Protocol title:	A feasibility study of Chinese herbs to manage cancer-related symptoms in patients with advanced non-small-cell- lung cancer
NCT number	**NCT02331394**
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LIST OF APPENDIXES

1. BACKGROUND

1.1 Can Chinese Herbs help in the treatment of Lung Cancer?

Lung cancer is the one of the most commonly occurring cancer and in 2012 there were an estimated 1.8 million new cases worldwide, representing 12.9% of all new cancers. Lung cancer is also the most common cause of death from cancer, with 1.59 million deaths (19.4% of total deaths; GLOBOCAN 2012) [1]. Despite advances in the design and administration of anti-cancer therapies over recent years, the majority of patients with non-small cell lung cancer (NSCLC) first present with advanced, inoperable disease and for these patients their overall 5-year survival rate is 2-4% and the median survival for stage IV (metastatic) disease is only 5-7 months [2]. In addition to their very poor chances of cure or extended survival, patients with advanced NSCLC frequently suffer a range of different symptoms related to both their disease and its treatment [3-6]. As a result there is a pressing need to develop more effective anti-cancer therapies and an imperative to enhance the effects of existing treatments and alleviate symptoms more effectively.

One type of complementary medical treatment with the potential to improve some outcomes in lung cancer is Traditional Chinese Medicine (TCM), in particular the use of carefully selected combinations of Chinese herbs (CH). Increasing numbers of patients with cancer are using complementary medicine, including CH, and evidence is accumulating from a growing number of laboratory studies and clinical trials, that CH may exert beneficial effects for cancer patients in the following ways:

(i) Through direct anti-cancer effects: Studies have suggested CH has potential anti-cancer effects by inhibiting tumor cell division, increasing tumor cell death [7-16].

(ii) Through enhancing potency and decreasing toxicity of standard anti-cancer treatment [17-27].

(iii) Through reduction in symptoms and improvement in general condition and quality of life [28-34].

The current proposal is a feasibility and acceptability study to establish the necessary groundwork for more detailed investigations into the role of CH in reducing symptoms and improving quality of life in NSCLC patients at the JGH. A standardized and easily administered form of CH will be used, incorporating a carefully selected combination of herbs designed to alleviate a range of common symptoms suffered by patients with advanced NSCLC.

1.2 Studies of use of CH in treatment of Cancer

Results of specific studies

There have been several clinical studies focused on the use of CH in the treatment of patients with a range of different cancers. Study designs vary from observational to three-arm double-blind trials and limited number of well designed randomized controlled trials (RCT) [25, 26, 28, 35]. There is considerable evidence that CH can lead to measurable improvements in symptoms and quality of life (QOL) [36-40]. For example a double-blind placebo-controlled trial by Mok et al [24] demonstrated that CH had a significant effect on the control of chemotherapy-associated nausea in patients with early-stage breast or colon cancers, but no parallel reduction in chemotherapy-related hematologic toxicity. In contrast a randomized, placebo-controlled trial in ovarian cancer patients (all stages) by Chan et al. [41] showed that the CH reduced cytokine levels and lessened the falls in lymphocyte count without any change in QOL. Indeed the role of CH to reduce leucopenia during chemotherapy has recently been the subject of an extensive literature review [42]. This review analysed 83 randomised controlled trials involving over 8,000 patients with a range of different cancers, CH formulations and chemotherapy treatments. They concluded that there was evidence of a beneficial effect of CH on leucocyte count and no reports of adverse events. However, the authors cautioned that the majority of these RCTs had a high risk of bias in answering the primary research question [42].

In lung cancer patients the literature suggests that combined treatment with chemotherapy and CH can improve survival rates, immediate tumor response, performance status and QOL for those with locally advanced and metastatic disease [43-45]. In a randomized controlled trial (RCT) of 61 patients with stage 3B/4 non-small-cell lung cancer the CH (Sheng-mai Injection (Table 1) in combination with Gu-

jin Granule) given in addition to chemotherapy (Navelbine and Cisplatin) improved median survival time (13 mo vs 9 mo, P=0.014) and the response rate increased to 48.5% (16/33), compared to 32.2% (9/28) in controls treated with the same chemotherapy alone(P=0.04) [46]. In another clinical trial using Shenqi-fuzheng (Table 1) injection (Lizhu Co., China) in 232 advanced NSCLC patients showed that CH significantly improved the response rate and QOL of lung cancer patients [47]. Furthermore, a randomized controlled trial using the Feiji Recipe (Table 1) CH treatment enhanced the clinical therapeutic efficacy and alleviated side-effects of chemotherapy [40] and improved many domains of QOL [48]. More recently, Liang et al. [49] used RCT to examine the effect of CH (modified Shu Yu Wan formula) on QoL and response rate to treatment and treatment toxicity in advanced NSCLC patients receiving platinum-based chemotherapy. This study demonstrated significant beneficial effect of CH on QOL and significantly less chemotherapy-related toxicity.

