from their baseline scores for any of the 12 domains.

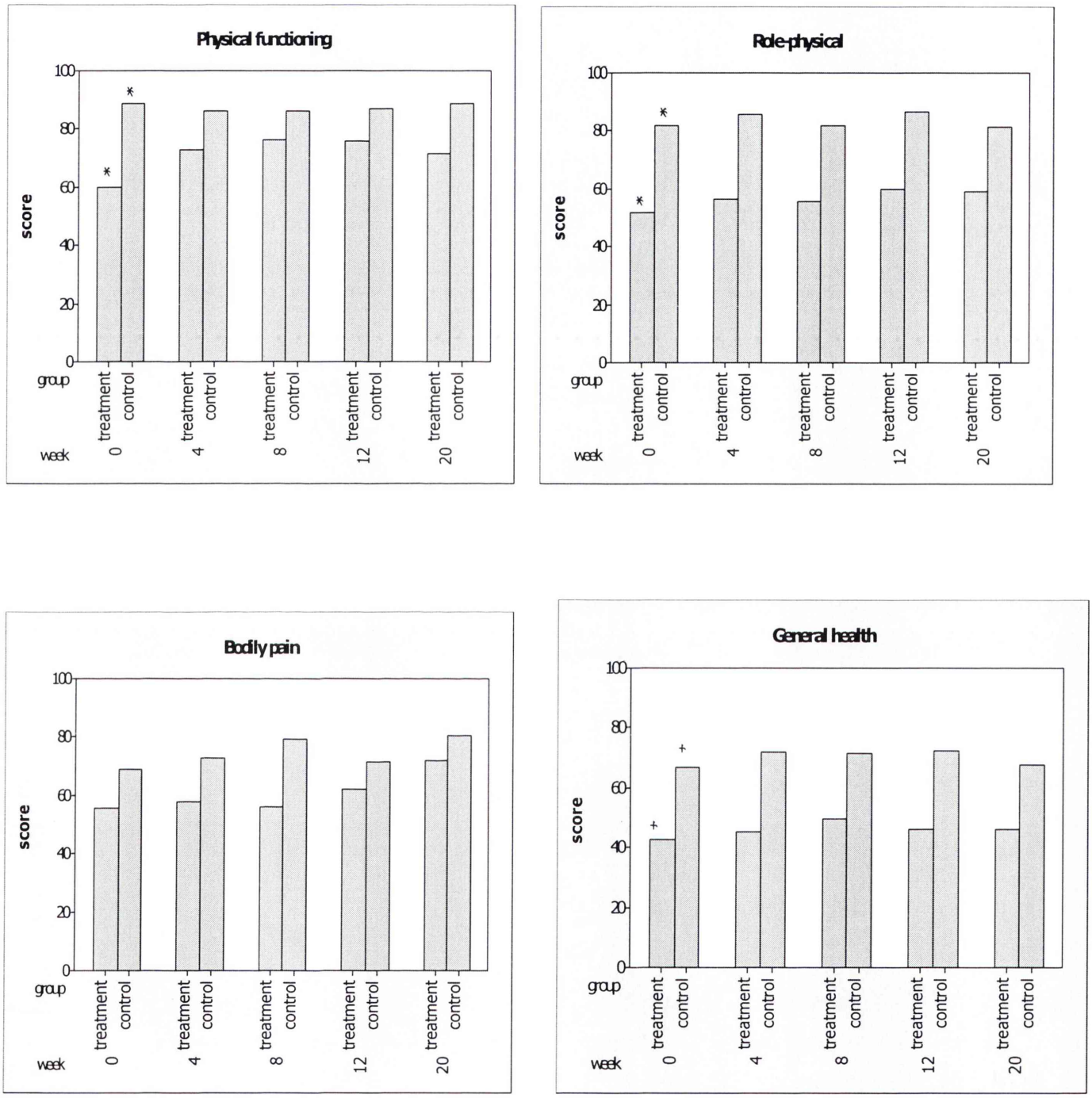
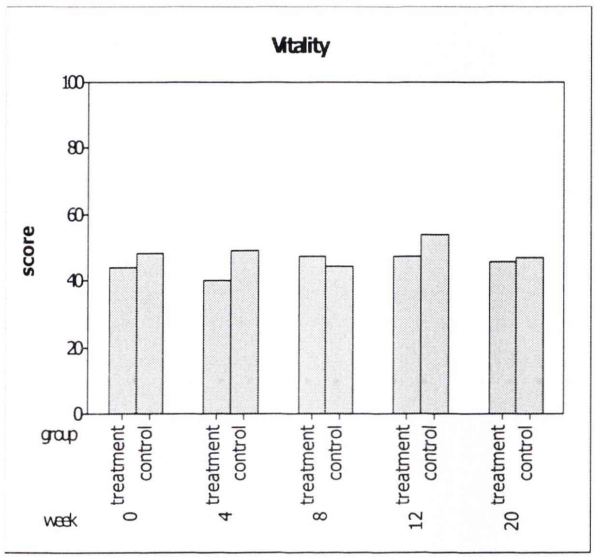
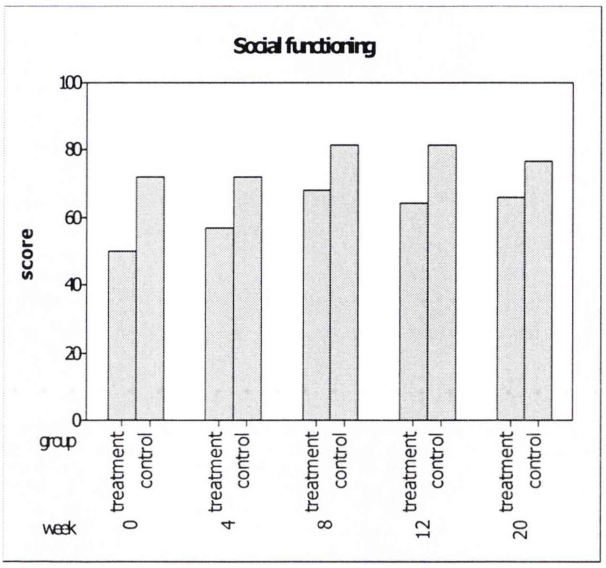
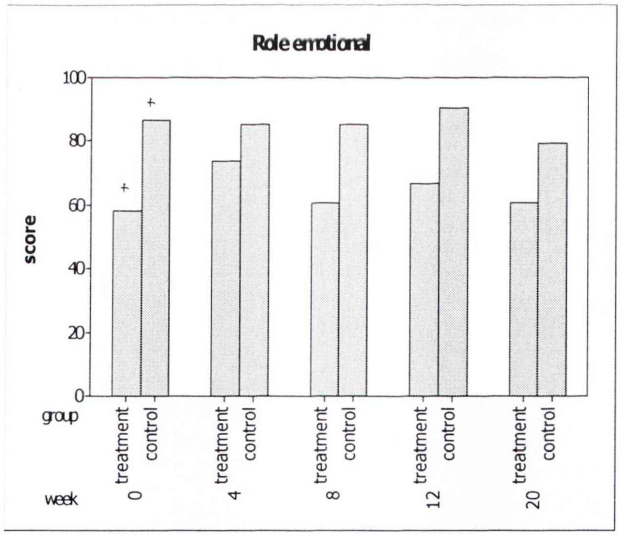


Figure 5.7: Mean scores for QoL domains for the treatment and control group across 20 weeks. Significant difference between the two groups at baseline are indicated * $p<0.05$ + $p<0.01$.







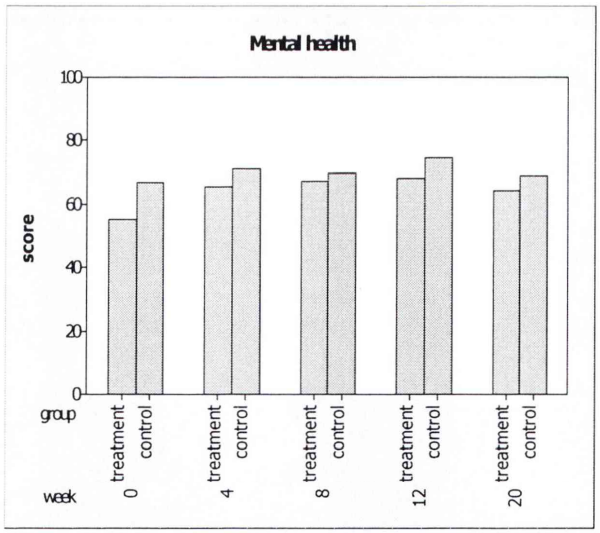
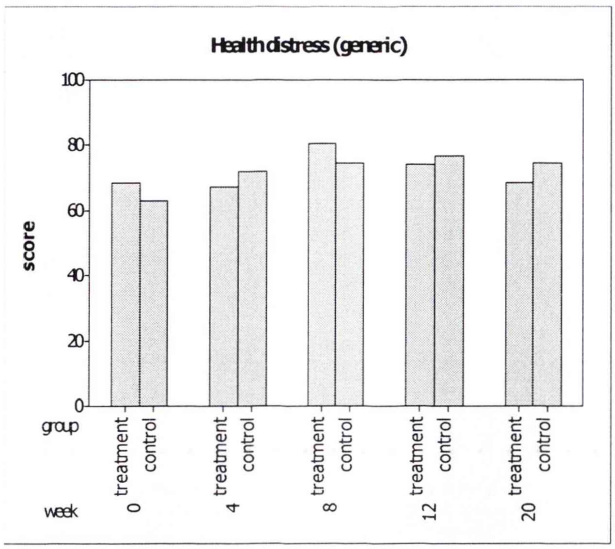
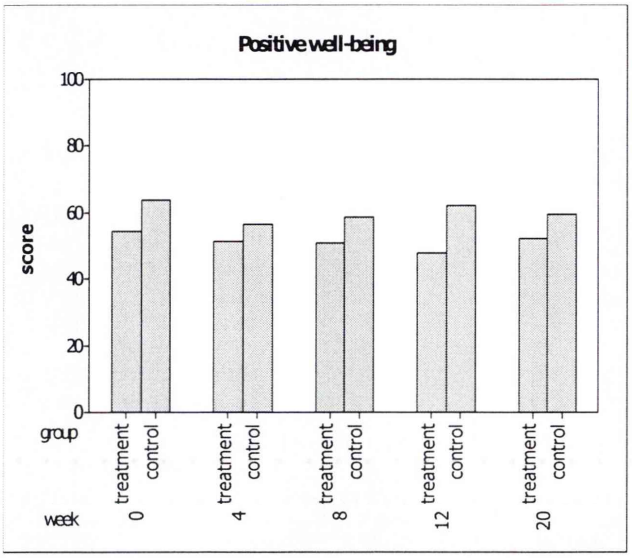
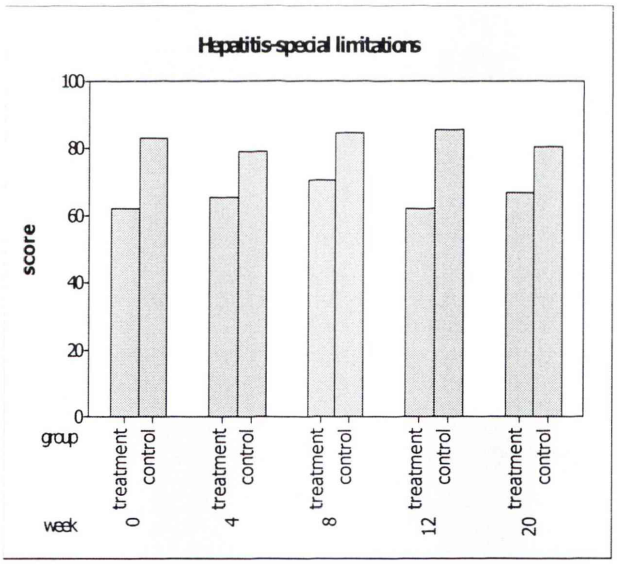


Figure 5.7 (Cont): Mean scores for QoL domains for the treatment and control group across 20 weeks. Significant difference between the two groups at baseline are indicated * $p<0.05$ + $p<0.01$.







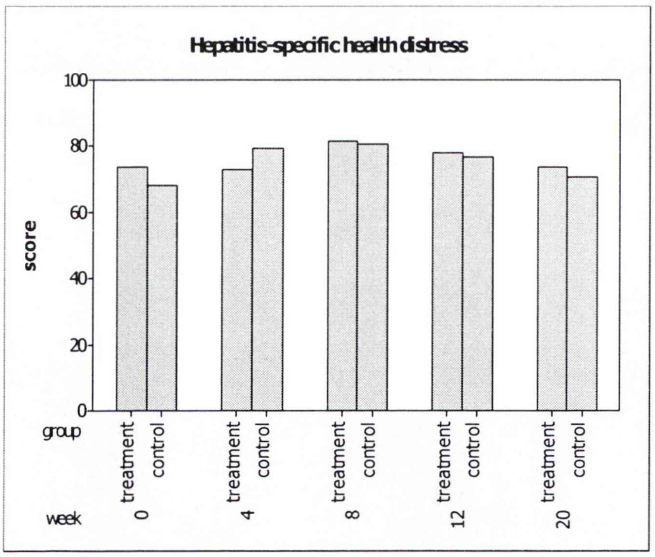


Figure 5.7 (cont): Mean scores for QoL domains for the treatment and control group across 20 weeks. Significant difference between the two groups at baseline are indicated * $p<0.05$ + $p<0.01$.

5.3.4 Acupuncture Treatment Credibility Questionnaire

This questionnaire comprised the following four questions and a seven point semantic differential scale:

1. How confident are you that this treatment can alleviate your complaint?
2. How logical does this treatment seem to you?
3. How confident would you be in recommending this treatment to a friend who suffered the same complaint?
4. How successful do you think this treatment would be in alleviating other complaints?

The questionnaire was administered at the conclusion of weeks 2, 6 and 12 to indirectly evaluate effectiveness of blinding both groups of participants. Figure 5.8 shows the mean ranks for the treatment and control group for each question for the three questionnaire administrations.

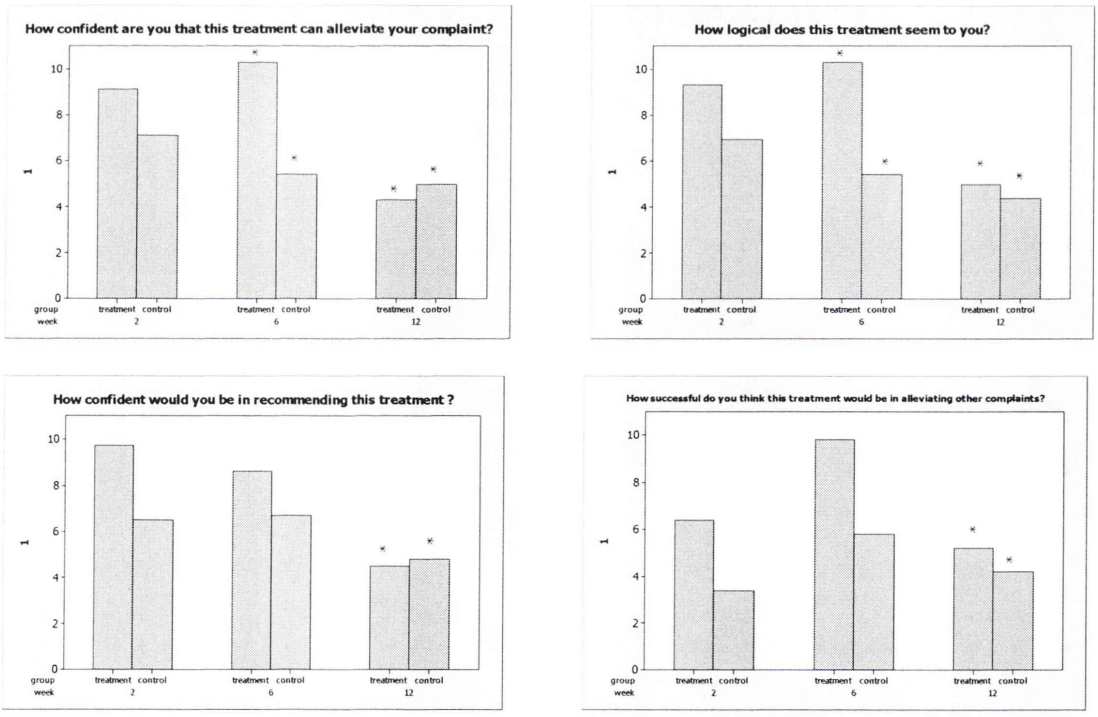


Figure 5.8: Mean ranks for the treatment and control group for each of the four questions administered at weeks 2, 6 and 12. Significant difference between the two groups is indicated * $p<0.05$.

Friedman Analysis for within group comparison failed to show any statistical change over time for the treatment group range (range for values p=0.12 – 1.0) or the control group (p=0.33 – 0.61). Analysis using Mann-Whitney U tests showed significant difference between the groups at two points in time (question 1 and 2 at week 6 and all questions at week 12). There appeared to be no consistent pattern in responses with the treatment group indicating their treatment to be more logical and recommend the treatment to their friends, however they also indicated that it would not be successful in alleviating other complaints.

Table 5.4 shows the responses to the additional question included on the week 12 questionnaire that asked participants which group they thought they were in and their reasons why. Seven subjects thought they received the real treatment (treatment group n=5, control group n = 2), two from the control group identified they were in the sham group and six (treatment group n=2, control group n = 4) didn't know. A Fisher Exact Probability test identified that neither the treatment nor control group identified the type of treatment they had received (p=0.18).

Group	**Belief of participants**		
	Getting real treatment	**Getting sham**	**Don't know**
Treatment group (n=7)	5	0	2
Control group (n=8)	2	2	4
Total (n=15)	**7**	**2**	**6**

Table 5.4 Participant response to which intervention they received.

The reasons given by participants are shown in full in Appendix 12. While 14 of the 15 participants gave reasons no pattern was evident among participants in either the treatment or control group. For example seven participants identified that they thought they were receiving the real treatment because of some health benefits. However two of these participants were in the control group.

Table 5.5 shows that eight subjects (treatment group n=5, control group n=3) in the pilot study had previously had acupuncture treatment prior to commencement of the trial while seven subjects (treatment group n=2, control group n=7) were acupuncture naïve, having never had acupuncture. A Fisher Exact Probability test showed that both groups were equivalent (p=0.32).

Group	Previously experienced acupuncture	
	Yes	No
Treatment group (n=7)	5	2
Control group (n=8)	3	5
Total	**8**	**7**

Table 5.5 Number of participants who had previously experienced acupuncture.

5.3.5 Acupuncture Needling Sensation Questionnaire

This questionnaire (Appendix 10) was administered at weeks one, four, eight and twelve. Respondents were required to indicate their answer by circling the level of their needling sensation experienced during the treatment on a four point likert scale ("not at all"; "mild"; "moderate" and "severe"). Table 5.6 represents the mean ranks for the treatment and control group. A Mann-Whitney U test confirmed that there were no significant differences observed between the treatment and control group at any measurement point (weeks one, four, eight and twelve). A Friedman test confirmed that there was no significant difference across the four time administration points for either group (treatment group p=0.5, control group p=0.6).

Group	Week 1 (Mean rank)	Week 4 (Mean rank)	Week 8 (Mean rank)	Week 12 (Mean rank)
Treatment group (n=7)	7.1	7.1	7.6	7.9
Control group (n=8)	8.8	8.8	8.3	8.1
p value	0.52	0.49	0.82	0.1

Table 5.6: Mean ranked scores and *p* values for the treatment and control group for the Acupuncture Needling Sensation Questionnaire administered (weeks one, four, eight and twelve).

5.3.6 Adverse reactions/events

The second section of the questionnaire required a "yes" or "no" answer to 10 possible adverse events experienced during or immediately after the acupuncture intervention. Six participants reported tiredness after an acupuncture treatment (four in the treatment group and two in the control group). No severe adverse reaction was seen in either group.

5.3.7 HCV/TCM pattern identification

Each participant's symptom/signs were systematically evaluated against the 17 HCV/TCM patterns using the HCV TCM pattern questionnaire prior to commencing the study to identify each participant's primary, secondary and tertiary TCM pattern. Results are presented for:

1. Baseline TCM pattern expression by all participants (treatment and control groups)
2. Primary TCM pattern expressed at baseline
3. Secondary TCM pattern expressed at baseline
4. Tertiary TCM pattern expressed at baseline
5. Comparison of the primary, secondary and tertiary TCM patterns at baseline and on completion of treatment

5.3.7.1 Baseline TCM pattern expression by all participants (treatment and control groups)

Of particular note is that all participants expressed nearly all the patterns simultaneously with some patterns being more strongly expressed than others.

Of the 17 TCM patterns, 6 TCM patterns were expressed by all 16 subjects (*liver yin vacuity, liver kidney yin vacuity, binding depression of liver qi, liver qi invading spleen, phlegm nodulation* and *cold dampness encumbering the spleen internally*). Nine TCM patterns showed some expression by a number of subjects; *damp heat brewing the spleen* (15 subjects), *spleen qi vacuity* (15 subjects), *spleen kidney yang vacuity* (15 subjects), *yin vacuity* (15 subjects), *qi vacuity* (14 subjects), *damp heat transforming fire and brewing toxins* (14 subjects), *liver gallbladder damp-heat* (13 subjects), *blood stasis obstructing the network vessels* (13 subjects), *liver qi stagnation and blood stasis* (10 subjects). Only one subject expressed *blood vacuity* symptoms and *blood stagnation* was not expressed by any subject. Table 5.7 shows the TCM patterns expressed by all participants at week 0 (baseline). The most commonly expressed pattern was *Liver Yin vacuity* which was the primary pattern for eight participants.

Pattern name	Primary pattern	Secondary pattern	Tertiary pattern	Other
Liver yin vacuity (n=16)	3, 4, 5, 7, 10, 11, 13, 16	1, 6, 8	12	2, 9, 14, 15
Liver-kidney yin vacuity (n=16)	1, 6	2, 3, 5, 10, 12	7, 9, 11, 13 14	4, 8, 15, 16
Binding depression of liver qi (n=16)	2, 9, 12, 14	4, 11, 15, 16	5, 8	1, 3, 6, 7, 10, 13
Damp heat brewing the spleen (n=15)		7, 13	2, 3, 4, 6, 9, 10, 11	1, 5, 8, 12, 14, 15
Liver qi invading the spleen (n=16)		14	15	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 16
Phlegm nodulation (n=16)	8, 15	9		1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13, 14, 16
Spleen qi vacuity (n=15)				1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
Cold dampness encumbering the spleen internally (n=16)				1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16
Spleen kidney yang vacuity (n=15)				1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
Yin vacuity (n=15)				1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
Qi vacuity (n=14)				1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15
Damp heat transforming into fire and brewing toxins (n=15)			16	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15
Liver gallbladder damp heat (n=14)			1	2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 15, 16
Blood stasis obstructing network vessels (n=14)				1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14, 15, 16
Liver qi stagnation and blood stasis (n=10)				1, 2, 3, 4, 5, 8, 9, 11, 13, 15
Blood vacuity (n=1)				4
Blood stagnation (n=0)				

Table 5.7: The TCM patterns expressed by all participants at week 0 (baseline). Each participant is represented by their ID number.

5.3.7.2 Primary TCM patterns at baseline

Four patterns emerged as the primary HCV TCM pattern expressed by the trial participants (n=16) at week 0 (baseline). *Liver yin vacuity* was expressed as the primary pattern by eight participants with a mean percentage expression of 62.5, followed by *binding depression of liver qi* which was expressed by four participants with a mean percentage expression of 55.6, two participants expressed *liver-kidney yin vacuity* (mean 46.5) and another two participants expressed *phlegm nodulation* as their primary pattern (mean 45) (Table 5.8).

Primary pattern	Participant ID number	Total number	Mean percentage
Liver yin vacuity	3, 4, 5, 7, 10, 11, 13, 16	8	62.5
Binding depression of liver qi	2, 9, 12, 14	4	55.6
Liver-kidney yin vacuity	1, 6	2	46.5
Phlegm nodulation	8, 15	2	45.0

Table 5.8: The primary HCV TCM pattern expression and mean percentage score of all participants (n=16) at week 0 (baseline).

5.3.7.3 Secondary TCM patterns at baseline

Six patterns were identified as secondary HCV TCM pattern expression by the trial participants (n=16) at week 0 (baseline). *Liver-kidney yin vacuity* was expressed by five participants as their secondary pattern with a mean percentage expression of 58.6, followed by *binding depression of liver qi* expressed by four participants with a mean percentage expression of 50, three participants expressed *liver yin vacuity* (mean 42.4), two participants *damp heat brewing the spleen* (42.9), l*iver qi invading the spleen* (33.3) and one participants expressed *phlegm nodulation* as their secondary pattern (mean 30) (Table 5.9).

Secondary pattern	Participant ID number	Total number	Mean percentage
Liver-kidney yin vacuity	2, 3, 5, 10, 12	5	58.6
Binding depression of liver qi	4, 11, 15, 16	4	50.0
Liver yin vacuity	1, 6, 8,	3	42.4
Damp heat brewing the spleen	7, 13	2	42.9
Liver qi invading spleen	14	1	33.3
Phlegm nodulation	9	1	30.0

Table 5.9: The secondary HCV TCM pattern expression and mean percentage score of all participants (n=16) at week 0 (baseline).

5.3.7.4 Tertiary TCM patterns at baseline

In total seven patterns were expressed as the tertiary patterns by participants (n=16). Two participants (participant 9 and 11) expressed two patterns with equal expression. *Damp heat brewing the spleen* was expressed by seven participants (mean percentage expression 40.8), followed by *liver-kidney yin vacuity* expressed by five participants (mean 40.0). *Binding depression of liver qi* was expressed by two participants (mean 50.0). *Liver yin vacuity, liver gallbladder damp heat* and *liver qi invading the spleen* were expressed by only one participant with a mean pattern expression of 38.5, 26.7 and 21.4 respectively (Table 5.10).

Tertiary pattern	Participant ID number	Total number	Mean percentage
Damp heat brewing the spleen	2, 3, 4, 6, 9, 10, 11	7	40.8
Liver–kidney yin vacuity	7, 9, 11, 13, 14	5	40.0
Binding depression of liver qi	5, 8	2	50.0
Liver yin vacuity	12	1	54.5
Liver gallbladder damp heat	1	1	38.5
Liver qi invading spleen	15	1	26.7
Damp heat transforming fire and brewing toxins	16	1	21.4

Table 5.10: The tertiary HCV TCM pattern expression and mean percentage score of all participants (n=16) at week 0 (baseline).

5.3.7.5 Comparison of the TCM pattern expression for primary, secondary and tertiary patterns at baseline

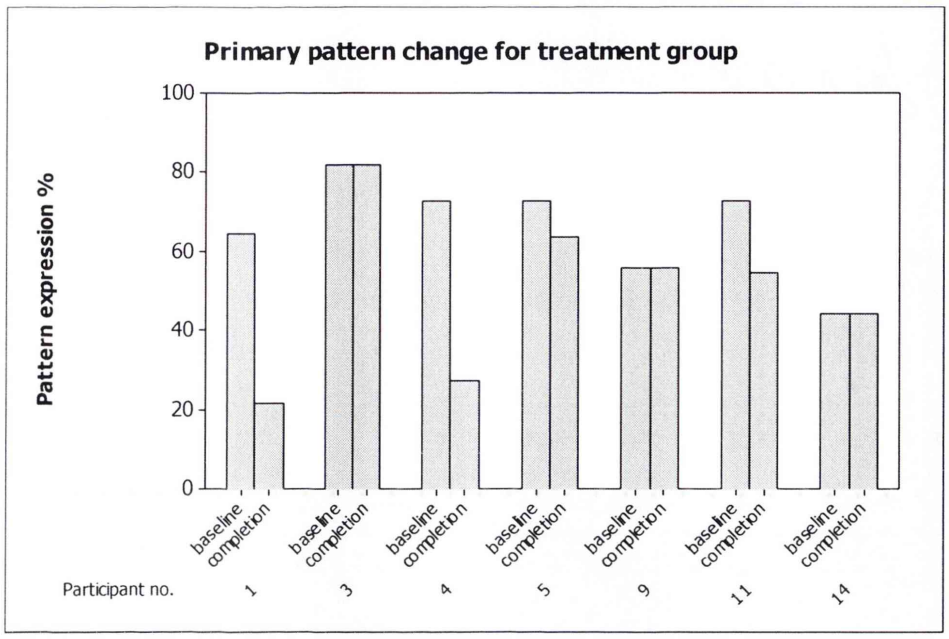
At baseline the treatment group showed a higher percentage expression for the primary TCM patterns compared to the control group (p=0.03). No difference in pattern expression at baseline was found between the two groups for the secondary or tertiary patterns.

5.3.7.6 Comparison of the primary, secondary and tertiary TCM patterns at baseline and on completion of treatment

The HCV TCM pattern questionnaire was again administered on completion of the treatment phase (week 12). There was a significant mean percentage decrease in pattern expression at week 12 when compared to baseline for the secondary and tertiary patterns of the treatment group (56.3% cf 47.5%; p=0.045 and 48.1% cf 33.6%; p=0.037 respectively). No significant change in expression was found for the primary, secondary or tertiary patterns for the control group or for the primary patterns associated with the treatment group (see Table 5.11 and Figures 5.9, 5.10 and 5.11).

TCM pattern	Group	Week 0	Week 12	*p* value
Primary	Treatment	66.3 (± 12.7)	49.8 (± 20.9)	0.07
	Control	50.6 (± 12.5)	47.4 (± 14.1)	0.08
Secondary	Treatment	56.3 (± 18.3)	47.5 (± 20.0)	**0.045**
	Control	42.8 (± 12.0)	38.5 (± 11.2)	0.21
Tertiary	Treatment	48.1 (± 15.9)	33.6 (± 16.3)	**0.037**
	Control	35.3 (±14.0)	30.6 (± 11.9)	0.16

Table 5.11: The mean expression percentage for the primary, secondary and tertiary TCM pattern at baseline (week 0) and on completion of treatment (week 12) for the treatment and control group. *p* values are shown in bold where significant.



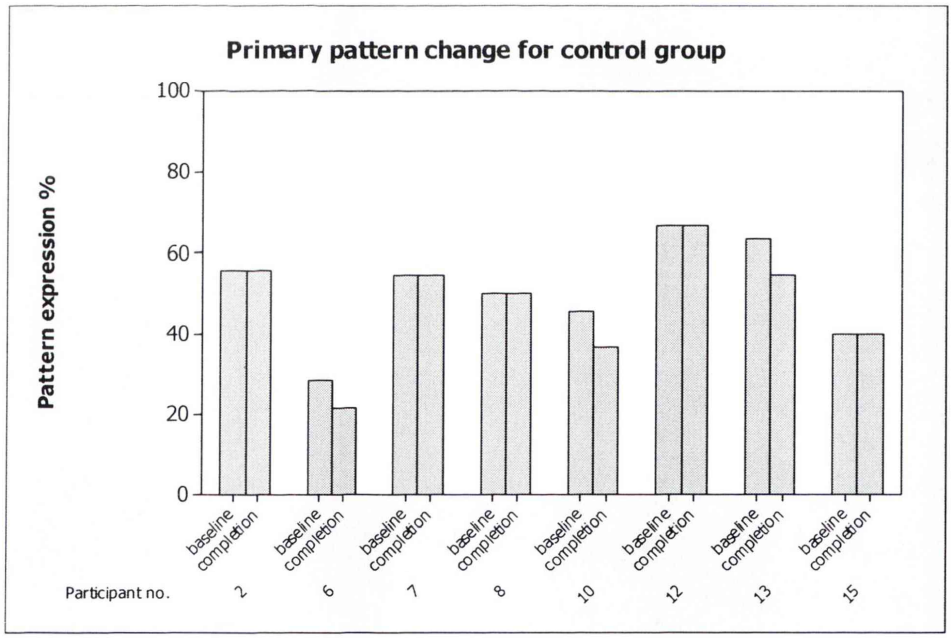
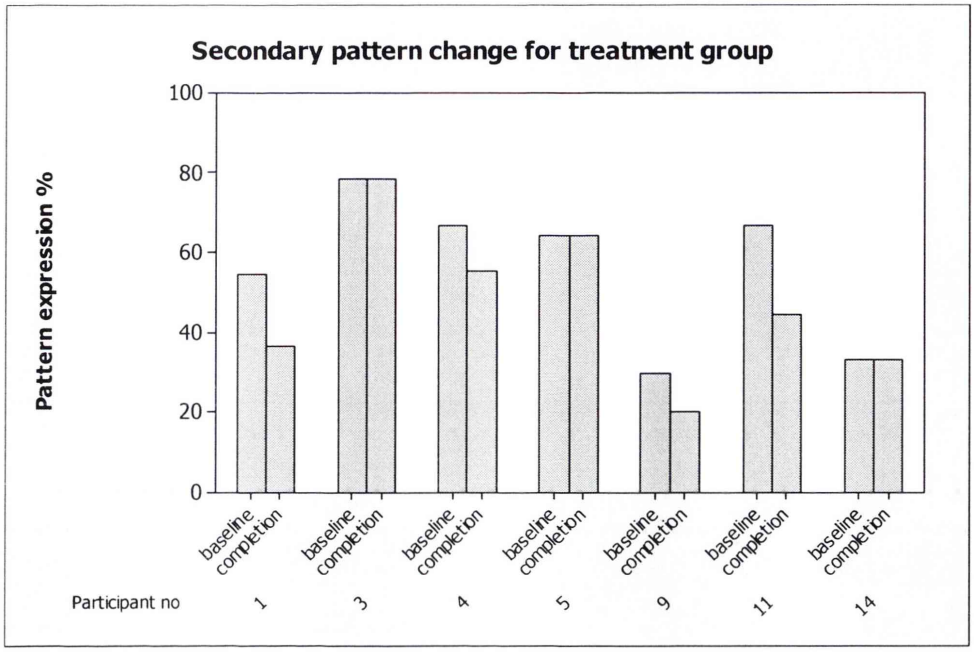


Figure 5.9: Pattern expression percentage change for the primary patterns for the treatment and control group.



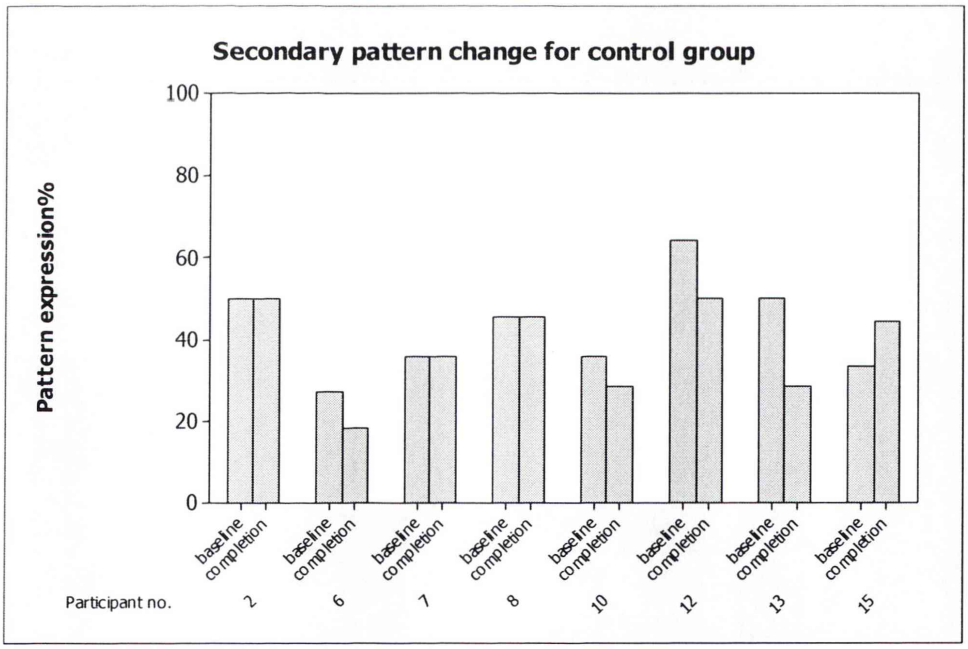
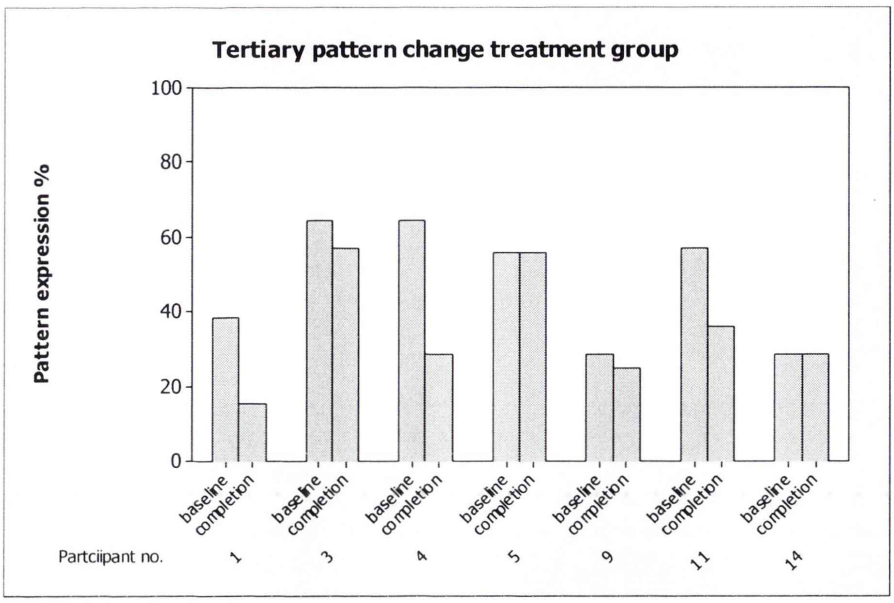


Figure 5.10: Pattern expression percentage change for the secondary patterns for the treatment and control group.



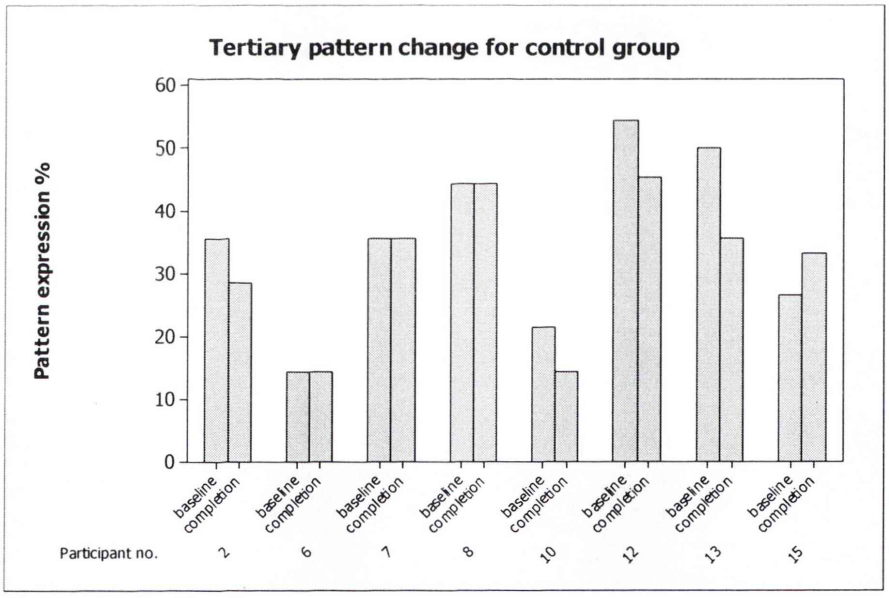


Figure 5.11: Pattern expression percentage change for tertiary patterns for the treatment and control group.

5.3.7.7 Individual participant comparison of TCM pattern expression

Appendix 13 shows individual participant's baseline TCM pattern expression minus on completion expression graphs.

Chapter 6: Discussion

Anecdotally many clinical textbooks have previously suggested that acupuncture can effectively treat HCV patients. However up to this point in time these claims have not been substantiated. This is the first randomised and controlled acupuncture study that used both objective (ALT and viral load) and quality of life measures to evaluate change in HCV patients. Surprisingly no significant difference or improvement was found between the two experimental groups for ALT levels, viral load or any domains of the QoL. However a significant decrease in the expression of the secondary and tertiary TCM patterns for the treatment group was observed suggesting an improvement in symptoms associated with these patterns. When an analysis was done to identify which symptoms changed over the treatment period it was found to be 'lack of appetite' and 'nausea'. This is not surprising as a number of systematic reviews have consistently reported strong levels of evidence regarding the antiemetic effects of acupuncture (Ezzo et al 2006; Jewell et al 2003). As mentioned in chapter one, the present study was initiated because participants at the drug rehabilitation centre reported a decrease in their ALT blood levels. Furthermore many of these same people also reported improvements in being able to 'cope with life' in a more positive manner. While the present study did not show any significant change for ALT levels or QoL, the TCM patterns did show respite for specific symptoms such as nausea and lack of appetite. The recent use of 'symptom clusters' for hepatitis bears a striking similarity to the TCM pattern approach and further research in identify and monitoring prominent diseases symptoms as a more sensitive measure of improvement is warranted (Lang et al 2006).

In support of this, Mollison et al, (2006) in their herbal medicine hepatitis study reported statistical significant ALT level improvements at weeks four and 24 compared with baseline ALT levels for the treatment group. However the quality of life measure used in the study (SF36) showed significant improvement over time for only one domain (bodily pain; p=0.02) at only one time point (week 24). This suggests that the instrument may lack sufficient sensitivity to detect small changes in perceived specific hepatitis related

symptoms and it is possible that evaluation of symptom clusters such as the TCM patterns may prove beneficial in monitoring symptom change in HCV patients.