Table 1 CH recipes used in the above mentioned clinical trials

***Shengmai* recipe**		**Shenqi-fuzheng recipe**		***Feiji recipe***	
Ingredients	*Dose*	Ingredients	*Dose*	Ingredients	*Dose*
RenShen	3-15g	*Dang Shen*	6-30g	*Sheng Di Huang*	30g
Dang Shen	(15-45g)	*RenShen*	1-9g	*Chi Shao*	15g
Xi Yang Shen	(15-45g)	*Fu Ling*	9-18g	*Huang Qin*	12g
Mai Men Dong	5-30g	*Dan Shen*	3-30g	*Dang Gui*	12 g
Wu Wei Zi	2-6g	*Chi Shao*	4.5-15g	*Fu Ling*	15g
		Qing Pi	3-10g	*Hong Hua*	10g
		Chen Pi	3-9g	*Gan Cao*	9g
		Zhi Ban Xia	3-14g	*Sheng Jiang*	30g
		Gan Cao	3-30g		

The results above provide support for the concept that integrating CH with standard chemotherapy for lung cancer patients may be beneficial. Furthermore there are additional data for positive effects of other CH recipes as adjunctive treatment during radiotherapy. Thus Dixiong Decoction [50], Liangxue Jiedu Huoxue Decoction [51], and Shenqi Fuzheng injection [52] reduced radiation pneumonitis and improved clinical radiographic physiologic dyspnea scores and the Radiation Therapy Oncology Group (RTOG) grading score, in groups of NSCLC patients undergoing radiotherapy treatment.

Results of systematic reviews and clinical guidelines

In recent years several systematic reviews have summarized the literature on the results of around 24 clinical trials using CH in NSCLC [18, 35, 53-55]. These reviews concur that CH has some advantages in NSCLC patients as an adjuvant to chemotherapy for treatment of non-small cell lung cancer to improve quality of life and improve toxicity of chemotherapy. However, the broad range and heterogeneity of CH interventions used and the outcomes assessed still make it challenging to draw firm conclusions to guide day-to-day practice.

In Western countries, such as the United States, Australia, Canada, and members of the European Union, the popular use of herbal medicine has led to establishment of research funding agencies such as the U.S. National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM; http://nccam.nih.gov/), and the Australian National Institute of Complementary Medicine (NICM; http://www.nicm.edu.au). As a result of these developments, the issue of integration of herbal therapy into modern medicine has been the subject of ongoing international discussions in the last few years in order to develop some guidance for use of CAM [56-59].

To date, three international guidelines have been published on the use of CAM in oncology (refs 58, 55, 59) but only one has focused specifically on lung cancer. In 2007 the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines published Complementary Therapies and Integrative Oncology in Lung Cancer [60]. This recommended the use of CH to treat the symptoms associated with cancer and its mainstream treatments, but only in the context of clinical trials. At that time the ACCP felt this should only be offered to patients who were no longer on active treatments [60] (Grade 1C recommendation: absence of directly applicable studies of good quality).

Evidently, the literature on the use of CH in treatment of NSCLC has expanded greatly over the seven years since the ACCP statement was published. Furthermore, improvements in the delivery of

cytotoxic chemotherapies and the advent of targeted treatments for lung cancer that are easier for patients to tolerate, has meant that an increasing proportion of patients including those with poor performance status are now being offered some anti-cancer treatment. Unfortunately, restricting the use of CH in NSCLC, to those who are no longer on active treatment will now select a very small group of patients with poor prognosis and means that the potential to confirm any effect of CH in alleviating cancer treatment-related symptoms is excluded. Furthermore it is notable that as of June 2014, 81 clinical trials with Chinese herbs are registered with the U.S. National Institutes of Health [59, 61]. Three of 81 trials are in lung cancer patients, two of which are using CH in combination with other chemotherapy:

- Clinical Study of Chemotherapy Combined With Chinese Medicine on Survival Affect of Elderly Patients With Lung Cancer (NCT01780181)
- Efficacy Study of Chinese Medicine Plus EGFR-TKI Versus EGFR-TKI in Advanced Pulmonary Adenocarcinoma (NCT01745302)
- Multi-center randomized double-blind controlled study of chemotherapy combined with or without traditional Chinese medicine on quality of life of postoperative non-small cell lung cancer patients (NCT01441752)

The patient perspective

The use of CH among cancer patients is growing and a recent cohort study with 453 cancer patients revealed that the percentage of patients using CH in combination with conventional treatment was as high as 77% [62]. For these patients CH was thought to have an important role in reducing therapy-associated toxicity, reducing cancer-related symptoms, supporting the immune system or even for its direct anti-cancer effects [63]. Reports from patients enrolled in studies of seven different cancer types, including lung cancer perceived CH to be an effective and harmless therapy. Subjects believed that conducting clinical research would be crucial for the recognition and dissemination of CH in Western countries [64]. A semi-structured interview of 12 lung cancer patients from JGH was conducted to explore their expectations and beliefs about complementary and alternative medicine including CH [65]. Positive beliefs and expectations were observed in all participants. Patients expressed four main beliefs that supported the used of CAM: maintaining a sense of control, preferring natural products or methods, valuing relationships with CAM providers, and being open to trying different strategies. Finally we have informal testimony from professionals at the Peter Brojde Centre at the JGH that confirms at least 12 recent patients with lung cancer used CH for the reasons stated above and most, if

not all, did so without declaring this to their oncologists. Overall this underlines a strong interest in CH amongst many patients with cancer, including lung cancer, and suggests that we should actively engage with patients on this subject and study the role of CH in clinical practice. In this way we will be better able to address the many questions and uncertainties about the potential benefits and risks of CH for our patients.

1.3 Clinical Safety of Chinese herbs

There are many areas of uncertainty and legitimate concern in trying to predict the potential toxicity of CH formulas such as the one proposed in clinical populations. We have identified the following general types of concerns and have addressed each one as it pertains to the proposed CH study at the Peter Brojde Lung Cancer Centre below:

A. The inherent variability in chemical composition of herbs due to cultivation conditions and different geographic sources. **Response**: The source company for the herbs in this study (BEMA) obtain their botanicals from reputable farms in Taiwan (San Ten Pharmaceutical Company) and the Certificate of Analysis are provided (Appendix 1)

B. The possibility of contamination with undeclared potentially toxic ingredients including heavy metals (arsenic, cadmium, lead and mercury) or microbial contamination (e.g. E. coli, Salmonellaspp, Staphylococcus aureus). **Response**: Each component has been independently tested at San Ten pharmaceuticals to confirm purity and absence of contamination and certificates confirming this are attached (Appendix 2)

C. The difficulty accurately predicting safety and efficacy of individual ingredients from CH when the only robust quantitative data available is from pre-clinical experiments using doses that are frequently far higher than those achievable in humans. **Response**: The components of the CH formula we plan to use have been used for therapeutic benefit for several hundred years, and continue to be used to treat cancer patients in China. Community studies of reported side-effects from over-the-counter i.e. unsupervised, CH use [66] most commonly (<10%) include minor side effects such as allergic reactions (e.g. erythema, itching), dizziness and gastro-intestinal symptoms (e.g. diarrhea, stomach ache and cramping). Other rare (<1%) reported side-effects of individual herbs at very high doses include: several weeks or months' use of higher doses (e.g. >600 mg/day) of Licorice can cause suppression of the renin-aldosterone axis

leading to hypertension and hypokalemia [67]; Increased risk of bleeding: dong quai (angelica senesis) at the dose of 4.5 g daily due to antiplatelet activity: concurrent use of anticoagulants is not recommended [68]; Neurological and psychiatric toxicity: Panax ginseng may cause insomnia, mania and/or euphoria when used in a dose >2 g daily over prolonged time (3 months) [69, 70]. The toxicities reported argue for supervised use of CH in clinical studies to monitor symptoms and parameters such as blood pressure.