Another limitation of this pilot study is the small sample size. At the initiation of the trial it was hoped to recruit 20 people for each arm of the pilot study however the sixteen subjects that were eventually recruited represented only a 12% recruitment rate. This low rate is a problem for any large acupuncture trial where large numbers of participants are required for a sufficient sample size for statistical reasons. Despite extensive advertising and media broadcasting very few participants were willing to become involved in a study that required acupuncture treatment twice a week for three months. This is borne out by the large percentage (N=88; 68%) who declined to be involved in the trial. A recent study looked at the financial and efficacy rate of a variety of recruitment methods for a clinical trial on acupuncture and irritable bowel syndrome (Chin Feman et al 2007). They reported that the most effective recruitment methods were physician referrals and flyers, two methods that were not extensively used in the present study. Future trials should utilise these methods in addition to the methods employed in this study to ensure sufficient recruitment of participants.

An interesting aspect of the study was the incorporation of a manualised TCM pattern approach to both the diagnosis and treatment. This approach attempted to replicate TCM practice within the framework of rigorous evidence based research and represents a novel clinical outcome measure could be further developed and used within future acupuncture or herbal medicine clinical trials. During the study however it became apparent a number of modifications could improve the sensitivity of the method. First, the TCM pattern collection sheet only allowed the researcher to record whether the symptom/sign was present or absent. It did not monitor incremental change of each symptom. The use of a rating scale for each symptom would accommodate symptom improvement or deterioration and allow a more sensitive evaluation of TCM pattern change. Second, in the present study there was no evaluation of the radial pulse or tongue information for the TCM pattern. This is problematic in that the information obtained from inspection of the tongue and palpation of the radial pulse at the wrist is generally thought to be pivotal in determining the primary TCM patterns in clinical practice. Over the last ten years two

systematic data collection methods involving diagnostic tongue features and radial pulse forms have been developed that demonstrate reasonable levels of reliability (Kim et al 2008; Walsh et al 2008). Future studies should therefore incorporate both these methods into the TCM patterns data collection process to consolidate the identification of the primary pattern.

Finally, participants could have benefited from regular TCM pattern reassessment during the treatment phase. In the present study we only assessed the TCM patterns at baseline and at the completion of the pilot study at three months. If the participants were reassessed regularly, it may have been possible to observe changes in the strength of the expression of the patterns and treatment protocols could have been changed or modified. This is very similar to clinical practice where patients are regularly assessed for change in their TCM pattern and their treatment modified accordingly. Not surprisingly, for 21 patterns (a primary, secondary and tertiary pattern for each individual) that were present for the seven participants in the treatment group at baseline, only 15 patterns of these initial 21 were still present as primary, secondary and tertiary patterns at the completion of the study. This represents a 28% decrease in the expression of these treatment patterns. In contrast, of the 24 primary, secondary and tertiary patterns expressed by the eight participants in the control group at baseline, proportionally more patterns were present at the completion of the study than compared to the treatment group (N= 19; 80% cf N=15, 72%).

The quantification of the TCM pattern in this study has permitted statistical evaluation of TCM pattern change. While TCM pattern identification has previously only been used as a basis for developing a treatment protocol in a clinical trial, this present study is the first time it has been employed as an outcome measure. While we have suggested a number of modifications and improvements to the method we believe that this approach is worthy of further study and incorporation into future acupuncture and Chinese medicine clinical trials.

Another criticism of the study is the failure to stratify participants who had previously unsuccessfully received combination therapy. Two previous Chinese herbal studies have commented that failure to stratify, based on whether participants had previously undergone unsuccessful combination treatment, could decrease the likelihood of demonstrating a benefit from treatment (Batey et al 1998; Jakkula et al 2004). Indeed in the present study five of the seven participants in the treatment group and only two of the eight in the control group reported they had previously received combination therapy. While we could not establish that our failure to stratify based on previous therapy confounded the results, we would strongly recommend that future studies stratify participants based on this criterion.

While conducting the study it became apparent that there were a number of flaws in the design. The first issue relates to the use of ALT levels to monitor the effect of acupuncture on the disease. ALT levels were initially chosen as a primary outcome measure because the five reviewed clinical studies had used them to monitor the disease. While ALT levels are often used as a surrogate marker of the disease process they can rapidly increase due to diet, alcohol and drug or medication intake (Farrell 2002). Indeed we observed fluctuating ALT levels in both the treatment group and the control group, both prior to initiating treatment as well as during and following the treatment. More recently an increasing number of HCV clinical studies have used a Scheuer score which is a measure of the liver cirrhosis and fibrosis. The score, which is determined following a liver biopsy and microscopic evaluation of the liver tissue, has been shown to be a more valid and reliable measure of liver disease progression. Unfortunately this was beyond the financial constraints of the present study. The failure to obtain a Scheuer score meant that we could not stratify participants according to existing liver damage or monitor ongoing liver damage. Future studies need to consider incorporation of Scheuer score as a stratification criterion to ensure equivalency between groups at baseline and as a potential disease measure.

Our study also required that for trial inclusion participants had to provide documented pathology evidence of an elevated ALT level of greater than or equal to 57 U/L during

the previous six months prior to entering the trial. Due to the fluctuating nature of ALT levels, although all participants met this criterion prior to trial entry five participants failed to achieve this requirement at baseline (mean of ALT tests at weeks -1, -3, -5). On observation there was a large standard deviation for the mean ALT baseline levels for both groups but especially for the treatment group (treatment group mean of 122 sd ± 110 cf control group mean of 99 sd ± 51.9). With the exception of three results (419 U/L, 478 U/L and 317 U/L) all scores were less than 245 U/L. These three scores were all obtained from treatment group participants. Two results (478 U/L, 317 U/L) belonged to one participant whose ALT levels dropped to 180 U/L within a month. The other participant's result elevated from 48 U/L (below eligibility criteria) to 419 U/L and then back to 47 U/L. This again highlights the erratic nature of ALT levels or the possibility of a pathology error.

Finally, ALT levels are known to increase following alcohol intake, poor dietary habits and drug and medication use. While we did attempt to monitor alcohol use no attention was given to monitoring other possible confounders. Future studies should require participants to use a diary to monitor alcohol, specific food as well as drug and medication use to ensure life style factors do not influence ALT levels.

Determining the most appropriate as well as the most adequate number of acupuncture treatments for this pilot study was difficult. There was a paucity of published HCV acupuncture studies. In addition, the author relied on her previous experience at the rehabilitation centre and the time constraints of the project to determine the length of the treatment course. It may well have been too short a treatment course for such a chronic condition.

Another interesting observation was the similar levels of needling sensation reported by both groups. While the use of an invasive sham needling remains controversial in acupuncture clinical trials it was used in the present study to control for both non specific psychological (placebo) and physiological (such as diffuse noxious inhibitory control) effects that result from needling the body irrespective of site. To monitor the levels of

needling sensation in both groups we used a questionnaire first developed by Vincent et al (Vincent et al 1989). Since the decision to use the Vincent questionnaire a number of published reports have criticised the validity of the questionnaire.

Park et al modified the Vincent scale by adding five sensations based on a comprehensive literature review. The Park questionnaire was further developed by Macpherson using a Delphi process to differentiate sensations believed to be associated with needling from pain. Twenty nine experts decided that seven sensations described needling sensation: aching, dull, heavy, numb, radiating, spreading and tingling and nine sensations expressed pain: burning, hot, hurting, pinching, pricking, sharp, shocking, stinging and tender (Macpherson et al 2006a). Both these scales have limitations in that they measure a range of sensations that were primarily drawn from a pain questionnaire, were not focused specifically on needling sensation and had not asked patients receiving acupuncture what sensations they had experienced.

When the responses from the control group of the present study were later examined for levels of needling sensation they experienced during the sham needling some noted that the use of the sham point in the thumb region (sham point H.1) was painful when needled. High scores for the pain sensations of hurting and stinging would have increased the sensation score contributing to the equivalency of the score for both groups. Future acupuncture studies, if they intend to use an invasive sham needling control, should use a questionnaire that differentiates pain from needling sensation. The recently developed Southampton Needling Sensation Questionnaire achieves this (White et al 2008). In addition needling of the sham acupoints should be piloted to ensure differing levels of needling sensation prior to developing the protocol.

Finally when sham needling is used as a control, the credibility of the two acupuncture treatments (acupuncture and invasive sham needling) should be assessed at intervals during the treatment phase using a series of standardised questions (Vincent 1990). While there have been criticisms about the validity of the specific questions used in the instrument developed for acupuncture studies by Vincent and others (White et al 2001;

Zaslawski et al 1997) there is little disagreement about the need for some form of credibility measure (Lewith et al 2002). In the present study we evaluated blinding using the modified Vincent credibility questionnaire. While there were differences between the two groups at certain time points no consistent pattern of responses was evident.

Finally, the present study used a recognised QoL questionnaire for hepatitis, the HQLQv2, which incorporated the Short Form 36 (SF36), a broad non-disease specific QoL measure with an additional four questions related to hepatitis. During the administration of the questionnaire it was noted that while the measurement tool was sensitive for general health and quality of life changes it was not disease specific. For instance, if a participant had chronic lumbar or knee pain, these symptoms would not have been expected to improve resulting in the participant recording no change for the pain domain. Any report of concurrent reduction in disease specific pain such as liver pain would have been eclipsed by the chronic pain. This may not be significant when the trial has sufficient statistical power, however in a small study such as the current trial where there were only 16 subjects it may confound the results. Future effort should be directed to developing a specific QoL measure that accurately reflects change in many of the symptoms associated with HCV. The use of a questionnaire that lists prevalent HCV symptom clusters to describe and monitor the disease and the severity of its symptoms is more likely to represent a valid clinical picture of the disease (Lang et al 2006).

Chapter 7: Conclusion

This pilot study is the first to evaluate the effects of acupuncture on people with HCV. It was a randomised single blind controlled pilot study with two parallel arms that used several objective outcome measures and a QoL measure. The TCM pattern identification process used in this study allowed the systematic assessment and measurement of the TCM patterns before and after the intervention phase. This process attempted to accommodate TCM practice within the framework of rigorous evidence based medical research while providing a standardised reproducible individually tailored treatment protocol. Although this process was used for an acupuncture trial it could be used for CHM or other TCM therapies that use pattern differentiation.

A number of limitations of the study were identified several suggestions were also made to improve future acupuncture clinical trials. These include:

- piloted needling of sham acupoints to ensure differing levels of needling sensation prior to developing the protocol. This should be in conjunction with the use of an appropriate needling sensation questionnaire such as the Southampton Needling Sensation Questionnaire;
- incorporation of recruitment methods such as physician referrals and flyers to facilitate recruitment of participants;
- quantification of TCM patterns for a specific disease which assists statistical evaluation of TCM pattern change and its use as a clinical outcome measure.

It is hoped that these suggestions are incorporated into the design of future acupuncture clinical trials. This will ensure a better understanding of acupuncture and facilitate the development of the evidenced based practice of acupuncture.

References:

ACMERC 1995, 'Hepatitis C: Western Background and TCM Treatment!' *Newsletter of Australian Chinese Medicine Education and Research Council.*

Ahn, A C and Kaptchuk, T J 2005, 'Advancing Acupuncture Research', *Alternative Therapies in Health and Medicine*, vol. 11, no. 3, pp. 40-45.

Allen, J B, Schnyer, R N and Kitt, S K 1998, 'The Efficacy of Acupuncture in the Treatment of Major Depression in Women', *Psychological Science*, vol. 9, no. 5, pp. 397-401.

Alter, H J, Conry-Cantilena, C, Melpolder, J, Tan, D, Van Raden, M, Herion, D, Lau, D and Hoofnagle, J H 1997, 'Hepatitis C in Asymptomatic Blood Donors', *Hepatology*, vol. 26, no. 3 (Suppl. 1), pp. 29S-33S.

Alter, M J, Margolis, H S, Krawczynski, K, Judson, F N, Mares, A, Alexander, W J, Hu, P Y, Miller, J K, Gerber, M A, Sampliner, R E and al, e 1992, 'The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team', *New England Journal of Medicine*, vol. 327, no. 27, pp. 1899-1905.

ASHM (ed.) 2004, *HIV/Viral hepatitis: a guide for primary care*, Australasian Society for HIV Medicine (ASHM).

Australian Government, DHAC 2005, *National Hepatitis C Strategy 2005-2008*, Report Number 0 642 82656 0, Australian Government, Department of Health and Ageing.

Auteroche, B, Gervais, G, Auteroche, M, Navailh, P and Toui-Kan, E 1992, *Acupuncture and Moxibustion. A Guide to Clinical Practice*, Churchill Livingstone, Edinburgh.

Batey, R G, Bensoussan, A, Yang, Y F, Bollipo, S and Ma, H 1998, 'Preliminary report of a randomized, double-blind placebo-controlled trial of a Chinese herbal medicine preparation CH-100 in the treatment of chronic hepatitis C', *Journal of Gastroenterology and Hepatology*, vol. 13, pp. 244-247.

Bayliss, M S, Gandek, B, Bungay, K M, Sugano, D, Hsu, M-A and Ware, J E 1998, 'A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C', *Quality of Life Research*, vol. 7, pp. 39-55.

Bensoussan, A, Talley, N, Hing, M, Menzies, R, Guo, A and Ngu, M 1998, 'Treatment of Irritable Bowel Syndrome With Chinese Herbal Medicine', *JAMA*, vol. 280, no. 18, pp. 1585-1589.

Berle, C A 1997, 'Report on the use of acupuncture for substance dependencies within the Australian setting', *The Third Australasian Acupuncture and Chinese Herbal Medicine Conference*, University of Technology, Sydney, Sydney, pp. 69-78.

Bonkovsky, H, Woolley, M and Group, T C I S 1999, 'Reduction of Health-Related Quality of Life in Chronic Hepatitis C and Improvement With Interferon Therapy', *Hepatology*, vol. 29, no. 1, pp. 264-270.

Campbell, J 1995, 'Abnormal Liver Function Tests (Hepatitis without Jaundice) A Pilot Study', *The Natural Therapist*.

Carithers, R, Sugano, D and Bayliss, M 1996, 'Health Assessment for Chronic HCV Infection', *Digestive Diseases and Sciences*, vol. 41, no. 12, pp. 75S-80S.

Chin Feman, S P, Nguyen, L T, Quilty, M T, Kerr, C E, Nam, B H, Conboy, L A, Singer, J P, Park, M, Lembo, A J, Kaptchuk, T J and Davis, R B 2007, 'Effectiveness of recruitment in clinical trials: an analysis of methods used in a trial for irritable bowel syndrome patients', *Contempory Clinical Trials*, vol. 29, no. 2, pp. 241-251.

Cohen, M R 2001, 'Herbal and Complementary and Alternative Medicine Therapies for Liver Disease - A Focus on Chinese Traditional Medicine in Hepatitis C Virus', *Clinics in Liver Disease*, vol. 5, no. 2, pp. 461-477.

Davis, G L, Balart, L A, Schiff, E R, Lindsay, K, Bodenheimer, H C, Perrillo, R P, Carey, W, Jacobson, I M, Payne, J, Dienstag, J L, Van Thiel, D H, Tamburro, C, Martino, F P, Sangvhi, B and Albrecht, J K 1994, 'Assessing Health-Related Quality of Life in Chronic Hepatitis C Using the Sickness Impact Profile', *Clinical Therapeutics*, vol. 16, no. 2, pp. 334-343.

Deadman, P, Al-Khafaji, M and Baker, M 2001, *A Manual of Acupuncture*, Journal of Chinese Medicine Publications.

Deng, T 1999, *Practical Diagnosis in Traditional Chinese Medicine*, Churchill Livingstone.

Dore, G 2006, 'Global genotype/subtype distribution pattern', *ASHM Day Course in Hepatitis C Medicine*, Sydney.

Dore, G J, Kaldor, J M and McCaughan, G W 1997, 'Systematic review of role of polymerase chain reaction in defining infectiousness among people infected with hepatitis C virus', *British Medical Journal*, vol. 315, p. 7104.

Ezzo, J M, Richardson, M A, Vickers, A, Allen, C, Dibble, S L, Issell, B F, Lao, L, Pearl, M, Ramirez, G, Roscoe, J A, Shen, J, Shivnan, J, Streitberger, K, Treish, I and Zhang, G 2006, *Acupuncture-point stimulation for chemotherapy-induced nausea and vomiting*, viewed April 19 <http://www.cochrane.org/reviews/en/ab002285.html>.

Farrell, G G 2002, *Hepatitis C other liver disorders and liver health: a practical guide*, MacLennan & Petty Pty Limited.

Flaws, B and Sionneau, P 2001, *The Treatment of Modern Western Medical Diseases with Chinese Medicine*, Blue Poppy Press
A Division of Blue Poppy Enterprises, Inc.

Foster, G R, Goldin, R D and Thomas, H C 1998, 'Chronic Hepatitis C Virus Infection Causes a Significant Reduction in Quality of Life in the Absence of Cirrhosis', *Hepatology*, vol. 27, no. 1, pp. 209-212.

HCCNSW 2007, *Hep C Factsheets: Symptoms of hepatitis C and their management.*

HCVPWG 2006, *Hepatitis C Virus Projections Working Group.*

Heller, T and Seeff, L 2005, 'Viral load as a predictor of progression of chronic hepatitis C?' *Hepatology*, vol. 42, no. 6, pp. 1261-1263.

Hepatitis C Caring Ambassadors Program 2002, 'Hepatitis C Choices', *The Hep C Review*, vol. 38, no. Spring, pp. 10-11.

Holmes, E C 1995, 'Revealing the history of infectious disease epidemics using phylogenetic trees', *Philosophical Transactions of the Royal Society of London Biological Sciences*, vol. 349, no. 1327, pp. 33-40.

Jakkula, M, Boucher, T A, Beyendorff, U, Conn, S M, Johnson, J E, Nolan, C J, Peine, C J and Albrecht, J H 2004, 'A Randomized Trial of Chinese Herbal Medicines for the Treatment of Symptomatic Hepatitis C', *Archives of Internal Medicine*, vol. 164, no. 12, p. 1341.

Jenkinson, Crispin, Coulter, Angela, Wright and Lucie 1993, 'Short Form 36 (SF36) Health Survey Questionnaire: Normative Data for Adults of Working Age', *British Medical Journal*, vol. 306 (6890), pp. 1437-1440.

Jewell, D and Young, G 2003, *Interventions for nausea and vomiting in early pregnancy*, <http://www.cochrane.org/reviews/en/ab000145.html>.

Kaptchuk, T J 1983, *Chinese Medicine - The Web that has no Weaver*, Rider & Company, An imprint of the Hutchinson Publishing Group, Great Britain.

Kenny-Walsh, E 1999, 'Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin', *The New England Journal of Medicine*, vol. 340, no. 16, pp. 1228-1233.

Kim, M, Cobbin, D and Zaslawski, C J 2008, 'Traditional Chinese medicine tongue inspection: an examination of the inter- and intrapractitioner reliability for specific tongue characteristics.' *Journal of Alternative and Complementary Medicine*, vol. 14, no. 5, pp. 527-536.

Lang, C A, Conrad, S, Garrett, L, Battistutta, D, Cooksley, G, Dunne, M P and Macdonald, G A 2006, 'Symptom Prevalence and Clustering of Symptoms in People Living with Chronic Hepatitis C Infection', *Journal of Pain and Symptom Management*, vol. 31, no. 4, pp. 335-344.

Leigh Brown, A J 1997, 'The Molecular Epidemiology of Human Immunodeficiency Virus Type 1 in Six Cities in Britain and Ireland', *Virology*, vol. 235, no. 1, pp. 166-177.

Lewith, G, Jonas, W B and Walach, H (eds) 2002, *Clinical Research in Complementary Therapies Principles, Problems and Solutions*, Churchill Livingstone.

Maciocia, G 1989, *The Foundations of Chinese Medicine*, Churchill Livingston.

Maclean, W and Lyttleton, J 2000, *Clinical Handbook of Internal Medicine - The Treatment of Disease with Traditional Chinese Medicine*, Second edn, vol. 1, University of Western Sydney.

MacPherson, H and Asghar, A 2006a, 'Acupuncture needle sensations associated with De Qi: a classification based on experts' ratings.' *Journal of Alternative and Complementary Medicine*, vol. 12, no. 7, pp. 633-637.

MacPherson, H and Schroer, S 2006b, 'Acupuncture as a complex intervention for depression: A consensus method to develop a standardised treatment protocol for a randomised controlled trial', *Complementary Therapies in Medicine*, vol. doi:10.1016/j.ctim.2006.09.006.

Medical Editorial Committee of China Cultural Corporation 1985, *Acupuncture Charts*, China Cultural Corporation, Charts 1, 2 and 3.

Micallef, J, Kaldor, J M and Dore, G J 2006, 'Spontaneous viral clearance following acute hepatitis C infection: a systematic review of lingitudinal studies', *Journal of Viral Hepatitis*, vol. 13, pp. 34-41.

Moher, D, Schulz, K F and Altman, D 2005, 'The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Rabndomised Trials 2001', *Explore*, vol. 1, no. 1, pp. 40-45.

Mollison, L, Totten, L, Flexman, J, Beaman, M and Batey, R 2006, 'Randomized double blind placebo-controlled trial of a Chinese herbal therapy (CH100) in chronic hepatitis C', *Journal of Gastroenterology and Hepatology*, vol. 21, no. 7, pp. 1184-1188.

NCHECR 2006, *HIV/AIDS, viral hepatitis & sexually transmissible infections in Australia Annual Surveillance Report 2006.*

Neary, M P, Cort, S, Bayliss, M S and Ware, J E 1999, 'Sustained Viirologic Response Is Associated With Improved Health-Related Quality of Life in Relapsed Chronic Hepatitis C Patients', *Seminars in Liver Disease*, vol. 19, no. Supplement 1, pp. 77-85.

Oleson, T 2003, *Auriculotherapy Manual Chinese and Western Systems of Ear Acupuncture*, Churchill Livingstone.

Poynard, T, Cacoub, P, Ratziu, V, Myers, R P, Dexailles, M H, Mercadier, A, Ghillani, P, Charlotte, F, Piette, J C and Moussailli, J 2002, 'Fatigue in patients with chronic hepatitis C', *Journal of Viral Hepatitis*, vol. 9, no. 4, pp. 295-303.

Poynard, T, Ratziu, V, Charlotte, F, Goodman, Z, McHutchison, J and Albrecht, J 2001, 'Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C', *Journal of Hepatology*, vol. 34, no. 5, pp. 730-739.

Rogers, C and Rogers, C 1989, *Point Location and Point Dynamics Manual,* Acupuncture Colleges (Australia), pp 220.

Schnyer, R and Allen, J J B 2002, 'Bridging the Gap in Complementary and Alternative Medicine Research: Manualization as a Means of Promoting Standardization and Flexibility of Treatment in Clinical Trials of Acupuncture', *The Journal of Alternative and Complementary Medicine*, vol. 8, no. 5, pp. 623-634.

Schnyer, R, Conboy, L, Jacobson, E, McKnight, P, Goddard, T, Moscatelli, F, Legedza, A, Kerr, C, Kaptchuk, T J and Wayne, P 2005, 'Development of a chinese Medicine Assessment Measure: An Interdisciplinary Approach Using the Delphi Method', *The Journal of Alternative and Complementary Medicine*, vol. 11, no. 6, pp. 1005-1013.

Schnyer, R, Wayne, P, Kaptchuk, T J, Cheng, X, Zhang, Z and Stason, W 2006, 'Standardization of Individualized Treatments in a Randomized Controlled Trial of Acupuncture for Stroke Rehabilitation', *The Journal of Alternative and Complementary Medicine*, vol. 12, no. 2, pp. 106-109.

Schnyer, R N and Allen, J B 2001, *Acupuncture in the treatment of depression: A manual for practice and research*, Churchill Livingstone, Edinburgh.

Seeff, L B, Miller, R N, Rabkin, C S, Buskell-Bales, Z, Straley-Eason, K D, Smoak, B L, Johnson, L D and Lee, S R 2000, '45-Year Follow-up of Hepatitis C Virus Infection in Healthy Young Adults', *Annals of Internal Medicine*, vol. 132, no. 2, pp. 105-111.

Simmonds, P 2001, '2000 Fleming Lecture. The origin and evolution of hepatitis viruses in humans', *Journal of General Virology*, vol. 82, pp. 693-712.

Simmonds, P, Mellor, J, Craxi, A, Sanchez-Tapias, J-M, Alberti, A, Prieto, J, Colombo, M, Rumi, M G, Lo Iacano, O, Ampurdanes-Mingall, S, Forns-Bernhardt, X, Chemello, L, Civeira, M-P, Frost, C and Dusheiko, G 1996, 'Epidemiological, clinical and therapeutic associations of hepatitis C types in western European patients', *Journal of Hepatology*, vol. 24, no. 5, pp. 517-524.

Stern, E 1997, 'Two Cases of Hepatitis C Treated with Herbs and Supplements', *The Journal of Alternative and Complementary Medicine*, vol. 3, no. 1, pp. 77-82.

Stux, G, Hammerschlag, R 2001, *Clinical Acupuncture Scientific Basis,* Springer-Verlag, Germany, pp. 188

Sung, J J Y, Leung, W K, Ching, J Y L, Lao, L, Zhang, G, Wu, J C Y, Liang, S M, Xie, H, Ho, Y P, Chan, L S, Berman, B and Chan, F K L 2004, 'Agreements among traditional Chinese medicine practitioners in the diagnosis and treatment of irritable bowel syndrome', *Alimentary Pharmacology and Therapeutics*, vol. 20, pp. 1205-1210.

The Academy of Traditional Chinese Medicine 1975, *An Outline of Chinese Acupuncture*, People's Republic of China, pp. 272.

Thomas, D L and Seeff, L B 2005, 'Natural History of Hepatitis C', *Clinics in Liver Disease*, vol. 9, pp. 383-398.

Tisminetzky, S G, Gerotto, M, Pontisso, P, Chemello, L, Ruvoletto, M G, Baralle, F and Alberti, A 1994, 'Genotypes of hepatitis C virus in Italian patients with chronic hepatitis C', *International Hepatological Communications*, vol. 2, no. 2, pp. 105-112.

Unschuld, P U 2003, *Huang Di Nei Jing Su Wen*, University of California press, Berkley.

van der Poel, C L and Cuypers, H T 1994, 'Hepatitis C Virus Six Years On', *Lancet*, vol. 344, no. 8935, p. 1475.

Vincent, C 1990, 'Credibility asessment in trials of acupuncture', *Complementary Medical Research*, vol. 4, no. 1, pp. 8-11.

Vincent, C A, Richardson, P H, Black, J J and Pither, C E 1989, 'The Significance of Needle Placement Site in Acupuncture', *Journal of Psychosomatic Research*, vol. 33, no. 4, pp. 489 - 496.

Vogt, M, Lang, T, Frosner, G, Klingler, C and al, e 1999, 'Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening', *New England Journal of Medicine*, vol. 341, no. 12, pp. 866-870.

Walsh, S and King, E 2008, *Pulse Diagnosis A Clinical Guide*, Churchill Livingstone.

Wang, R and Seifert, G 1996, 'The Use of TCM in the Treatment of Hepatitis', *Pacific Journal of Oriental Medicine*, vol. 8, pp. 53-56.

Ware, J E, Bayliss, M S, Mannocchia, M, Davis, G L and Group, I H I T 1999, 'Health-Related Quality of Life in Chronic Hepatitis C: Impact of Disease and Treatment Response', *Hepatology*, vol. 30, no. 2, pp. 550-555.

Ware, J E, Bungay, K, Gandek, B and Bayliss, M 1994, 'Assessment of the Health-Related Quality of Life (HQL) of Patients with Chronic Hepatitis C (CHC)', *Gastroenterology*, vol. 106, no. April, p. A33.

White, A R, Filshie, J and Cummings, T M 2001, 'Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding', *Complementary Therapies in Medicine*, vol. 9, pp. 237-245.

White, P, Bishop, F, Hardy, H, Abdollahian, S, White, A, Park, J, Kaptchuk, T J and Lewith, G 2008, 'Southampton needle sensation questionnaire: development and validation of a measure to gauge acupuncture needle sensation', *Journal of Alternative and Complementary Medicine*, vol. 14, no. 4, pp. 373-379.

WHO 2007, *WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region*, WHO.

Wieland, S F and Chisari, F V 2005, 'Stealth and Currning: Hepatitis B and Hepatitis C Viruses', *Journal of Virology*, vol. 79, no. 15, pp. 9369-9380.

Wiese, M, Berr, F, Lafrenz, M, Porst, H, Oesen, U and Group, f t E G H C S 2000, 'Low Frequency of Cirrhosis in a Hepatitis C (Genotype 1b) Single-Source Outbreak in Germany: A 20-Year Multicenter Study', *Hepatology*, vol. 32, no. 1, pp. 91-96.

Wiseman, N and Ye, F 1998, *A Practical Dictionary of Chinese Medicine*, Second Edition edn, Paradigm Publications, 44 Linden Street, Brookline, Massachusetts 02146 USA.

Zaslawski, C, Rogers, C, Garvey, M, Ryan, D, Yang, C X and Zhang, S P 1997, 'Strategies to Maintain the Credibility of Sham Acupuncture Used as a Control Treatment in Clinical Trials', *The Journal of Alternative and Complementary Medicine*, vol. 3, no. 3, pp. 257-266.

APPENDIX 1: Comprehensive report on HCV risk factors/transmission, current Australian profile, global and Australian snapshot and epidemiology

Risk factors/transmission

There are a number of risk factors for contracting HCV, many of which people unknowingly engage in, thereby putting themselves at risk. The leading risk behaviour responsible for 80 percent of current infections and 90 percent of new infections is the sharing of injecting equipment by IDUs. According to the Hepatitis C Council of NSW (HCCNSW) fact sheet it was estimated in 2002 that 55% of those with HCV were currently injecting. In 1997 it was estimated that 100,000 Australians regularly injected drugs, with an additional 175,000 involved in occasional injecting without dependence or social disruptions (NHCS 2005). In support of this, a study reported that 57% of males and 61% females that attended a needle and syringe program reported that they were HCV positive (NCHECR 2006).

Other modes of HCV transmission include:

- non-sterile medical or dental procedures. Anecdotal evidence suggests that approximately 10-15 percent of people with HCV are from culturally and linguistically diverse backgrounds which have high HCV prevalence. In particular are those born in the Middle East where HCV affects four percent of the population, southern Europe (2.5%), Asia (2.1-4%), and Africa which has very little data and percentages vary between different localities. The risk of HCV transmission through medical procedures in Australia is considered minimal due to the introduction of standard infection control procedures;
- non-sterile tattooing or body piercing procedures;
- needle-stick injuries and accidental exposure to infected blood or blood products;
- blood-to-blood contact due to physical assault;
- mother-to-child transmission during pregnancy and delivery (less than 5 percent of vertical transmission);
- Sharing personal toiletries such as toothbrushes and razors.

Incarceration is also an independent risk factor because of the high prevalence of HCV amongst the custodial population due to such behaviours as tattooing and body piercing.

The current Australian profile (estimated percentages) of people with HCV include IDUs 82.3%, Australian immigrants 10.9%, recipients of contaminated blood/blood products or through other exposure routes such as unsterile tattooing or mother-to-child transmission 6.8% see Figure 1).

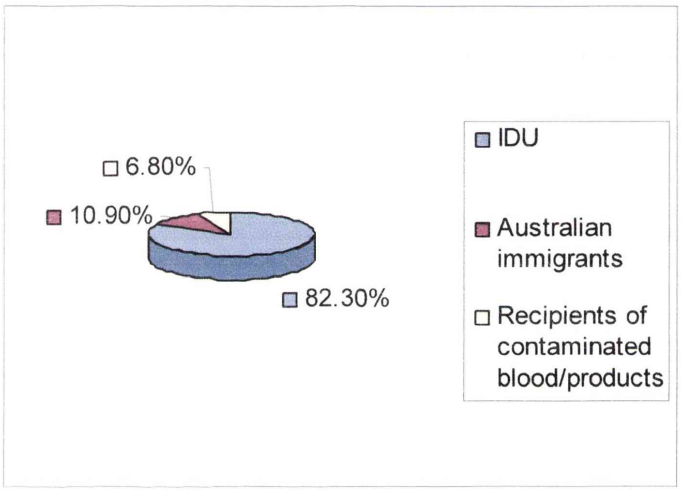


Figure 1: Model of current Australian HCV population

Before the introduction of blood screening in Australia in 1990, transfusion of HCV infected blood and blood products contributed to the transmission of the virus. Approximately five to ten percent of people currently infected with HCV acquired the virus through blood and blood products during the 1970s and 1980s. Haemophiliacs who received large quantities of blood products have a high incidence of HCV. A large percentage of people with haemophilia in Australia who have the human immunodeficiency virus (HIV) are also co-infected with HCV.

The virus is not transmitted through casual contact and is not defined as a sexually transmitted infection although uncommonly sexual transmission has been documented.

Global snapshot

The World Health Organisation has estimated that 170 million people worldwide are infected with the HCV.

Australian snapshot

HCV infection has been a notifiable disease in all Australian States and Territories since 1995. It is one of the most commonly reported notifiable infectious diseases in Australia. At the end on 2005, a total of over 225,000 HCV diagnoses were reported to State and Territory surveillance systems (HCVPWG 2006; NCHECR 2006). Approximately 80 per cent of people with HCV in Australia are estimated to have been diagnosed (Australian Government 2005).

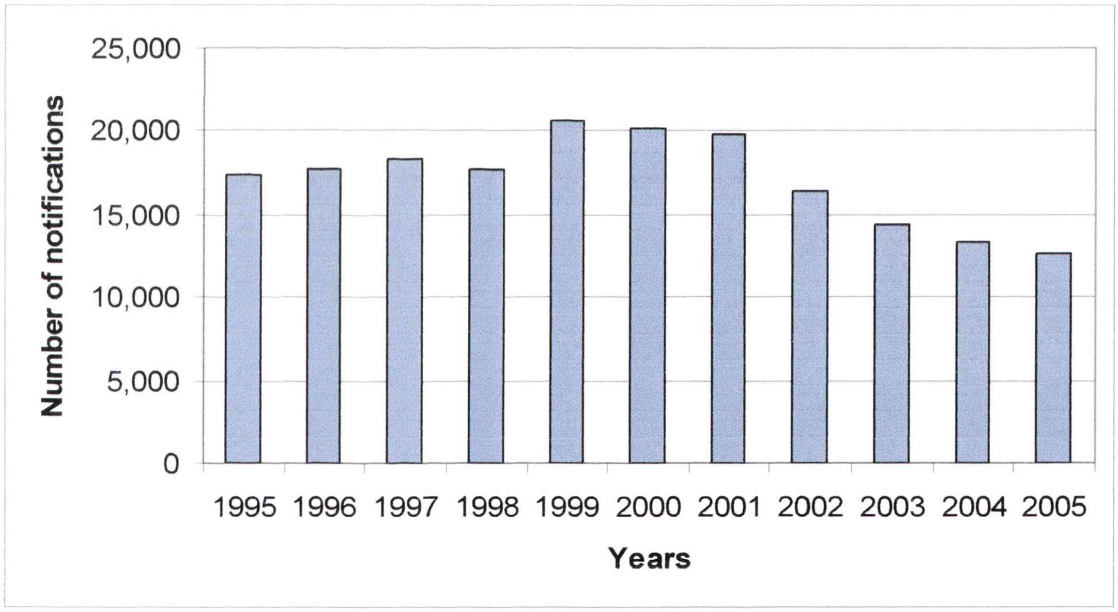


Figure 2: Notification rates of HCV in Australia (National Notifiable Diseases Surveillance System

HCV notifications increased from 17,296 to over 20,000 new HCV diagnoses annually during the period 1995 - 2000, but has since declined to 15,000 - 13,000 notifications during the 2002 to 2005 period (HCVPWG 2006; NCHECR 2006) (see Figure 2). Between 1998 and 2005 various data sources have indicated that there was a reduction in heroin supplies in Australia (Day et al 2003; Topp et al 2003). As IDU is the major risk

behaviour for transmission of HCV, it was widely acknowledged that this caused a reduction in IDU incidences and therefore a reduction in HCV transmission.

The long asymptomatic stage of HCV infection and its slow disease progression make future medical demands difficult to assess. Estimates of future HCV outcomes are vital for government health planning in terms of treatment needs and preventive measures. Reliable estimates and projections of HCV infection rates and long term sequelae are necessary. For instance, if all those infected with HCV were to progress to chronic liver failure or liver cancer, this would become an intolerable burden on health resources. Mathematical models have been developed to estimate both the pattern of past HCV incidence and the progression of HCV in Australia. HCV transmission has been modelled on two components. Firstly, HCV incidence through injecting drug use which is based on assumed patterns of injecting drug use and secondly HCV prevalence in immigration. Using this mathematical model it is estimated that there were around 264,000 people living with HCV antibodies in Australia in 2005 (plausible range 206,000 to 318,000) (HCVPWG 2006). The HCCNSW estimated that over half of these people live in NSW.

Approximately 65% of HCV notifications have been people aged 20-39 years with approximately 35% of notifications from females (AGDHA 2006). However, the proportion of female HCV notifications is larger than 35% in younger age-groups, particular in the 15-19 group where there are similar numbers of men and women notified (AGDHA 2006).

Recent evidence shows that the number of new HCV infections may be declining. It is projected that by the year 2020 there will be between 321,000 - 836,000 people in Australia living with HCV (Australian Government 2005; Law et al 2003). This projection is dependent upon future harm minimisation programs and injecting drug patterns.

Conservative estimates of direct and indirect costs of HCV infection to the community in 1996-97 amounted to $107.5 million for people with existing infections, with estimated lifetime costs rising by $46.6 million for every 1,000 new infections.

Epidemiology

Within the general community there is a one percent HCV prevalence rate. The National Hepatitis C Strategy 2005-2008 recognised that action must focus towards high prevalence populations for effective outcomes. These groups include;

- approximately 80 per cent of current infections and 90 percent of new infections are estimated to be due to unsafe injecting drug use practices. In 1997 it was estimated that 100,000 Australians regularly injected drugs, with an additional 175,000 involved in occasional injecting without dependence or social disruption;
- 22,000 (range 13,000 to 37,000) indigenous Australians were living with HCV antibodies in 2005. Of these 16,000 (range 10,000 to 28,000) were living with chronic HCV infection.
- Of the 30,000 to 35,000 people held in Australia prisons during 2005, it was estimated that between 30 to 40 percent of all prisoners (50 to 70 percent of female prisoners) have HCV infection.

Of the estimated 264,000 people living with HCV antibodies in Australia at the end of 2005, it was estimated that;

- 67,000 (25%) had cleared their HCV infection
- 154,000 (58%) had chronic HCV infection and stage F0/1 liver disease
- 38,000 (15%) had chronic HCV infection and stage F2/3 liver disease
- 5,300 (2%) were living with HCV related cirrhosis

During 2005 it was estimated that:

- 210 people developed HCV related liver failures
- 105 people developed HCV related HCC.

Current medical treatment

The current medical treatment for HCV is a combination of two drugs, pegylated interferon and ribavirin, commonly known as pegylated combination therapy. Treatment duration and success rate is dependent upon the HCV genotype.

Interferon is a glycoprotein formed by cells exposed to a virus or another foreign particle of nucleic acid to help defend against infection. Synthetically manufactured interferon in large doses can help to reduce HCV levels in the body and slow down the disease process. Pegylated interferon has an altered molecular structure which ensures it remains circulating in the bloodstream for a longer period of time compared to standard unpegylated interferon. Pegylated combination therapy involves a once-weekly injection as opposed to thrice-weekly injections for standard interferon. Ribavirin is a drug which helps to reduce the rate of HCV replication. Ribavirin has been shown to work optimally in combination with interferon rather than as a treatment on its own.

Combination therapy is listed on the Pharmaceutical Benefits Scheme (PBS) and is available for those people who meet specific criteria. Under the PBS combination therapy will cost no more than $20 per month. However, without government subsidy, combination therapy costs approximately $22,000 per year.

Currently 50 percent of people who undergo combination therapy are cured. Cure is defined as no detectable virus in the blood six months after treatment completion. Treatment time and response rate is dependent upon virus genotype. Genotypes 2 and 3 (42% of the HCV infected population) require six months of treatment and have an 80% clearance success rate. Genotype 1 which is the dominant genotype in Australia (50% of the HCV infected population) requires from 12 to 24 months of treatment and only has a 35% clearance success rate. There is a much lower response rate in individuals with more advanced disease, such as cirrhosis. Effective early stage HCV treatment may be able to prevent much of the end-stage liver disease associated with untreated HCV.

Side effects of combination therapy vary for each person and often decrease as treatment continues. A potential side effect of Ribavirin is anaemia caused by the destruction of red blood cells. Blood counts are monitored closely within the first few weeks of treatment to evaluate if there needs to be a dose reduction. Ribavirin has also been linked to birth defects in trial animals. Therefore Ribavirin must not be prescribed for pregnant women, those currently breast feeding, or for any person (male or female) not taking contraceptive precautions during and for several months following treatment. Interferon alfa has been associated with depression and suicide and therefore all users are monitored carefully. Due to the side effects of combination therapy and the previously mandatory liver biopsy examination pre-treatment test previously only 2,000 people underwent combination therapy treatment per annum. From April 2006 liver biopsy is no longer a mandatory requirement for people wanting to access combination therapy treatment. Therefore it is expected that the number of people wishing to undertake combination therapy will increase.

References:

AGDHA 2006, *National Notifiable Diseases Surveillance System*.

Australian Government, DHAC 2005, *National Hepatitis C Strategy 2005-2008*, Report Number 0 642 82656 0, Australian Government, Department of Health and Ageing.

Day, C, Topp, L, Rouen, D, Darke, S, Hall, W and Dolan, K 2003, 'Decreased heroin availability in Sydney in early 2001', *Addiction*, vol. 98, no. 1, pp. 93-95.