D. There is genuine difficulty in predicting potential clinically important interactions between CH and other chemicals or biomolecules at physiologically relevant concentrations. This in turn raises the possibility that for patients receiving potentially highly toxic treatments such as chemotherapy, CH may increase the risk of toxicity. Additionally, for patients being treated with curative intent there is potential that any additional treatment such as CH may reduce rather than enhance any anti-cancer effect and jeopardise survival. **Response**: In recent years there has been a rapid increase in the number of published studies using CH in cancer patients, including many studies using CH at the same time as chemotherapy. Not one of these studies has reported an increase in symptoms or adverse effects due to CH despite use in a variety of different patient groups, and many claim that CH enhances rather than reduces anti-cancer treatment effects. This protocol is deliberately designed to test CH in stage IV lung cancer patients, where anti-cancer treatment is intended to reduce or control symptoms and improve quality rather than extend life. To be able to better identify if CH are causing, rather than reducing toxicity for those on chemotherapy, we will start CH only in patients who have no chemotherapy planned or in those starting chemotherapy CH will be initiated only if they are clinically stable and have completed at least the first cycle of chemotherapy. Furthermore, to reduce the potential for other toxicities, patients will be instructed not to take other over-the-counter CH.

1.4 Rationale, composition and safety data for the of the study formula - Shu Yu Wan (Chinese Yam Pill) formula

The basis for the formula chosen is the "Eight treasure deconcoction" (Protocol Table 2: 1-8) that is used to improve energy and combat fatigue in otherwise healthy individuals. This fundamental formula is represented in the majority of deconcotions studied in the recent review by Ma et al [ref]. In the context of other diseases the Eight Treasures combination is not thought to be strong enough and the remaining 13 herbs are added for their anticipated supplementary effects in treating symptoms in

the context of lung cancer. These include herbs to help with lung symptoms such as cough (10,11,15) and dry mouth (17), poor appetite and early satiety (13, 14,20, 21), emotional stress (18) and to strengthen the individual's natural defences (12, 19,22,23) in the face of severe illness. The classical Shu Yu Wan formula dates back to the late Han dynasty c. 220 AD and includes 21 herbs. This formula has been used for hundreds of years as a treatment for severe illness-induced fatigue and weakness. However, two of the classical ingredients (Da Dou Huang, Bai Lan) are not approved in the NHPD list and have been substituted with appropriately selected additional herbs that are on NHPD approved list (Table 2:15,20,22,23). In Traditional Chinese Medicine there is considerable scope for individual practitioners to choose different herbs from each botanical family to treat different patients with the same symptom. Interestingly, another group in China has published on a study of their own version of a modified Shu Yu Wan formula [49] and its use for improving QoL for patients with Non-small cell lung cancer. Liang et al's formula included 25 herbs, of which 21 are exactly the same as the ones chosen for the Shu Yu Wan formula selected for our study.

In choosing the CH used in this study, the aim was to identify a balanced combination that would be generally applicable and effective in reducing symptoms for patients with advanced lung cancer. As described above this study will use the modified **Shu Yu Wan** formula with 23 different herbs (Table 2). In addition it was our express intention to include the botanicals that are most likely to improve symptoms and quality of life in patients with advanced lung cancer and not to include botanicals because of any potential anti-cancer activity. In contrast to the usual TCM practice, we will use a standardized formula suitable for all patients, rather than an individualized CH prescription with only selected components.

All the components of the modified **Shu Yu Wan in this protocol** have been approved by Health Canada and listed as acceptable medical ingredients[71, 72], and were the subject of in-depth analysis process as part of a prior CIHR grant application to determine efficacy and safety of CH in cancer patients [73]. Although some mild side effects have been reported when single herbs from the **Shu Yu Wan formula** have been used in doses far exceeding that in our formula, none of the component of this formula are listed as a herbals to be used with caution in *Herb Contraindications and Drug Interactions, 4th edition*[74]. Furthermore most of the ingredients have a high therapeutic index and are unlikely to cause toxicity even used in considerable excess. In general, use of combinations of smaller quantities of herbs seems to cause fewer adverse reactions than larger doses of single herbs, and

combining 23 herbs in one formula allows the use of smaller doses of herbs with synergistic beneficial effects.

More details of individual potential herbal-drug interactions of the components the modified Shu Yu Wan formula is presented in the Appendix 3. It should be noted that most of the data on toxicities reported here come from studies cited in Chinese Herbology textbooks [75].