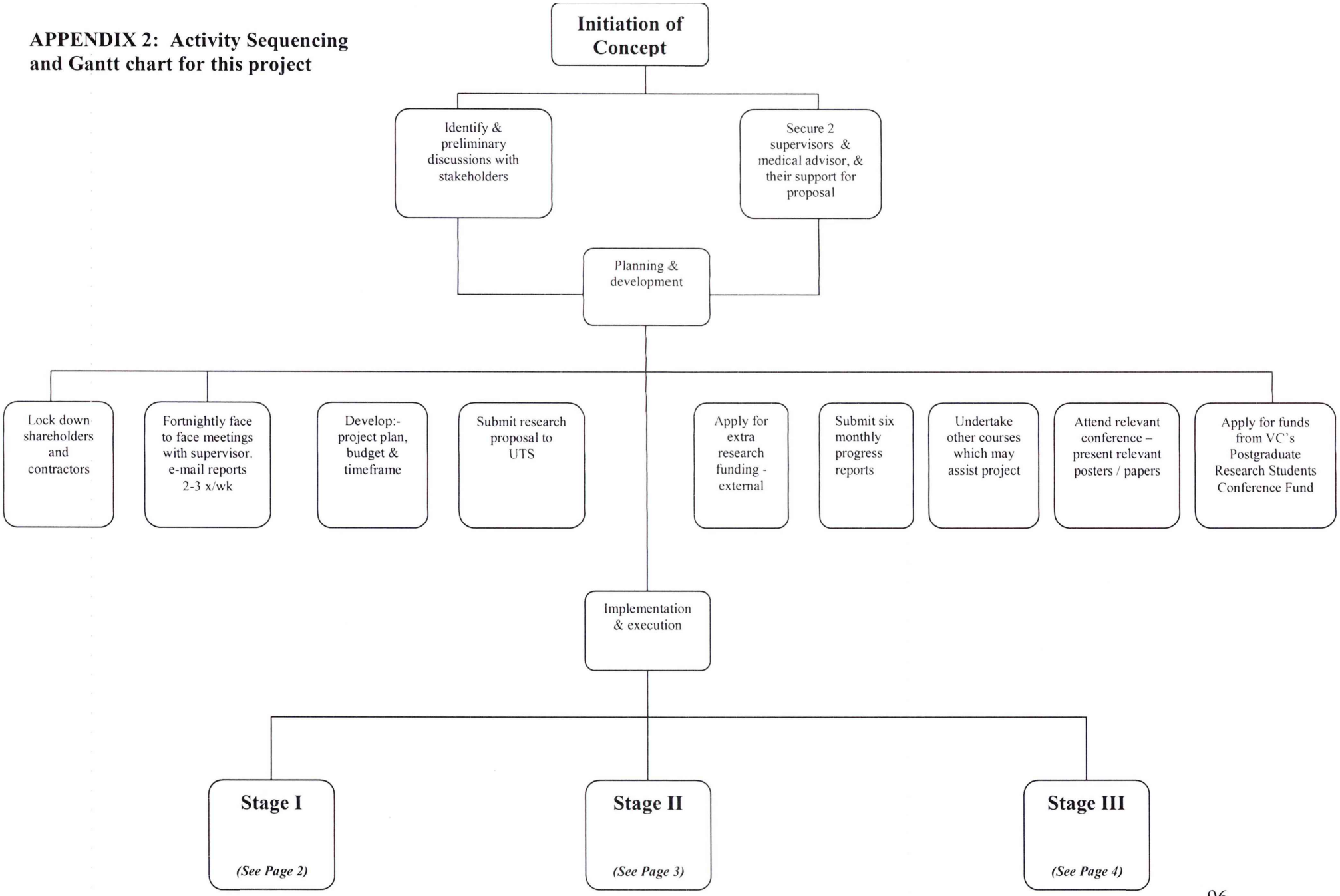
HCVPWG 2006, *Hepatitis C Virus Projections Working Group*.

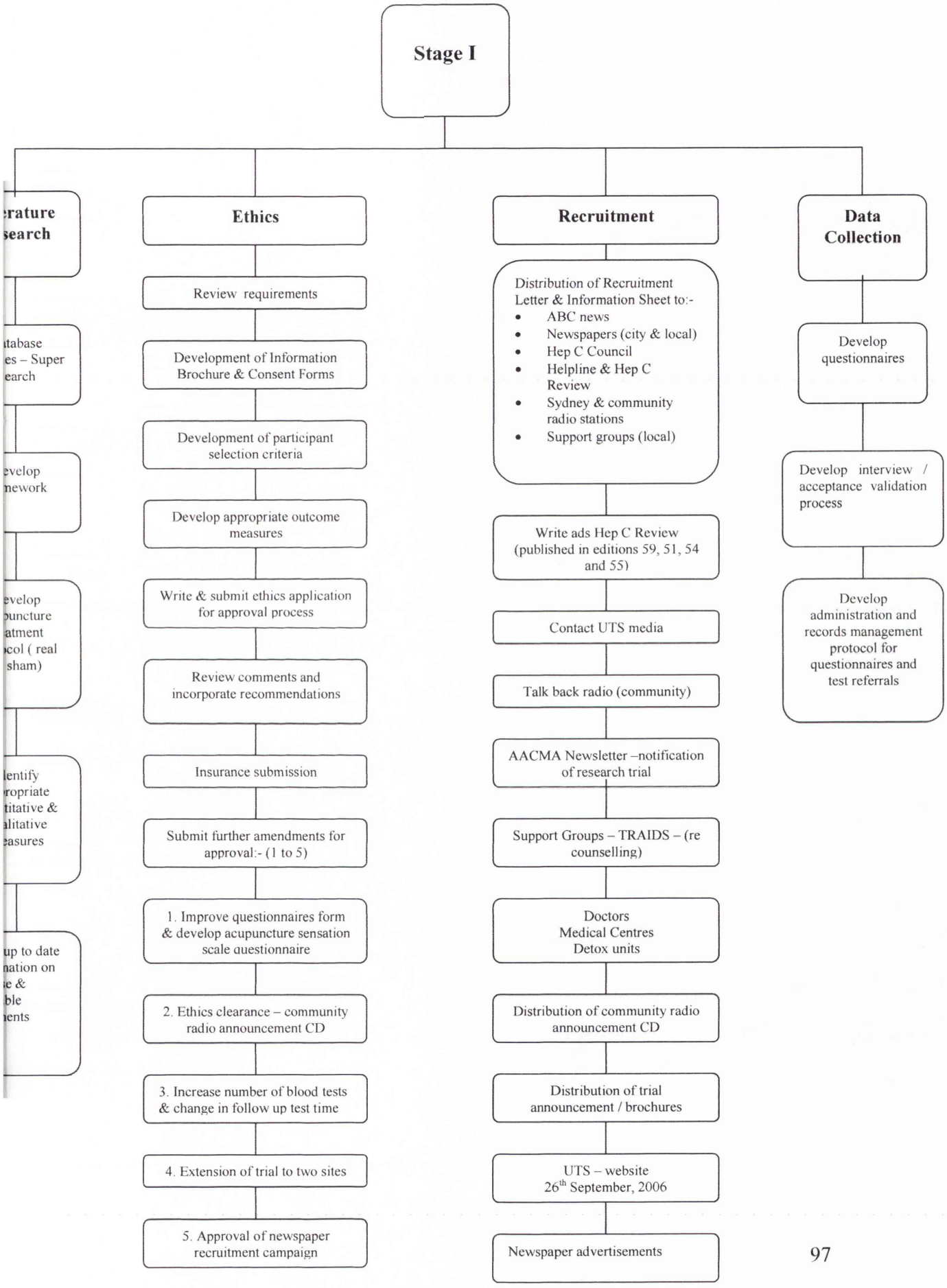
Law, M G, Dore, G J, Bath, N, Thompson, S, Crofts, N, Dolan, K, Giles, W, Gow, P, Kaldor, J, Loveday, S, Powell, E, Spencer, J and Wodak, A 2003, 'Modelling hepatitis C virus incidence, prevalence and long-term sequelae in Australia, 2001', *International Journal of Epidemiology*, vol. 32, no. 5, pp. 717-724.

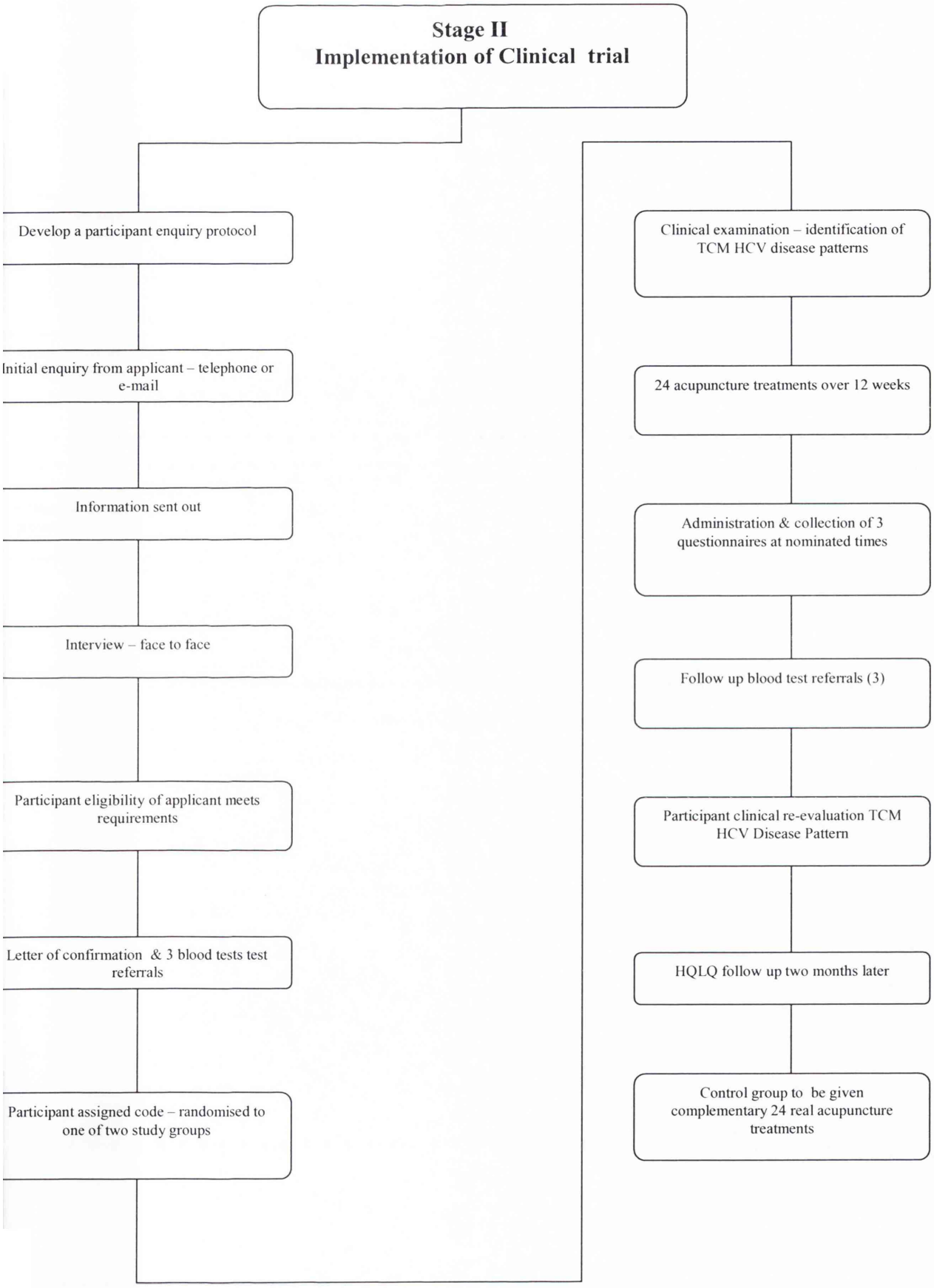
NCHECR 2006, *HIV/AIDS, viral hepatitis & sexually transmissible infections in Australia Annual Surveillance Report 2006*.

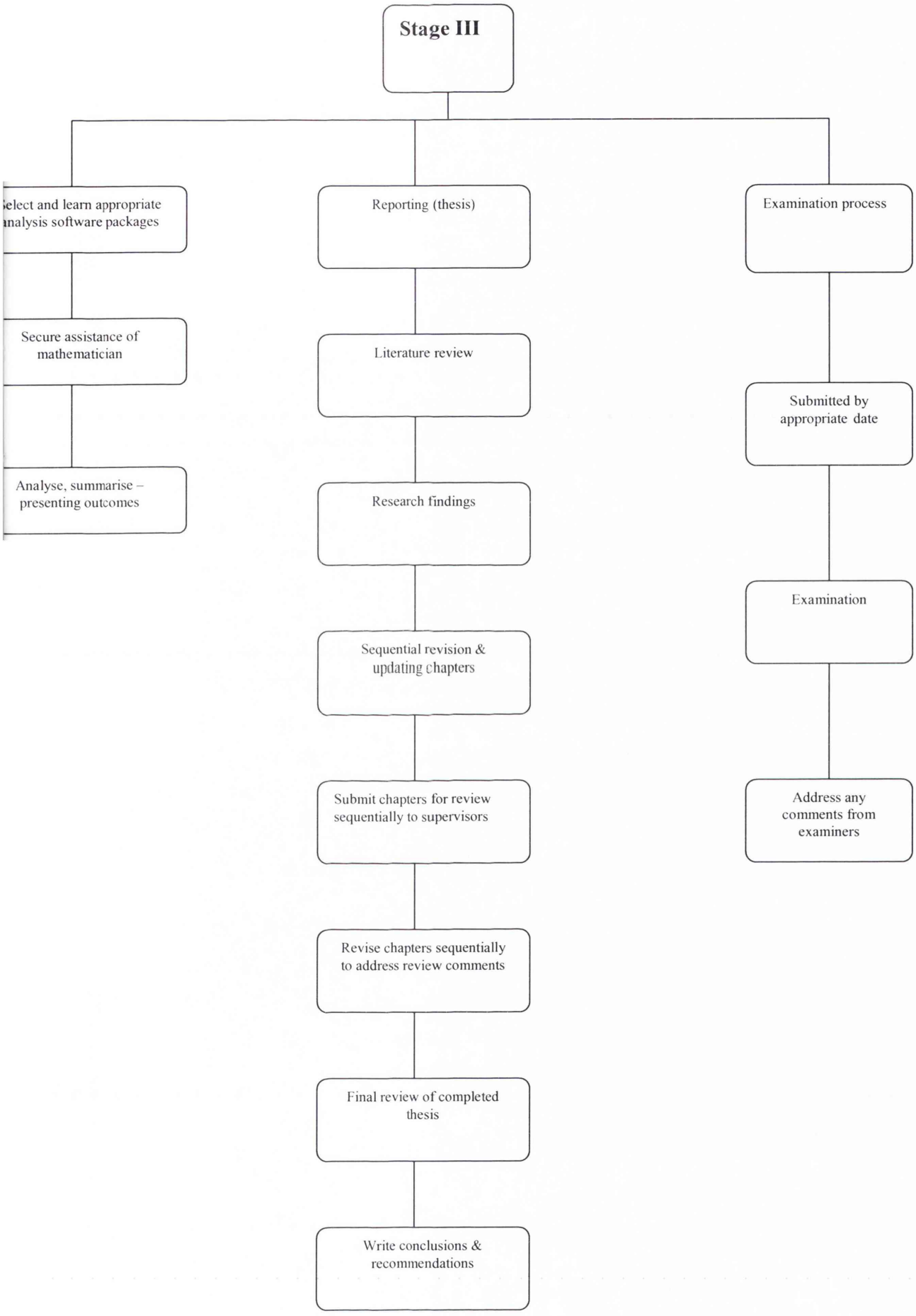
Topp, L, Day, C and Degenhardt, L 2003, 'Changes in patterns of drug injection concurrent with a sustained reduction in the availability of heroin in Australia', *Drug and Alcohol Dependence*, vol. 70, no. 3, pp. 275-286.

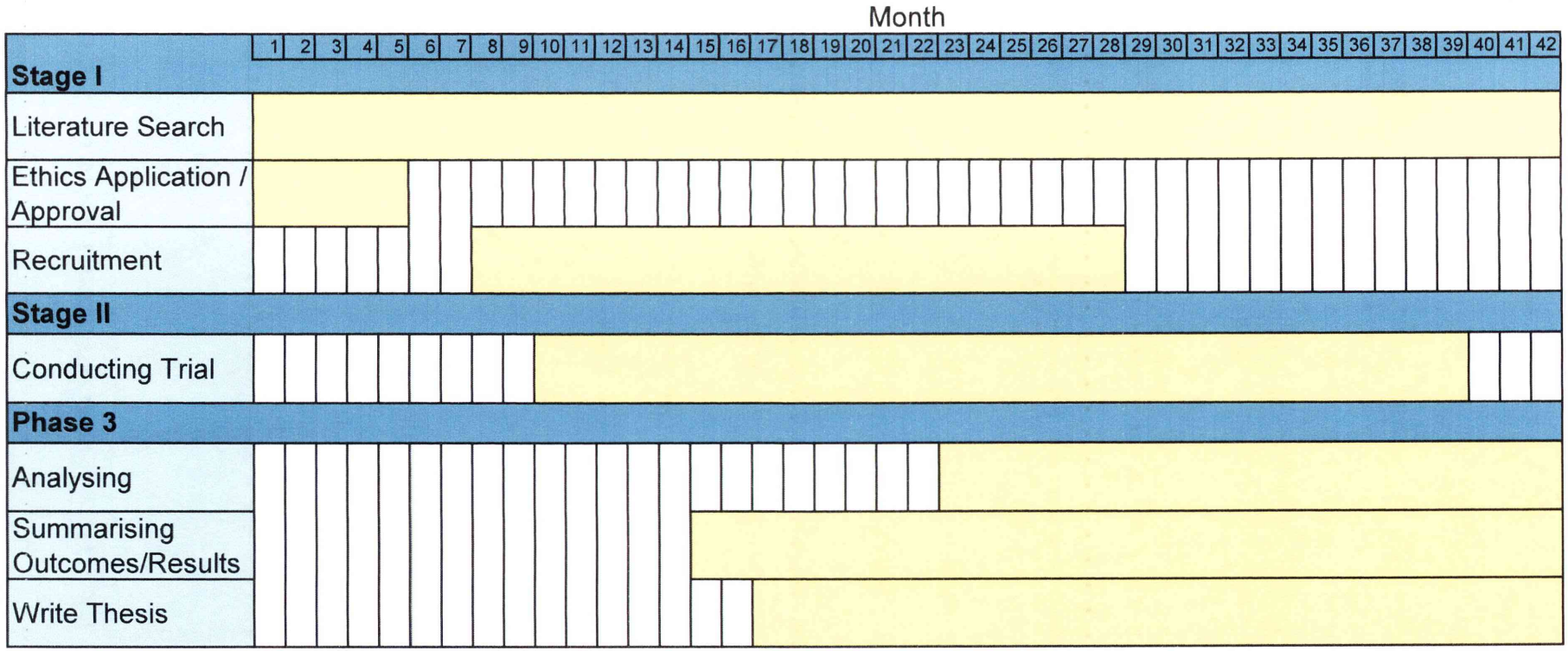
APPENDIX 2: Activity Sequencing and Gantt chart for this project




Stage I
erature search
tabase es – Super earch
evelop nework
evelop puncture atment col (real sham)
lentify ropriate titative & alitative easures
up to date nation on e & ble nents
Ethics
Review requirements
Development of Information Brochure & Consent Forms
Development of participant selection criteria
Develop appropriate outcome measures
Write & submit ethics application for approval process
Review comments and incorporate recommendations
Insurance submission
Submit further amendments for approval:- (1 to 5)
1. Improve questionnaires form & develop acupuncture sensation scale questionnaire
2. Ethics clearance – community radio announcement CD
3. Increase number of blood tests & change in follow up test time
4. Extension of trial to two sites
5. Approval of newspaper recruitment campaign
Recruitment
Distribution of Recruitment Letter & Information Sheet to:-
ABC news
Newspapers (city & local)
Hep C Council
Helpline & Hep C Review
Sydney & community radio stations
Support groups (local)
Write ads Hep C Review (published in editions 59, 51, 54 and 55)
Contact UTS media
Talk back radio (community)
AACMA Newsletter –notification of research trial
Support Groups – TRAIDS – (re counselling)
Doctors
Medical Centres
Detox units
Distribution of community radio announcement CD
Distribution of trial announcement / brochures
UTS – website
26th September, 2006
Newspaper advertisements
Data Collection
Develop questionnaires
Develop interview / acceptance validation process
Develop administration and records management protocol for questionnaires and test referrals


Stage II
Implementation of Clinical trial
Develop a participant enquiry protocol
Initial enquiry from applicant – telephone or e-mail
Information sent out
Interview – face to face
Participant eligibility of applicant meets requirements
Letter of confirmation & 3 blood tests test referrals
Participant assigned code – randomised to one of two study groups
Clinical examination – identification of TCM HCV disease patterns
24 acupuncture treatments over 12 weeks
Administration & collection of 3 questionnaires at nominated times
Follow up blood test referrals (3)
Participant clinical re-evaluation TCM HCV Disease Pattern
HQLQ follow up two months later
Control group to be given complementary 24 real acupuncture treatments


Stage III
Select and learn appropriate analysis software packages
Secure assistance of mathematician
Analyse, summarise – presenting outcomes
Reporting (thesis)
Literature review
Research findings
Sequential revision & updating chapters
Submit chapters for review sequentially to supervisors
Revise chapters sequentially to address review comments
Final review of completed thesis
Write conclusions & recommendations
Examination process
Submitted by appropriate date
Examination
Address any comments from examiners


Month
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42
Stage I
Literature Search
Ethics Application / Approval
Recruitment
Stage II
Conducting Trial
Phase 3
Analysing
Summarising Outcomes/Results
Write Thesis

ENDIX 3.1: Information Sheet and Brochures

UNIVERSITY OF TECHNOLOGY SYDNEY

A CONTROLLED TRIAL OF ACUPUNCTURE FOR THE TREATMENT FOR PEOPLE WHO ARE HEPATITIS C ANTIBODY POSITIVE: A PILOT STUDY

(UTS HREC REF NO. 2005-37A)

WHO IS DOING THE RESEARCH?