The closely related modified Shu Yu Wan formula used in another study of advanced lung cancer patient receiving chemotherapy led to significantly fewer adverse reaction when compared to chemotherapy alone [49]. However we note that most of the herbs are metabolized in the liver and that there is potential for reversible hepatotoxicity at high doses or in susceptible patients [76]. This general point will be taken into account in patient selection for the current study. Thus, we propose to exclude patients with abnormal liver function or those taking drugs with long half-lives namely anti-convulsants, anticoagulants, or lithium where minor changes in drug metabolism may lead to delayed and potentially serious sequelae.

2. OBJECTIVES

2.1 Primary objectives:

- To assess the acceptability and feasibility of conducting a 6-week intervention with a standard CH formula designed to treat symptoms commonly experienced by patients with advanced NSCLC.

Acceptability will be assessed using the following questions at the end of the study:

- **Indirectly** from adherence and feasibility (see below)
- **Directly** from responses to the following questions:

i) " *Was the Chinese Herb treatment used in this study easy to take?* " Yes / No

ii) " *If you experienced any problems or side effects taking the Chinese Herb treatment used in this study, please tell us what these were.* " (Free text)

iii) " *If it was available, would you be willing to take the Chinese Herb treatment used in this study again ?* " Yes / No / Don't know

Feasibility will be assessed using the following indices:

- Willingness to participate: proportion of subjects enrolled from number of patients approached .
- Completion rates: proportion of enrolled subjects who completed study (including final assessment) (threshold for positive study: 60%)
- Adherence rates: Proportion of doses taken of number prescribed (threshold for positive study: 66%)

2.2 Secondary objectives:

a) Assess the magnitude of the patients' quality of life response and symptoms change after the 6 -week intervention compared to baseline.

b) Estimate an appropriate sample size for the fully implemented study

3. STUDY DESIGN

3.1 Description of the study

This is a prospective, longitudinal cohort study of a 6-week clinical intervention with Chinese herbs in advanced (Stage 4) NSCLC patients at the Peter Brojde Lung Cancer Centre of the Jewish General Hospital in Montreal. All the active patients who have histologically or cytologically proven metastatic NSCLC with ECOG performance status of 0 -2 will be eligible to participate in the study.

3.2 Sample size

15 patients with advanced non- small- cell- lung cancer will be recruited over a 12- month period at a rate of 1-2 patients per month to receive CH plus standard care. We intend to approach 80 patients from a pool of 200 active advanced NSCLC patients who meet eligibility criteria. Estimated length of the study would be about 18 months.

4. MATERIALS AND METHODS

4.1 Patients

Patients may be screened if they have locally advanced or metastatic NSCLC (per the Union Internationale Contre le Cancer [UICC]/American Joint Committee on Cancer [AJCC] staging system)

4.2 Inclusion Criteria

1. Age 18 years or older
2. Diagnosis of advanced or metastatic NSCLC

3. Stages 4
4. ECOG performance 0-2
5. Life expectancy greater than ≥ 3 months
6. No planned chemotherapy within the next 6 weeks or completed at least 1 cycle of current standard chemotherapy and clinically stable.

4.3 Exclusion Criteria

1. Receiving TKI (Tarceva, Iressa)
2. Brain metastases
3. Patients or families who do not speak English or French
4. Abnormal liver function: Alanine aminotransaminase (ALT) > 40 U/L, Aspartate aminotransaminase (AST) > 55 U/L, Alkaline phosphatase (ALP) > 145 U/L , Bilirubin > 1.7 umol/L.
5. Taking regular anti-convulsants, Coumadin or related anti-coagulant, lithium
6. Taking regular immunosuppressive medications: azathioprine (Imuran), basiliximab (Simulect), cyclosporine (Neoral, Sandimmune), daclizumab (Zenapax), muromonab-CD3 (OKT3, Orthoclone OKT3), mycophenolate (CellCept), tacrolimus (FK506, Prograf), sirolimus (Rapamune)
7. Pregnancy

4.4 Method of Treatment

After written informed consent has been obtained and eligibility has been established the patient will be asked to complete FACT-L and ESAS questionnaires. The patients will be offered the choice of taking the CH formula in capsules or sachets and given instructions about recommendations to improve palatability. The formula should be taken with meals 3 times a day (each dose is either 1 sachet or 4 capsules) for six-weeks. Patient will be instructed to complete a diary each day to confirm adherence to treatment and to indicate the reason(s) that any doses were missed or treatment was stopped. A two-week supply of the CH capsules/sachets will be dispensed to patient at the start of the study. Every two weeks thereafter diaries will be collected/checked with the patient and a new diary dispensed with the next two-week supply of formula. The written instructions about dosage, frequency, dosage timing and what to do in the event of an adverse reaction will be given to patients.

Patients will be allowed to maintain their concomitant medications during the trial with exception of over-the-counter herbal supplements.

4.5 Withdrawal.

Patients may withdraw at any time during the trial for the following reasons:

1. Patient no longer wishes to participate
2. The patient's doctor makes the decision to withdraw the patient if any side effects are suspected.
3. An allergic response or adverse reaction to the Chinese herbs
4. A change in clinical status necessitating emergency admission for treatment
5. Evidence of worsening liver function or need to start medication included in the exclusion criteria.
6. Reduction of chemotherapy dose due to Grade 3 toxicity

In case if participation terminated prematurely, patient will still be asked to attend for the end of the study visit.

5. STUDY TREATMENT

5.1 Chinese herbs Formulation, Packaging, and Handling:

Chinese herbs for study formula (**Shu Yu Wan**)will be imported from Sun Ten Pharmaceutical Company in Taiwan and will be manufactured as a sachets and capsules by BEMA Botanicals distribution company in Vancouver. As described above BEMA have in place processes for certifying sourcing of herbs and verification of absence of contaminants and complies with Health Canada's Good Manufacturing Practices. BEMA will compound the capsules and sachets (http://www.bemabotanicals.com/).The signed copy of certificate of analysis (COA) provided by Bema's supplier will be kept with BEMA. The BEMA Botanicals obliged periodically inspect the cultivation site and analyze the samples to ensure they are fresh and not sulfur fumigated.

BEMA's quality assurance department also will keep a copy together with all batch manufacturing records. All the basic testing such as heavy metals, microbiological test, etc. is conducted by SUNTEN's quality assurance department.

The formula will be shipped in light opaque-white HDPE jars that contain an estimated 500 caps/sachets to the Peter Brojde Lung Cancer Clinic in Montreal by UPS (about 3 days), and stored at room temperature.

Table 2 **Study formula - Shu Yu Wan (*Chinese Yam Pill*)**

	Ingredients	Ratio	Percent	Daily dose (mg)
1	**RenShen** (*Radix et Rizoma Ginseng*)	7	3.5%	350
2	**Bai Zhu** (*Rhizoma Atractylodis*)	6	3.0%	300
3	**Fu Ling** (*Poriae*)	5	2.5%	250
4	**Zhi Gan Cao** (Radix *GlycyrrhizaPreparata*)	20	10.0%	1000
5	**Shu Di Huang** (*Rehmannia glutinosa*)	10	5.0%	500
6	**Bai Shao** (*Radix Paeoniae Alba*)	6	3.0%	300
7	**Dang Gui** (*Radix Angelica sinensis*)	10	5.0%	500
8	**ChuanXiong** (*Rhizoma Chuang xiong*)	6	3.0%	300
9	**Gui Zhi** (*Ramulus Cinnamomum*)	10	5.0%	500
10	**Xing Ren** (*Semen armeniaca amarum*)	6	3.0%	300
11	**JieGeng** (*RadixPlatycodonois*)	5	2.5%	250
12	**Fang Feng** (*Radix Saposhnikoviae*)	6	3.0%	300
13	**Da Zao** (*Fructus Jujubae*)	5	2.5%	250
14	**ShenQu** (*Massa Medica Fermentata*)	10	5.0%	500
15	**Dong Chong Xia Cao**(*Cordyceps*)	10	5.0%	500
16	**Shan Yao**(*RhizomaDioscoreae*)	30	15.0%	1500
17	**Mai Men Dong** (*Radix Ophiopogonis*)	6	3.0%	300
18	**Chai Hu** (*Radix Bupleuri*)	5	2.5%	250
19	**E Jiao** (*Colla Corii asini*)	7	3.5%	350
20	**Bai Bian Dou** (*Semen Lablab Album*)	10	5.0%	500
21	**Gan Jiang** (*Rhizoma Zingiberis*)	3	1.5%	150
22	**Ling Zhi** (*Ganoderma*)	10	5.0%	500
23	**Hong ZhingTian** (*Rhodiolae Crenulatae*)	7	3.5%	350

	Total	200	100	10g

5.2 Study assessments

Flowcharts of scheduled study assessments are provided in Table 3. Patients will be closely monitored for safety and tolerability throughout the study. At each visit patients will be asked about new or worsening of existing symptoms. The severity of the adverse reaction will be determined by Common Terminology Criteria for Adverse Events (CTC AE) version 3.0. All assessments must be performed and documented for each patient in the CRF.