My name is Christine Berle and I am a current Masters research student at UTS. My Chief Supervisor is Mr Christopher Zaslawski, Co-supervisor Dr Deirdre Cobbin and Co-investigator, Dr Jacob George.

WHAT IS THIS RESEARCH ABOUT?

This research is to find out whether acupuncture treatment has an effect on the health outcomes of people who have Hepatitis C.

IF I SAY YES, WHAT WILL IT INVOLVE?

You will be randomised into one of two groups; one group receiving real acupuncture and the other receiving sham acupuncture (needle put into non acupuncture points). Initially your medial history will be taken. Then three blood samples will be taken (at two week intervals) during the six week period prior to starting the acupuncture treatment. You will then receive two acupuncture treatments (approximately 1 hour per session) per week for twelve weeks (a total of 24 treatments) at an acupuncture clinic (Guildford or Broadway). A blood sample will be taken at the completion of the acupuncture treatments, another one month later and a final blood sample two months following completion (a total of 6). Pathology sampling/tests have been organised through various Douglass Hanly Moir Pathology clinics which would be at a convenient/local location for each participant. You will be expected to complete a Hepatitis C Quality of Life Questionnaire (HQLQ) prior to treatment, monthly for three months and at the follow up six months. It is expected that the sessions which include questionnaires will take an extra half hour.

You will also be requested to participate in an acupuncture monitoring questionnaire during the second, sixth and twelfth weeks to evaluate whether you think you have been receiving the real or sham treatment. However you will not officially know until debriefing (which will be approximately one month after you have completed the trial) as to which group you were allocated. At this time you will receive a copy of your test results. Overall group results will not identify any individual and will be disseminated after the analysis of all the results (which will include the two month follow-up).

If there has been a positive outcome for the real acupuncture treatment group and you were part the sham acupuncture group, you will be offered twenty four free real acupuncture treatments the same as that administered to the acupuncture treatment group.

ARE THERE ANY RISKS?

There are minimal risks. Acupuncture procedure involves the insertion of fine "single use" disposable needles into the skin. Side effects in acupuncture are infrequent and generally limited to bruising and spot bleeding. On rare occasions patients may feel faint and nauseous. In the unlikely event that this occurs, the treatment session would be terminated.

WHY HAVE I BEEN ASKED?

You have been asked through a recruitment campaign because you:-

- have a documented positive serum Hepatitis C Virus PCR (polymerase chain reaction) viral detection test
- are aged between 18 to 70 years
- have had an elevated alanine aminotransferase (ALT), (≥57 and ≤350 U/L) during the last 6 months prior to enrolment in this project

Unfortunately you will be excluded from the research project if you have:-

- recently (within the last 3 months of screening) or are currently undertaking combination therapy (interferon/ribavirin) and/or
- have a current alcohol consumption greater than 2 standard drinks daily (42 g [1.5 oz], 80 proof; 336 g [12 oz], 5% beer; or 150 g [5 oz], 12%-17% wine)
- been a liver transplant recipient
- currently participating in another treatment trial (includes herbal trials)

DO I HAVE TO SAY YES?

You don't have to participant if you don't want to. As there is currently pharmaceutical treatment available for Hepatitis C, you may prefer to choose combination therapy (interferon/ribavirin). If during the trial you decide you would prefer to have combination therapy I will thank you for your time and will not contact you about this research again.

WHAT WILL HAPPEN IF I SAY NO?

Nothing. I will thank you for your time so far and won't contact you about this research again.

IF I SAY YES, CAN I CHANGE MY MIND LATER?

You can change your mind at any time and are under no obligation to advise why. I will thank you for your time so far and won't contact you about this research again.

WHAT IF I HAVE CONCERNS OR A COMPLAINT?

If you have concerns about the research that you think I or my supervisor can help you with, please feel free to contact me, Christine Berle at my clinic (9632 8989) or Chris Zaslawski (9514 7856).

If you would like to talk to someone who is not connected with the research, you may wish to contact Susanna Davis, UTS Research Ethics Manager on 02 9514 9615, and quote this number (UTS HREC REF NO. 2005-37A).

AHEC refers to the Australian Health Ethics Committee. AHEC is a principal subcommittee of the National Health and Medical Research Council (NHMRC). Ethics committees registered with AHEC must comply with its guidelines and make an annual compliance report. The UTS HREC is a registered AHEC committee. Page 3 of 16 of UTS Policies – Ethical Conduct of Research Policy Appendix 2.

A CONTROLLED TRIAL OF ACUPUNCTURE TREATMENT FOR PEOPLE WHO HAVE HEPATITIS C: A PILOT STUDY

(UTS HREC REF NO. 2005-37A)

A clinical trial to find out whether acupuncture treatment has an effect on the health outcomes of people with hepatitis C is being undertaken as part of a Masters Degree research project at the University of Technology, Sydney. Recruitment of participants will continue until the mid / end September depending on interest.

To be eligible participants will:

- have a documented positive PCR viral detection test
- be aged between 18 to 70 years
- have had an elevated ALT blood test ($\geq$57 and $\leq$350 U/L) during the last 6 months
- not currently, or within the last three months have undertaken combination therapy

Treatment will include:

- three blood tests two weeks apart prior to acupuncture treatment
- two acupuncture treatments per week over a twelve week period (24 treatments)
- another three blood tests (one on completion of treatment, one a month later and another two months after completion of treatment)
- participants will be expected to complete questionnaires throughout the trial.

Participants will be randomised into one of two groups; one group receiving real acupuncture and the other receiving sham acupuncture (needle put into non acupuncture points). Participants will not be informed until debriefing (approximately one month after completion of the trial) as to which group they were allocated. All participants who were part of the sham group will then be offered twenty-four free real acupuncture treatments the same as that administered to the real acupuncture group.

Treatment will be available at two clinic locations:

- University of Technology (city campus) – Monday and Thursday afternoons
- Guildford – Tuesday and Saturday

If you would like an information brochure or want to know more about this project please contact Christine Berle on (02) 9632 8989 or email Christine.A.Berle@student.uts.edu.au

APPENDIX 3.3: Information Sheet and Brochures

University of Technology, Sydney

A CONTROLLED TRIAL OF ACUPUNCTURE FOR THE TREATMENT FOR PEOPLE WHO ARE HEPATITIS C ANTIBODY POSITIVE: A PILOT STUDY

(UTS HREC REF NO. 2005-37A)

P1

ACKNOWLEDGEMENTS
- Hepatitis C Council of NSW
- Helio Supply Co. Pty. Ltd.
- Australian Acupuncture & Chinese Medicine Association Ltd (AACMA)

If you want to know more about this project please contact Christine Berle on 9632 8989 or email:
Christine.A.Berle@student.uts.edu.au

P6

WHO IS DOING THE RESEARCH?
The trial is being undertaken at the University of Technology, Sydney. Christine Berle is a current Masters coordinating the project. Chief Supervisor is Dr Christopher Zaslawski, Co-supervisor Dr Deirdre Cobbin and Co-investigator, Dr Jacob George.

WHAT IS THIS RESEARCH ABOUT?
This research is to find out whether acupuncture treatment has an effect on the health outcomes of people who have Hepatitis C.

WHAT IF I HAVE CONCERNS OR A COMPLAINT?
If you have concerns about the research you can contact Christine Berle on 9632 8989 or Chris Zaslawski on 9514 7856.

If you wish to talk to someone who is not connected with the research, you may contact Susanna Davis, UTS Research Ethics Manager on 9514 9615, and quote this number (UTS HREC REF NO. 2005-37A). The UTS HREC is a registered Australian Health Ethics Committee (AHEC). AHEC is a principal subcommittee of the National Health and Medical Research Council (NHMRC). Ethics committees registered with AHEC must comply with its guidelines and m an annual compliance reports.

P5

IF I SAY YES, WHAT WILL IT INVOLVE?
You will be randomised into one of two groups: one group receiving real acupuncture and the other receiving sham acupuncture (needle put into non acupuncture points). Initially your medical history will be taken. Then three blood samples will be taken (at two week intervals) during the six week period prior to starting the acupuncture treatment. You will then receive two acupuncture treatments (approximately 1 hour per session) per week for twelve weeks (a total of 24 treatments). A blood sample will be taken at the completion of the acupuncture treatments another one month later and another two months following the completion of treatment (a total of 6). Pathology sampling/tests have been organised through various Douglass Hanly Moir Pathology clinics which would be at a convenient/local location for each participant. You will be expected to complete a Hepatitis C Quality of Life Questionnaire (HQLQ) prior to treatment, monthly for three months and at the follow up six months. It is expected that the sessions which include questionnaires will take an extra half hour.
You will also be requested to participate in an acupuncture monitoring questionnaire during the second, sixth and twelfth weeks to evaluate whether you think you have been receiving the real or sham

P2

treatment. However you will not officially know until debriefing (which will be approximately one month after you have completed the trial) as to which group you were allocated. At this time you will receive a copy of your test results. Overall group results will not identify any individual and will be disseminated after the analysis of all the results (which will include the six month follow-up).
If there has been a positive outcome for the real acupuncture treatment group and you were part the sham acupuncture group, you will be offered twenty four free real acupuncture treatments the same as that administered to the acupuncture treatment group.

ARE THERE ANY RISKS?
There are minimal risks. Acupuncture procedure involves the insertion of fine "single use" disposable needles into the skin. Side effects in acupuncture are infrequent and generally limited to bruising and spot bleeding. On rare occasions patients may feel faint and nauseous. In the unlikely event that this occurs, the treatment session would be terminated.

P3

ELLIGIBILITY CRITERIA?
- have a documented positive serum Hepatitis C Virus PCR (polymerase chain reaction) viral detection test
- are aged between 18 to 70 years
- have had an elevated alanine aminotransferase (ALT), (≥57 and ≤350 U/L) during the last 6 months prior to enrolment in this project

Unfortunately you will be excluded from the research project if you have:-
- recently (within the last 3 months of screening) or are currently undertaking combination therapy (interferon/ribavirin) and/or
- have a current alcohol consumption greater than 2 standard drinks daily (42 g [1.5 oz], 80 proof; 336 g [12 oz], 5% beer; or 150 g [5 oz], 12%-17% wine)
- been a liver transplant recipient
- currently participating in another treatment trial (includes herbal trials)

DO I HAVE TO SAY YES?
As there is currently pharmaceutical treatment available for Hepatitis C, you may prefer to choose combination therapy (interferon/ribavirin). If during the trial you decide you would prefer to have combination therapy you will be thanked for your time and will not be contacted about this research again.

P4

APPENDIX 4: Recruitment Strategy

Published articles included;

- Various newspaper articles; Parramatta Sun (Wednesday, August 10, 2005), Parramatta Advertiser (Wednesday, August 24, 2005 p 30), The Sydney Morning Herald (Postgraduate Study lift-out, September 12, 2005 p 7), The Sydney Morning Herald (Essential lift-out, October 10, 2006, p 10), Parramatta Advertiser (Wednesday, October 11, 2006), Parramatta Sun (Wednesday, October 18, 2006) and The Glebe (Thursday, March 22, 2007) (Appendix 4.1).
- The Hepatitis C Council of NSW printed four advertisements in The Hep C Review (Edition 50 September 2005, Edition 51 December 2005, Edition 54 September 2006 and Edition 55 December 2006) (Appendix 4.2).
- UTS published a notice in the universities monthly magazine U (June, 2006) (Appendix 4.3).

Radio;

- ABC Sydney Radio News, ABC Radio NSW Statewide and Sydney 2RN reported on the trial on Friday, August 12, 2005.
- Four studio radio interviews took place (2BFM Bankstown - December 13 and 20, 2005, 2GLF Liverpool – December 15, 2005 and 2SER Sydney – July 3, 2006 aired on Gaolbreak a month later).
- A community radio announcement CD (Appendix 4.4) was produced and circulated to 10 local radio stations (2GLF 89.3FM, BFM 100.9, Radio 106.5, 2RRR 88.5FM, 2NB 90.1, Radio 2SER, Radio Station The Edge, Radio 2CH 1170, Radio 2GB 873 and Radio 2RPH1224). To our knowledge only three stations repeatedly played the announcement (2BFM, 2GLF and 2SER).

Websites/internet;

- UTS posted a media release on the UTS website for one week in September 2006 (Appendix 4.5).
- HCCNSW posted a notice on the research section of their website and also sent out a notice on Heplink, an internet HCV forum. There were over 13 enquires from various agencies from this source.

- The AACMA (the major Australian acupuncture and Chinese medical association) sent a notice to all members advising them of the trial encouraging recruitment referral.

Doctor referrals;

- Several referrals were made by a local city practitioner and the medical adviser to the trial also made a referral.

Paid advertisements;

Recruitment was slow and difficult with only one in eight being either eligible or prepared to undertake a seven month (verum treatment) or ten months (control group) project, although many strategies had been put in place. It was decided that several paid newspaper advertisements would be placed in an effort to boost trial numbers. A 2MW (2 Module Wide – 9cm(h) x 13cm(w)) advertisement was published in Parramatta Advertiser (7th February and 7th March, 2007), Fairfield Advance (7th February, 7th March, 2007), The Glebe (8th February and 8th March, 2007), Eastern Suburbs Spectator, Paddington Times, Randwick Leader and Coogee Chronicle (weeks ending 23rd February, 2007 (Appendix 4.6). Editorial was also sought through these papers but only The Glebe published.

Appendix 4.1.1: Published in the Parramatta Sun, Wednesday, August 10, 2005, Page 9

Fairfax Community Newspapers News

A point about hep C

By **Isabell Petrinic**

A Guildford businesswoman is seeking 30 volunteers to test the efficacy of acupuncture in the treatment of hepatitis C.

Christine Berle, of the Acupuncture and Remedial Massage Clinic, Guildford, is undertaking the study for a master of science thesis at the University of Technology, Sydney.

The Hepatitis C Council of NSW has estimated that more than 250,000 Australians are infected with the hepatitis C virus.

'I'm not saying we are going to replace medicine but I think there is a place for [acupuncture]'
Christine Berle

Ms Berle said that estimated transmission rates for the virus had increased by 45 per cent in the past four years with no signs of slowing.

Ms Berle needs the volunteers to take part in a controlled trial of acupuncture for the treatment of people who are hepatitis C antibody-positive.

Her study is being undertaken with UTS academics Christopher Zaslawski and Dr Deirdre Cobbin, and Westmead Hospital hepatologist Dr Jacob George.

The reason for the study, which has support from the Hepatitis C Council of NSW, is to see if acupuncture has any effect on people with hepatitis C.

"Depending upon the outcome of this study, acupuncture may have the potential to have significant health and financial benefits to the Australian population, either as an adjunctive treatment or alongside pharmaceutical care," Ms Berle said.

"I'm not saying we are going to replace medicine but I think there is a place for [acupuncture]."

Ms Berle is a former vice-president of the World Federation of Acupuncture/Moxibustion Societies.

She was among the practitioners to lobby for health care rebates for acupuncture in the late 1970s.

To participate in the study, call Ms Berle on 9632 8989.

❑ A support group for people with hepatitis C meets on the first Thursday of each month at Parramatta Health Services, 158 Marsden Street. Details: 9843 3143.

Stuck on a good idea: Christine Berle practices acupuncture on a patient in Guildford. **Picture: Natalie Spiteri**

ɔendix 4.1.2: Published in the Parramatta Advertiser, Wednesday, August 24, 2005, Page 30

HEALTH

Fighting hepatitis C

PETA GARRETT

A PILOT study on acupuncture hopes to prove the power of the needle is as great as the tablet for some hepatitis C sufferers.

Guildford Chamber of Commerce president and acupuncture therapist Christine Berle is one of the researchers in the project, being run by the University of Technology, Sydney and Westmead Hospital.

Hepatitis C is a viral infection of the liver and is spread primarily by contact with human blood.

Ms Berle said during the mid-1990s people with hepatitis C who lived in a Sydney alcohol and other drugs rehabilitation centre reported a drop in liver cell damage after having acupuncture treatment for three months.

"We want to authenticate those observations and evaluate whether acupuncture treatment has an effect on the health outcomes of people who have hepatitis C," she said.

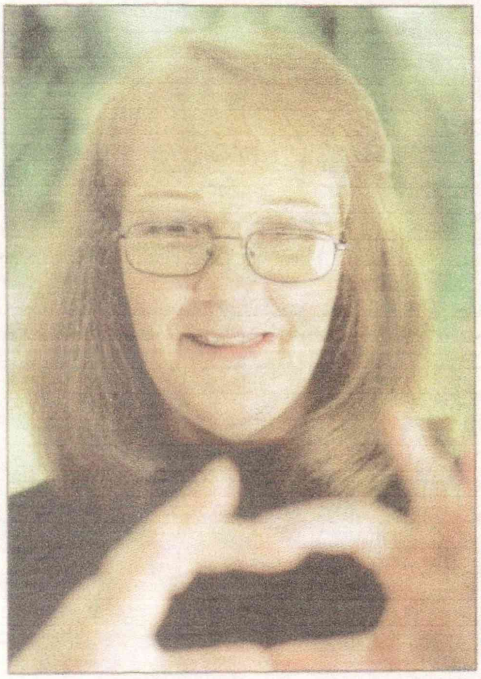
Current treatment for hepatitis C is limited, expensive and can have varying response rates among patients.

"Depending on the outcome of this study, acupuncture may have the potential to have significant health and financial benefits to the Australian population either as an adjunctive treatment or alongside pharmaceutical care.

"Treatment availability may also be more obtainable for both Australians and people living in developing countries."

According to the Hepatitis C Council of NSW, more than 250,000 Australians live with the disease.

Researchers are looking for people with hepatitis C to join the trial. People must be aged 18 to 70 and available for two acupuncture treatments a week for 12 weeks. Details: 9632 8989.



Christine Berle hopes an acupuncture trial will improve treatment for people with hepatitis C.

Appendix 4.1.3: Published in the Sydney Morning Herald – Post Graduate Study, Wednesday, September 12, 2005, Page 7

The Sydney Morning Herald

Make the world a better place

Doing original research is an exciting way to build expertise and help others, writes SAMANTHA KEEN.

Louis Pasteur's discovery in the late 1800s that most infectious diseases are caused by germs is one of the most important finds in medical history. His work became the foundation of microbiology and a cornerstone of modern medicine.

Throughout Australia last year, there were 11,658 postgraduate students quietly undertaking research for PhDs or master's degrees. It is possible some of those students could make discoveries that change the world as we know it.

One such student is Christine Berle, who is undertaking research for a master of science degree at UTS College of Traditional Chinese Medicine, to find out if acupuncture could help people with hepatitis C.

We need to know what people are getting out of acupuncture.
- Chris Zaslawski, UTS College of TCM

Berle had the idea for the study almost 10 years ago after she saw spositive results while treating people in a drug and alcohol clinic in Redfern.

"Quite by accident we found people who had been identified with hepatitis C, after about three months of acupuncture treatments, were showing liver function back to normal," she says.

"I kept trying to encourage [acupuncture] students to look into this area. No one did it, so two years ago I did a course on research methods and now I am doing the research degree."

Berle is conducting a pilot study of 30 people with hepatitis C. Of these subjects, 15 receive acupuncture and 15 receive "sham" acupuncture, where needles are lightly inserted into spots that are not acupuncture points.

"For this pilot study all we are trying to clarify is that acupuncture will have positive outcome on ALT [alanine aminotransferase] blood tests," Berle says.

She says about 250,000 people in Australia have been diagnosed with hepatitis C, a disease of the liver caused by the hepatitis C virus.

In August, prisoner advocacy group Justice Action warned that more than one third of the nation's prison population now has hepatitis C.

Berle is one of about 10 students at the UTS College of Traditional Chinese Medicine researching the effects of acupuncture or herbal medicine on health.

These studies could move Chinese medicine treatments further into the mainstream and give this form of therapy more authority among health professionals, says Chris Zaslawski, director of UTS College of Traditional Chinese Medicine.

Zaslawski is passionate about the benefits of research into complementary medicine, particularly after he attended a recent World Health Organisation conference in Korea to rewrite the organisation's guidelines for clinical research in acupuncture.

"We need to know what people are getting out of acupuncture because people are using it. We need to identify how helpful it is," Zaslawski says.

Another example of research that could change the way people think is work on meals and weight loss by Michelle Palmer at the University of Newcastle.