5.3 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit. Demographic data will include age, sex, and self-reported race/ethnicity.

5.4 Patient-Reported Outcomes

Symptoms and health status will be assessed using the Functional Assessment of Cancer Therapy-lung (FACT-L) and ESAS, (Edmonton Symptom Assessment System)(Appendix 3). The FACT-L is a 36-item self-report questionnaire that evaluates quality of life in lung cancer patients [77, 78]. Twenty-nine items measure physical, social, emotional and functional well-being; The final 7 items constitute the Lung Cancer Symptom Scale (LCSS)[79].

The questionnaires, available in French and English, will be distributed by the staff and completed by the patient. The questionnaire(s) will be completed on Day 1 (prior to any other discussions with study personnel) and at each visit (every 2 weeks) until study completion at 6 weeks. Study personnel will review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires will be kept in the patient's research record for data verification.

hTable 3 **Schedule of Assessments**

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	Screening visit	Visit1 (0)	Visit 2 (2 wks)	Visit 3 (4 wks)	Study end (6wks)
Written Consent	+				
Medical history (including other medical conditions, cancer type and stage and all medications)	+				
Update medical history and verify all medication		+	+	+	+
Blood test as per standard of care	+	+	+	+	+
INR test			+		+
Physical exam as per standard of care	+	+	+	+	+
Vital signs	+	+	+	+	+
Height	+	+			+
Weight	+	+	+	+	+
Karnofsky performance status	+	+	+	+	+
CT chest as per standard of practice					
Revised Edmonton Symptom Assessment System		+	+	+	+
FACT-L		+	+	+	+
Chinese herbs Dispensed		+	+	+	
Diary Returned/Dispensed		+	+	+	+
End of study acceptability questionnaire					+

6.0 CONFIDENTIALITY AND DATA HANDLING

6.1 Patient Confidentiality

All the information collected during the study will remain confidential within the limits of the Law. The principal investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On any study documents subjects should not be identified by their names, but by a unique subject ID number (identification code). The principal investigator should keep a subject enrollment log showing codes, names and addresses. This log will be kept for the period of one year after the end of the study. None of the information collected from this register will be for research purposes and all information will be destroyed after 12 months following the end of your participation in this study. All the other study information will be kept for 25 years by the principal investigator of the study.

The study results could be printed/published in medical journals or shared with other people at scientific meetings. The study team will comply with the requirements for publication of study results.

For the purpose of monitoring this research, and research study files as well as medical records of participants could be checked by a person authorized by the Research Ethics Committee of the Jewish General Hospital. These people are obliged to respect information privacy.

6.2 Access to source documents and data handling

Access to patient information gathered throughout the course of this study will be strictly restricted to the members of the research team, specifically, the study investigators, research assistants involved in data collection and data entry, the statistician, and others in the event of a serious adverse event. Others who may gain access to the data would include the members of the Hospital Institutional Ethics Board who oversee the ethical conduct of the study; monitors assessing the accuracy of the data collection and entry; and Natural Health Product Directorate, Health Canada that oversees the use of Natural Health Products, including Traditional Chinese Medicine.

7.0 COMPENSATION

There will be no costs to patients for participating in this study. The study drug and research procedures will be provided to them free of charge.

Taxi vouchers will be provided to cover the cost of getting to and from the hospital for 3 out of 5 visits. The remaining 2 visits are considered standard of care.

If patient suffer an injury as a result of participating in the study, necessary medical treatment will be available at no additional cost. Unless required by law, compensation for such things as lost wages, disability or discomfort due to such an injury will not be offered.

8.0 CONTRIBURION OF THIS STUDY TO THE FIELD OF RESEARCH AND HEALTH

This pilot will make an important contribution to the field of cancer care and clinical research by providing essential information on the acceptability for patients and the feasibility of administering this standardized CH formula (***Shu Yu Wan***) as an adjunctive therapy to help manage the symptoms of lung cancer patients in the clinical setting. We anticipate that the data collected on symptoms may give some preliminary evidence of treatment effectiveness. Both types of information are required before

mounting further clinical trials to evaluate more fully the potential contribution of the formula to improve quality of life and symptom management of patients with lung cancer.

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