Palmer, who is doing a PhD in nutrition dietetics, is researching meal patterns among obese participants. Weight is one of the most topical study subjects, considering the World Health Organisation said in 2000 that obesity is a global epidemic.

Additionally, researchers were worried by a report in August that found thousands of school children have the first signs of chronic diseases because of their weight.

The study of 500 students uncovered alarming levels of insulin and a protein implicated in heart disease.

Dr Michael Booth, from the NSW Centre for Overweight and Obesity, says what they disturbed them.

Palmer says her research could help people with weight problems by debunking a lot of myths about diet.

"This could definitely impact best practice for weight loss," she says.

"A lot of information on diet is not evidence-based."

To promote research by students in Australia, the federal Department of Education, Science and Training has set up the National Research Priority Standing Committee to report on research priorities.

There are four national research priorities: an environmentally sustainable Australia; promoting and maintaining good health; frontier technologies for building and transforming Australian industries; and safeguarding Australia.

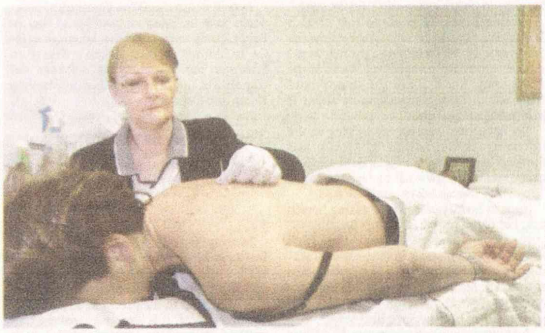


Photo: Angela Brkic

New ground ... Christine Berle is researching the effect of acupunture on hepatitis C.

pendix 4.1.4: Published in the Sydney Morning Herald – Essential Health, October 5, 2006, Page 10

essential
Health

Can acupuncture provide relief from hepatitis C symptoms?

Working in a drug rehabilitation unit, Sydney acupuncturist Christine Berle worked with people who had hepatitis C – the chronic viral disease infecting the livers of 242,000 people in Australia, and causing 16,000 new infections annually. When her patients went for routine tests after a few weeks of acupuncture, their liver function had dramatically improved. Now Berle, a postgraduate student at UTS, is conducting a trial to see whether 12 weeks of acupuncture has any effect on liver function in people with hepatitis C. The drug treatment available to clear the virus does not work for everyone. Anyone interested in joining the trial at the UTS Traditional Chinese Medicine Clinic, Broadway, or at Berle's practice in Guildford, should phone 9632 8989.

Appendix 4.1.5: Published in the Parramatta Advertiser, Wednesday, October 11, 2006, Page 13

NEWS

Acupuncture hepatitis hope

SARAH LAW

LIKE the many great scientific discoveries uncovered unexpectedly, a decade-old coincidence has hinted at treating Hepatitis C with acupuncture.

Christine Berle, who runs an acupuncture clinic in Guildford, was working at an inner-city alcohol rehabilitation unit 10-years ago when she noticed an improvement in patient liver function following acupuncture treatment.

Ms Berle was helping alcoholics to detoxify.

Many of the patients additionally reported they suffered from Hepatitis C.

"All of a sudden we noticed their liver function tests started coming back as normal, and this was after acupuncture treatment," Ms Berle said.

"It may have been because they weren't under stress, or for once they were getting three square meals a day. But this result didn't happen with the group that were doing meditation."

Ms Berle said the surprise find was worth further study, especially if it meant improved treatment for the 240,000 Hepatitis C sufferers in Australia.

Christine Berle is seeking volunteers for a medical trial using acupuncture to treat hepatitis-C.

Ms Berle is conducting a clinical trial at the University of Technology Sydney to evaluate whether acupuncture has an affect on the health of people with Hepatitis C.

Australia reports 16,000 new infections every year.

While it is thought there are more than 170 million people worldwide with the disease, combined drug therapy can cost $21,000 per person for just six months of treatment.

Liver failure is one of the main symptoms of Hepatitis C.

The disease is the most common reason for liver transplants in Australia.

Ms Berle is looking for volunteers for her clinical trial. For details on eligibility contact 9632 8989 or christine.a.berle@student.uts.edu.au

Appendix 4.1.6: Published in the Parramatta Sun, Wednesday, October 18, 2006, Page 75

Acupuncture angel

By **John Macdonald**

NEEDLE Christine Berle about acupuncture and she's liable to get a little sharp with you.

"It's my passion," she said of practising the treatment, and practising it so well she's held a bewildering number of senior positions with the national and world acupuncture bodies.

She's also travelled the world attending conferences and sharpening her knowledge.

Her other passion? "You can take Holroyd out of the girl but you can't take the girl out of Holroyd," is her husband's description of her enthusiasm for the district.

Ms Berle no longer lives in the district but the former Merrylands Public School-High School girl has her acupuncture centre there and is Guildford Chamber of Commerce president.

Now she's involved in a project which could see acupuncture at the centre of hepatitis C treatment.

She's attached to the University of NSW and doing a master's thesis on acupuncture treatment for the disease, and studying the effects on a control group.

The study was prompted by her noticing hepatitis C sufferers seemingly improved their liver function tests after undergoing treatment.

She said this might also have been attributable to other factors, such as proper meals, hence the clinical test. Ms Berle said more than 90 per cent of sufferers caught the disease by sharing needles and liver function failure was a major side effect of hepatitis C.

Sharp: Christine Berle's work on hepatitis C sufferers could validate the point of acupuncture. **Picture: Natalie Spiteri**

In the US, drug offenders were given the choice of jail or strictly controlled treatment.

"It's better to spend $1000 a year than $45,000 a year," she said of the comparative costs of treatment and incarceration.

But repeating the approach in Australia had so far "fallen on deaf ears".

The university is listening, of course, but it wasn't always so.

When Ms Berle began as an acupuncturist in the early 1970s, it was perceived as odd and an Asian treatment practised by Asians.

"I didn't do it for very altruistic reasons – I originally wanted to be an osteopath," she said.

And it wasn't seen as a proper career for a young lady. "My father-in-law didn't want people to know what I was studying."

Then the thirst for knowledge took over. "More acupuncturists were coming out of China and Europe, it was opening up," she said. Ms Berle is a past Holroyd citizen of the year but the best is yet to come if the trial with hepatitis C sufferers validates the point of acupuncture.

APPENDIX 4.2: The Hepatitis C Council of NSW Advertisements

Appendix 4.2.1: The Hep C Review Edition 59 September 2005 Page 39

Acupuncture & hepatitis C

Announcing a clinical trial to find out whether acupuncture treatment has an effect on the health outcomes of people with hepatitis C is being undertaken as part of a Masters Degree research project.

Participants need to:

- have a documented positive PCR viral detection test
- be aged between 18 to 70 years
- be not currently undertaking combination therapy (or have been on it within the last three months).

Treatment will include two acupuncture treatments per week over a twelve week period (24 treatments) at a Guildford (NSW) acupuncture clinic. Five blood samples will also be taken over a six-month period. Participants will also be expected to complete questionnaires during the trial.

If you want to know more about this project, please contact Christine Berle on (02) 9632 8989 or email.. Christine.A.Berle@student.uts.edu.au

Image downloaded with thanks from www.google.com/images

Oct 03 Release of the AHC's needs assessment report, *A sense of belonging: National Hepatitis C Needs Assessment.*

Oct 03 Tony Abbott appointed as Australian Federal Minister for Health & Ageing.

Oct 03 *What is this Hep C Thing?*, a website targeted at school students and focusing on HCV prevention in tattooing and body piercing context launched by the HCCV, the Alfred Hospital, Access Information Centre and La Trobe University.

Oct 03 Launch of the NSW Justice Health strategy document, *Hepatitis C, the challenges, the response - Strategic Directions 2003- 2006.*

Oct 03 Release of the strategy document, *Action on Hepatitis C Prevention*, by NZ MoH.

Oct 03 Launch of the Multicultural Health Support Service (Victoria).

Oct 03 Release of *Hepatitis C: an update*, by the RACGP in their journal, Australian Family Physician, and on their website.

ACUPUNCTURE & HEPATITIS C

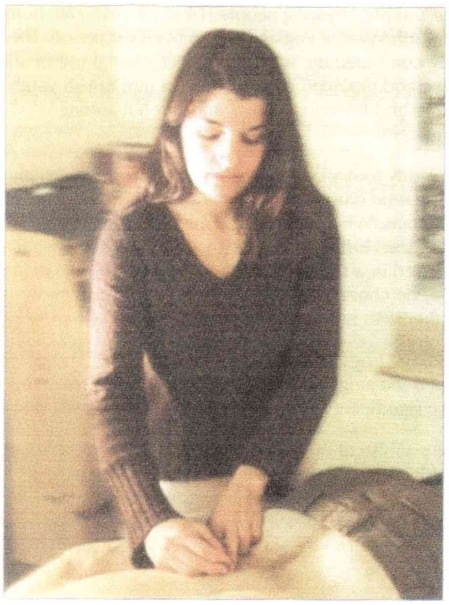
Announcing a clinical trial to find out whether acupuncture treatment has any effect on the health outcomes of people with hepatitis C. The trial is being undertaken at the University of Technology, Sydney, as part of a Master's Degree research project.

Participants need to:

- have a documented positive PCR viral detection test
- be aged between 18 to 70 years
- be not currently undertaking combination therapy (or have been on it within the last three months)

Treatment will include two acupuncture treatments per week over a twelve week period (24 treatments) at a Guilford acupuncture clinic. Five blood samples will also be taken over a six-month period. Participants will also be expected to complete questionnaires during the trial.

■ If you want to know more about this project, please contact Christine Berle on 9632 8989 or Christine.A.Berle@student.uts.edu.au



This image, detail from
http://www.nashuaacupuncture.com/images/sarah34needle.jpg

Appendix 4.2.3: The Hep C Review Edition 54 September 2006 Page 45

ACUPUNCTURE & HEPATITIS C

Announcing a clinical trial to find out whether acupuncture treatment has any effect on the health outcomes of people with hepatitis C. The trial is being undertaken at the University of Technology, Sydney, as part of a Master's Degree research project.

Participants need to:

- have a documented positive PCR viral detection test
- be aged between 18 to 70 years
- be not currently undertaking combination therapy (or have been on it within the last three months)

Treatment will include two acupuncture treatments per week over a twelve week period (24 treatments) at a Guilford, Sydney, acupuncture clinic. Five blood samples will also be taken over a six-month period. Participants will also be expected to complete questionnaires during the trial.

■ If you want to know more about this project, please contact Christine Berle on 9632 8989 or Christine.A.Berle@student.uts.edu.au

Graphics from Google or Yahoo images

Appendix 4.2.4: The Hep C Review Edition 55 December 2006 Page 45

ACUPUNCTURE & HEPATITIS C

Announcing a clinical trial to find out whether acupuncture treatment has any effect on the health outcomes of people with hepatitis C. The trial is being undertaken at the University of Technology, Sydney, as part of a Master's Degree research project.

Participants need to:

- have a documented positive PCR viral detection test
- be aged between 18 to 70 years
- be not currently undertaking combination therapy (or have been on it within the last three months)

Treatment will include two acupuncture treatments per week over a twelve week period (24 treatments) at a Guilford, Sydney, acupuncture clinic. Five blood samples will also be taken over a six-month period. Participants will also be expected to complete questionnaires during the trial.

■ If you want to know more about this project, please contact Christine Berle on 9632 8989 or Christine.A.Berle@student.uts.edu.au

APPENDIX 4.3: Notice in U, the magazine of the University of Technology, Sydney

Helping hepatitis

More than 240 000 people in Australia are estimated to have Hepatitis C Viral infection, and there are approximately 16 000 new infections per year. While some are not affected by it, 75 per cent will have progressive ill health and many will suffer liver damage. Hepatitis C is the most common reason for liver transplant in Australia.

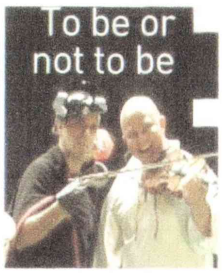
Acupuncture practitioner and UTS Master's student **Christine Berle** has designed a scientifically rigorous clinical trial to determine if acupuncture can be proven to reduce the effects of the Hepatitis C virus (HCV).

Berle says, "During the last decade many HCV sufferers who received acupuncture in a Sydney drug and alcohol rehabilitation clinic reported decreases in their Alanine Aminotransferase (ALT) blood levels. Increased levels of ALT can reflect damage to major liver cells known as hepatocytes, while a decrease in these levels indicates the opposite."

Berle will now lead a research team from the UTS College of Traditional Chinese Medicine to conduct the clinical trial – the first of its kind in Australia – to determine the affect of acupuncture on individuals with HCV.

Su McInerney
Marketing and Communication Unit

Treatment will be offered to thirty volunteers at the UTS Acupuncture Clinic in the city and at Berle's Guildford clinic.
Email: Christine.A.Berle@student.uts.edu.au



That is the question posed in an interactive gestural game designed and produced by **Roman Danylak** of the Faculty of IT, Creativity and Cognition Studios (CCS). The narrative-based game that draws from Hamlet has been designed to engage the user in an intuitive way. Players take their cue from a large screen that provides an interactive map that indicates which of the 36 sensor pads on the floor should be moved to next, as well as lines from Shakespeare's infamous soliloquy. "Gestures are sequenced with the language," says Danylak "so you are acting out gesture and words simultaneously, in the same way that an actor would on stage." There are 22 sequences that the user must perform before a movie in which actors from Playback Theatre, as well as Danylak himself, enact scenes from a pirate style Hamlet. Danylak is currently undertaking user testing of the game and the results will inform his PhD study on the semiotic analysis of intuition in human computer interaction. Featuring at UTS Information Day, *To be or not to be*, was produced in collaboration with the Faculty of Humanities and Social Sciences film and TV studio and will be exhibited at the CCS interactive lab.

Frances Morgan
Marketing and Communication Unit
Photo: Roman Danylak

:10

APPENDIX 4.4: Community Radio Announcement

TEXT OF CD (46 seconds)

Did you know that Hepatitis C is one of the fastest growing diseases in the world?

It's estimated tat at least one in every hundred Australians now suffers with this chronic illness.

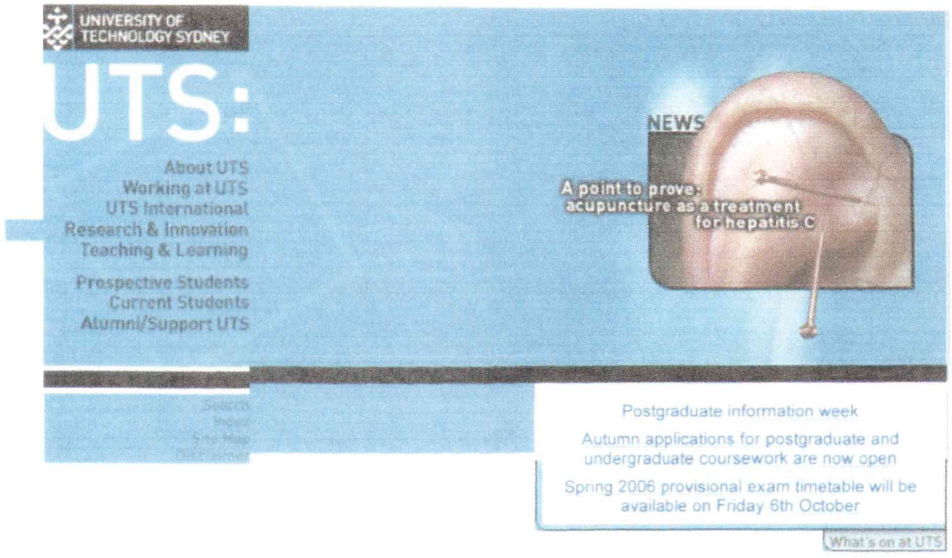
A research program by the University of Technology Sydney is investigating whether acupuncture can help control the debilitating symptoms of Hep C.

The study is looking for volunteers among Hep C sufferers who would like to be part of this research.

This would involve two one hour visits a week for three months to a Guildford acupuncture clinic.

It you want to know more, please contact the program coordinator, Christine on 9632 8989 – that's 9632 8989 or the Hepatitis Helpline on 1800 803 990.

APPENDIX 4.5: Media release on the UTS website



A point to prove: acupuncture as a treatment for hepatitis C

- Newsroom
- **Media Releases**
- UTS Experts
- UTSpeaks

Christine Berle

Ten years ago, working in a Sydney drug and alcohol rehabilitation unit, acupuncturist Christine Berle became convinced that acupuncture treatments were having a positive effect on the health of residents suffering hepatitis C.

Today, as a Master's student in the UTS College of Traditional Chinese Medicine in the Faculty of Science, she is undertaking a scientifically rigorous clinical trial to test what she saw ten years ago.

The trial – the first of its kind in Australia – will evaluate whether acupuncture treatment has an effect on the health outcomes of people who have contracted the hepatitis C virus (HCV).

More than 240,000 people in Australia are estimated to be infected by HCV and there are about 16,000 new infections per year.

While some are not affected by it, 75 per cent will have progressive ill health and many will suffer liver damage. Hepatitis C is the most common reason for liver transplant in Australia.

Berle said what she had seen among the residents of the rehabilitation centre had long warranted authentication.

"Residents with hepatitis C who were having ear acupuncture as part of their treatment program began reporting improvements in their liver function tests after about three months of regular acupuncture," Berle said.

"Their blood test results were showing decreased alanine aminotransferase (ALT) levels. ALTs are a measure of liver damage – increased ALTs can reflect damage to major liver

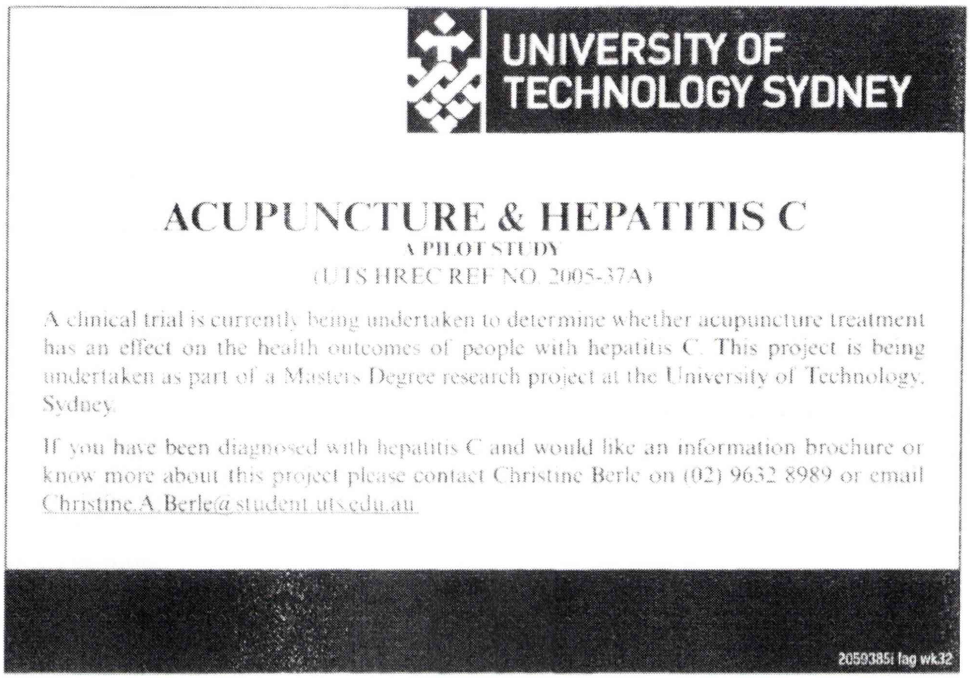
cells known as hepatocytes, while a decrease in these levels indicates the opposite."

For the clinical trial treatment is being offered to 30 HCV positive volunteers at the UTS Acupuncture Clinic in the city and at Berle's Guildford clinic. It involves 12 weeks of acupuncture with a series of blood tests before and after the treatment period. Co-investigator is hepatologist Dr Jacob George from Westmead Hospital.

For details about eligibility for participation in the project contact Christine Berle on (02) 9632 8989 or by email at Christine.A.Berle@student.uts.edu.au.

The study is being undertaken under the supervision of Christopher Zaslawski of the School of Traditional Chinese Medicine and Dr Deirdre Cobbin of the Department of Medical and Molecular Biosciences.

APPENDIX 4.6: Newspaper advertisements



Draft newspaper advertisements:

Parramatta Advertiser	7th February/7th March, 2007
Fairfield Advance	7th February/7th March, 2007
The Glebe	8th February/8th March, 2007
Eastern Suburbs Spectator	week ending 23rd February, 2007
Paddington Times	week ending 23rd February, 2007
Randwick Leader	week ending 23rd February, 2007
Coogee Chronicle	week ending 23rd February, 2007

Appendix 5: Consent form

UNIVERSITY OF TECHNOLOGY SYDNEY

CONSENT FORM

I _____ agree to participate in the research project "A Controlled Trial of Acupuncture for the Treatment for people who are Hepatitis C antibody positive: A Pilot Study" (UTS HREC Ref No. 2005-37A) being conducted by Christine Berle (ph. 9632 8989), as part of a Master's Research Degree.

I understand that the purpose of this study is to identify if there are any health benefits from the use of acupuncture for people with Hepatitis C.

My participation in this research will involve me receiving acupuncture treatment twice weekly for twelve weeks (approximately 1 hour per session) at an acupuncture clinic (Guildford or Broadway). Three blood samples will be taken (at two week intervals) during the six week period prior to starting the acupuncture treatment, one at completion, another one month later and a final blood sample two months following completion (a total of 6). Pathology sampling/tests have been organised through various Douglass Hanly Moir Pathology clinics which would be at a convenient/local location for each participant. Participants are expected to complete a Hepatitis C Quality of Life Questionnaire (HQLQ) prior to treatment, monthly for three months and a follow up at two months.

I am aware that acupuncture involves the insertion of fine needles into the skin. Side effects in acupuncture are infrequent and generally limited to bruising and spot bleeding. On rare occasions patients may feel faint and nauseous. In the unlikely event that this occurs, the treatment session will be terminated.

I am aware that I will be randomised into one of two groups; one group receiving real acupuncture and the other receiving sham acupuncture (needle put into non acupuncture points). Prior to the first acupuncture session a medical history will be taken and 3 blood samples. Another blood sample will be taken at the completion of treatment, one at completion, another one month later and a final blood sample after two months. I will be expected to participate in the Hepatitis C Quality of Life Questionnaires (5) and the acupuncture treatment monitoring questionnaires (3). I understand that at the debriefing I will be informed which group I was allocated and I will receive a copy of my test results. If there has been a positive outcome for the real acupuncture group and I was a part of the sham group, I understand that I will be offered 24 free acupuncture treatments the same as that administered to the acupuncture treatment group.

I am aware that I can contact Christine Berle at her clinic (9632 8989) or her Supervisor, Chris Zaslawski (9514 7856) if I have any concerns about the research. I also understand that I am free to withdraw my participation from this research project at any time if I wish, without consequences, and without giving a reason.

I agree that the research data gathered from this project may be published in a form that does not identify me in any way.

_____ ____/____/____
Signature (participant)

_____ ____/____/____
Signature (researcher or delegate)

NOTE: This study has been approved by the University of Technology, Sydney Human Research Ethics Committee. If you have any complaints or reservations about any aspect of your participation in this research which you cannot resolve with the researcher, you may contact the Ethics Committee through the Research Ethics Officer (ph: 02 9514 9615, Research.Ethics@uts.edu.au), and quote the UTS HREC reference number. Any complaint you make will be treated in confidence and investigated fully and you will be informed of the outcome.

APPENDIX 6: HCV/TCM Pattern Questionnaire

UTS ACUPUNCTURE CLINICAL TRIAL – INITIAL INTERVIEW FORM

UTS HREC REF NO. 2005-37A

NOTE: To be stored separate to Health Evaluation Form

Date_____

Surname_____ First Name_____Middle Initial_____

Address_____

Suburb_____ Postcode_____

Home Ph: _____ Bus Ph: _____Mob: _____

Date of Birth_____ Gender: Male/Female

Occupation _____

Code Number 2005-37A-_____

UTS ACUPUNCTURE CLINICAL TRIAL
HCV/TCM Questionnaire

NOTE: To be stored separate to Initial Interview Form

Code Number 2005-37A-_____ Personal Code Name: _____

Date: _____

Actual age at the date of the initial interview: _____

Have you ever had acupuncture before? ☐ Yes ☐ No

Are you currently undertaking any concurrent therapies? ☐ Yes ☐ No

How were you referred to this Research Project?

☐ Hepatitis C Council ☐ Westmead Hospital ☐ Information Sheet

☐ Newspapers ☐ Health Professional ☐ Support Group

☐ Previous Patient ☐ TCM Staff Member ☐ TCM Student

☐ UTS Clinic ☐ Other _____

Questions about you:

1. When were you diagnosed with Hepatitis C? _____
2. Have you had a positive serum HCV PCR viral detection test? _____
3. Have you had an elevated ALT during the last 6 months? (≥57 ≤350) _____
4. Have you recently (within 3 months) or are you currently undertaking Combination therapy? ☐ Yes ☐ No
5. Have you had a HCV PCR viral load test in the last 3 months? ☐ Yes ☐ No
6. Have you had a HCV PCR genotype test in the last 3 months? ☐ Yes ☐ No
7. What is your current daily alcohol consumption (standard drinks)
   ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5+

Medical History

☐ Cancer ☐ High Blood Pressure ☐ Heart Disease ☐ Asthma

☐ Diabetes ☐ Compromised Immunity ☐ Hepatitis A/B ☐ Seizures

☐ Currently Pregnant ☐ Other_____

Please list any allergies: _____

Please list any medications: _____

Please list any Surgery (type and date): _____

Please list any injury (type and date): _____

Do you Smoke? ☐☐ Yes ☐☐ No Amount: _____

Please state any other problems/symptoms? _____

_____

General

☐ Chill ☐ Fever ☐ Low Fever ☐ Afternoon Fevers
☐ Hot Flushes ☐ Alternating chills/fever ☐ Aversion to Cold
☐ Cold hands/feet (feels cold) ☐ Sweats easily ☐ Fatigue
☐ Heavy body ☐ Sighing ☐ Brittle Nails ☐ Pain - worse at night
☐ Warm palms & soles of feet ☐ Oedema ☐ Weakness of the Spirit

Emotional

☐ Depression ☐ Anxiety ☐ Occupational ☐ Emotional stress
☐ Irritability ☐ Quick Temper ☐ Susceptibility to fright

Sleep

☐ Dreamy Sleep ☐ Insomnia ☐ Night sweats ☐ Restlessness
☐ Heavy Sleep
☐ Wakes (time) _____

Notes: _____

_____

Average Daily Diet

Morning / noon: _____Evening _____

Cravings: _____Thirst (hot / cold): _____

Musculoskeletal

- ☐ Muscle spasms
- ☐ Muscle weakness
- ☐ Numb limbs
- ☐ Lower back tired & sore
- ☐ Legs & knees tired & sore
- ☐ Muscle pain
- ☐ Joint pain
- ☐ Bone pain

Describe nature and location of pain: _____

Digestive:

- ☐ Bad Breath
- ☐ Inability to taste flavours
- ☐ Dry mouth
- ☐ Burping & Belching
- ☐ Appetite poor/strong
- ☐ Nausea/Vomiting
- ☐ Cramps
- ☐ Stuffy chest & abdomen
- ☐ Bitter taste in the mouth
- ☐ Dislike of oil/oily food
- ☐ Sticky, slimy, unclean feeling in the mouth
- ☐ Flatulence/Bloating
- ☐ Indigestion/Long Term/Heart Burn
- ☐ Borborygmus
- ☐ Pain

Stools

- ☐ Constipation
- ☐ Diarrhoea/Loose
- ☐ Anal burning after defecation
- ☐ Foul smelling
- ☐ Mucus in the stools
- ☐ Sometimes constipation, sometimes diarrhoea
- ☐ Loose–early morning diarrhoea
- ☐ Difficulty eliminating faeces
- ☐ Blood in stools
- ☐ Undigested food in stools

Bowel Movement:

Frequency: _____ Colour: _____ Form: _____

Notes: _____

_____

Urinary

- ☐ Pain on urination
- ☐ Urgency to urinate
- ☐ Dribbling
- ☐ Dark urine
- ☐ Blood in urine
- ☐ Frequency: How often: _____
- ☐ Wakes to urinate: How often: _____

Notes: _____

_____

Head, Eyes, Ears, Nose, Throat

- ☐ Eye strain
- ☐ Spots in vision
- ☐ Ear aches
- ☐ Mucus
- ☐ Dry mouth
- ☐ Obstruction in throat
- ☐ Eye pain
- ☐ Blurry Vision
- ☐ Ringing in ears
- ☐ Dry throat
- ☐ Mouth ulcers
- ☐ Grinding of teeth
- ☐ Dry eyes
- ☐ Red Eyes
- ☐ Sinus problem
- ☐ Sore throat
- ☐ Gum problems

Headaches (where, when, duration, nature): _____

_____

Notes: _____

Respiratory

- ☐ Dry Cough
- ☐ Wheezing
- ☐ Shortness of breath
- ☐ Productive Cough
- ☐ Tight chest
- ☐ Bronchitis
- ☐ Asthma
- ☐ Difficulty breathing
- ☐ Profuse phlegm

Mucus/phlegm (colour, consistency etc.) _____

_____

Notes: _____

_____

_____

Cardiovascular

- ☐ High BP
- ☐ Difficulty breathing
- ☐ Dizziness
- ☐ Low BP
- ☐ Chest pain
- ☐ Swollen ankles
- ☐ Palpitations
- ☐ Fainting

Notes: _____

_____

_____

Bleeding

☐ Nose bleeding ☐ Bleeding Gums
☐ Bleeding under the skin (purple spots & patches)
☐ Spider veins (where) _____

_____

Complexion

☐ Bright white face ☐ Darkish/dull ☐ Pale or sallow
☐ Reddish cheeks ☐ Purplish lips ☐ Jaundice
☐ Withered and yellowish
☐ Rashes, reddish spots and red threads (describe and identify where) _____

_____

_____

Skin

☐ Rashes ☐ Eczema ☐ Purpura ☐ Acne ☐ Pimples ☐ Itching

Notes:_____

_____

Female Reproductive

Age at first menses: Duration ---------- Period (days)

Eg.	Menses
5 13 -- --	___ -- --

Menstrual Irregularities

☐ Irregular periods ☐ Amenorrhoea ☐ Dysmenorrhoea ☐ Other _____

☐ Painful & Dark menstruation with blood clots

Describe type and nature of menses in relation to:

Flow: _____ Clots (size): _____

Discharge: _____ Colour: _____

_____

☐ Premenstrual Syndrome

Changes in body/psyche prior to menstruation: _____

No. of pregnancies: _____ No. of miscarriages: _____ Contraceptives:_____

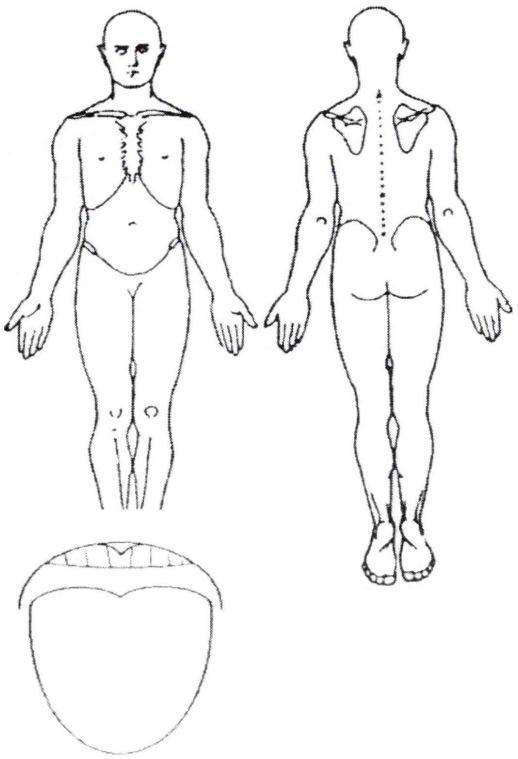
Notes: _____

General Comments: _____

_____

PRACTITIONER USE ONLY:

Mark areas of pain/ tenderness, skin lesions etc on the diagram below



Note tender Mu points: _____

_____

Note tender Shu points: _____

_____

Note areas of abdominal tenderness:

_____

Liver:

☐ Enlarged liver

☐ Abdomen hurts with movement

Rib-side

☐ Nodules/lumps under skin

☐ Abdominal distension (swelling with pressure) & tenderness

Pain ☐ Piercing ☐ Dull

Tongue: Indicate cracks / ulcerations / teeth (mark on diagram)

Shape:	☐ Pointed	☐ Splayed	☐ Swollen
Coat:	☐ Dry	☐ Greasy	☐ Moist
	☐ Peeled	☐ Ulcerated	☐ Papillae
Coat Colour:	☐ Yellow	☐ White	☐ No coat
	☐ Other _____		
Body Colour:	☐ Red	☐ Pale	☐ Purple
	☐ Other _____		

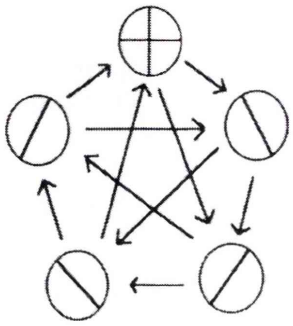
Notes: _____

Body Shape:

☐ Underweight ☐ Average ☐ Overweight

Pulse

Mark excess/deficient pulse positions on diagram



Left/right balance: _____

Cun/Guan/Chi:

Rate: _____

Depth: _____

Rhythm: _____

Diagnosis:

_____

_____

_____

Treatment Principle: _____

_____

Treatment: _____

_____

_____

_____

_____

_____

_____

_____

APPENDIX 7: TCM Hepatitis Acupuncture Treatment Protocol

TCM Pattern	1st Treatment in week	2nd Treatment in week
I. LIVER YIN VACUITY	Supplement: LR8, LR14, GB43 Left Ear Shenmen, Sympathetic, Kidney, Liver, Upper Lung	Supplement: BL17, BL18 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
II. BINDING DEPRESSION OF LIVER QI	Reducing method: GB34, LR3, LR14 Left Ear Shenmen, Sympathetic, Kidney, Liver, Upper Lung	Reducing method: BL18, BL19 Right Ear Shenmen, Sympathetic, Kidney, Liver, Upper Lung
III. LIVER QI STAGNATION AND BLOOD STASIS If OBSTRUCTING THE NETWORK VESSELS	Reducing method: GB34, LR3, SP10 Left Ear Shenmen, Sympathetic, Kidney, LR, Upper Lung Reducing method: LR13 Marked concomitant LR depression LR3 Pain in rib-side TE6 Severe blood stasis LI4, SP6. Concomitant blood vacuity SP6. Concomitant qi vacuity ST36	Reducing method: BL17, BL18 Right Ear Shenmen, Sympathetic, Kidney, Liver, Upper Lung Reducing method BL19
IV. LIVER-GALLBLADDER DAMP-HEAT	Reducing Method: LR14, GB34, SP9, LI11 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Reducing method: BL18, BL19 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
V. LIVER QI INVADING SPLEEN	Reducing Method: LR3, GB34 Supplement: ST36, SP6 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Reducing method: BL18 Supplement: BL20, BL21 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
VI. LIVER-KIDNEY YIN VACUITY	Supplement: LR8, KI3, SP6 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Supplement: BL18, BL23 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
VII. SPLEEN QI VACUITY	Supplement: ST36, CV12, PC6, LR13 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Supplement BL20, BL21 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
VIII. SPLEEN-KIDNEY YANG VACUITY	Supplement: ST36 (with moxa +), KI3, KI7 (add moxa for cold hands and feet) Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Supplement: BL20, BL23, GV4 all with Moxa Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
IX. DAMP HEAT BREWING THE SPLEEN	Supplement: ST36 Reducing method: SP9, GB34 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Reducing method: BL20, BL21 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
X. DAMP HEAT TRANSFORMING INTO FIRE & BREWING TOXINS If bleeding:– DAMP HEAT HARASSING THE CONSTRUCTIVE & BLOOD	Reducing method: LR14, GB34, GB40, SP9, LI11 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU For nose bleeding PC4, hematuria SP6, vomiting blood ST44, PC4, bleeding gums LI4, ST44	Reducing method: BL18, BL19 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
XI. PHLEGM NODULATION PATTERN	Supplementation: ST36 Reducing Method: LR13 (care when needling with hepatomegaly), SP9, ST40	Reducing method: BL17, BL18

	Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
XII. COLD DAMPNESS ENCUMBERING THE SPLEEN INTERNALLY	Supplement St36 (moxa) Reducing method: SP9 & CV 12 with moxa Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Reducing method: BL18, BL20 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
XIII. QI VACUITY	Supplement: ST36, CV12, PC6, LR13 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Supplement: BL20, BL21 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
XIV. YIN VACUITY	Supplement: SP6, KI3, KI6 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Supplement: BL18, BL23 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
XV. XUE (BLOOD) VACUITY	Supplement: ST36, SP6, SP10 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Supplement: BL17 (with direct moxa), BL20 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU
XVI. XUE (BLOOD) STAGNATION	Reducing method: GB34, LR3, SP10 Left Ear Shenmen, Sympathetic, KI, LR, Upper LU	Reducing method: BL17, BL18 Right Ear Shenmen, Sympathetic, KI, LR, Upper LU

APPENDIX 8: QoL Questionnaire

Hepatitis Quality of Life Questionnaire, Version 2 (HQLQv2) Revised to include SF-36v2™

Your Health and Well-Being

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
O_1	O_2	O_3	O_4	O_5

2. **Compared to one year ago**, how would you rate your health in general **now**?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
O_1	O_2	O_3	O_4	O_5

3. The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	O_1	O_2	O_3
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	O_1	O_2	O_3
c) Lifting or carrying groceries	O_1	O_2	O_3
d) Climbing **several** flights of stairs	O_1	O_2	O_3
e) Climbing **one** flight of stairs	O_1	O_2	O_3
f) Bending, kneeling, or stooping	O_1	O_2	O_3
g) Walking **more than a mile**	O_1	O_2	O_3
h) Walking **several hundred yards**	O_1	O_2	O_3
i) Walking **one hundred yards**	O_1	O_2	O_3
j) Bathing or dressing yourself	O_1	O_2	O_3

4. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	○1	○2	○3	○4	○5
b) **Accomplished less** than you would like	○1	○2	○3	○4	○5
c) Were limited in the **kind** of work or other activities	○1	○2	○3	○4	○5
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	○1	○2	○3	○4	○5

5. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	○1	○2	○3	○4	○5
b) **Accomplished less** than you would like	○1	○2	○3	○4	○5
c) Did work or other activities **less carefully than usual**	○1	○2	○3	○4	○5

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
○1	○2	○3	○4	○5

7. How much **bodily** pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe
○1	○2	○3	○4	○5	○6

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
O_1	O_2	O_3	O_4	O_5

9. These questions are about how you feel and how things have been with you during the **past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	O_1	O_2	O_3	O_4	O_5
b) Have you been very nervous?	O_1	O_2	O_3	O_4	O_5
c) Have you felt so down in the dumps that nothing could cheer you up?	O_1	O_2	O_3	O_4	O_5
d) Have you felt calm and peaceful?	O_1	O_2	O_3	O_4	O_5
e) Did you have a lot of energy?	O_1	O_2	O_3	O_4	O_5
f) Have you felt downhearted and depressed?	O_1	O_2	O_3	O_4	O_5
g) Did you feel worn out?	O_1	O_2	O_3	O_4	O_5
h) Have you been happy?	O_1	O_2	O_3	O_4	O_5
i) Did you feel tired?	O_1	O_2	O_3	O_4	O_5

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

All of the Time	Most of the time	Some of the time	A little of the time	None of the time
O_1	O_2	O_3	O_4	O_5

11. How TRUE or FALSE are **each** of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	O_1	O_2	O_3	O_4	O_5
b) I am as healthy as anybody I know	O_1	O_2	O_3	O_4	O_5
c) I expect my health to get worse	O_1	O_2	O_3	O_4	O_5
d) My health is excellent	O_1	O_2	O_3	O_4	O_5

12. How much of the time during the **past 4 weeks**...

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a) Were you discouraged by your health problems?	O_1	O_2	O_3	O_4	O_5	O_6
b) Did you feel weighted down by your health problems?	O_1	O_2	O_3	O_4	O_5	O_6
c) Was your health a worry in your life?	O_1	O_2	O_3	O_4	O_5	O_6
d) Were you frustrated by your health?	O_1	O_2	O_3	O_4	O_5	O_6

13. How much of the time during the **past 4 weeks**...

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a) Have you generally enjoyed the things you do?	O_1	O_2	O_3	O_4	O_5	O_6
b) Has your daily life been full of things that were interesting to you?	O_1	O_2	O_3	O_4	O_5	O_6
c) Have you felt cheerful, lighthearted?	O_1	O_2	O_3	O_4	O_5	O_6
d) Has living been a wonderful adventure for you?	O_1	O_2	O_3	O_4	O_5	O_6

14. How much of the time during the **past 4 weeks** has your hepatitis limited you in:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a) Your everyday physical activities such as walking or climbing stairs, carrying groceries or participating in sports?	O_1	O_2	O_3	O_4	O_5	O_6
b) Your daily work, both work outside the home and housework?	O_1	O_2	O_3	O_4	O_5	O_6
c) Your normal social activities with family, friends, neighbors or groups?	O_1	O_2	O_3	O_4	O_5	O_6

15. How much of the time during the **past 4 weeks**...

		All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a)	Were you discouraged because of your hepatitis?	○1	○2	○3	○4	○5	○6
b)	Did you feel weighted down by your hepatitis?	○1	○2	○3	○4	○5	○6
c)	Was having hepatitis a worry in your life?	○1	○2	○3	○4	○5	○6
d)	Were you frustrated because of having hepatitis?	○1	○2	○3	○4	○5	○6