An Evaluation of Proglucamune in the Treatment of Protective Qi

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Protocol for a proof-of-concept and feasibility study to evaluate the effect of ß-glucan on Protective Qi Deficiency in Adults

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Abstract

Introduction: Protective Qi is a Traditional Chinese Medicine (TCM) concept important for human defense against pathogenic invasion. We hypothesized that β-glucan, a polysaccharide that enhances mucosal immunity, mitigates Protective Qi deficiency (PQD). This protocol outlines a non-randomized (uncontrolled) proof-of-principle study to determine the potential effect of β-glucan on PQD in adults of both sexes.

Method and analysis: TCM practitioner will recruit 29 participants in one month from March 2018. The PQD status of the qualified participants will be assessed via a standardized method and conventional method at the same time. Subsequently, the participants will be treated with β-glucan in a dose of 200 mg/day for 8 weeks and assessed by a single TCM practitioner throughout the study. The primary outcome will include β-glucan's effect on improving PQD. Secondary outcome will be β-glucan's effect on improving Generic Qi deficiency (GQD).

Ethics and dissemination: Ethics approval was obtained from the Institutional Review Board (Advarra®, Toronto, Canada Pro00024034). The research followed guidelines of the Declaration of Helsinki and Tokyo for human subjects. This study will inform the decision to proceed with randomized controlled trial to assess the effect of this intervention.

Trail registration number NCT03829228

1. Introduction

Qi is a central concept of traditional Chinese medicine (TCM) and was first documented in the oldest TCM writings more than 2000 years ago. Generally speaking, Qi refers to the vital energy of the body and is derived from two primary sources: 1) inborn Qi (that may be construed as genetics), and 2) pectoral Qi (can be construed as metabolism). Moreover, Qi manifests itself in two forms: Nutritive Qi and Protective Qi (PQi), which can be understood to reflect an individual's nutritional state and immune health, respectively. Regarding the latter, PQi functions to defend the body from the invasion of external pathogens. In the language of TCM, PQi is associated with Yang (as opposed to Yin) and metal (as opposed other elements such as water, wood, fire, and earth). TCM also emphasizes that PQi works primarily on the body surface as a defensive barrier. In this context, PQi is analogous to the anatomical barriers and immune cells of the innate immune system located for example, at the mucosal surfaces of the respiratory and digestive tract.

Protective Qi deficiency (PQD) manifests as a predisposition to cold* (*, as defined in TCM), susceptibility to wind* (that carries pathogens), abnormal sweating, and fatigue. Clinical examination of individuals with PQD reveals a feeble or weak pulse as well abnormal tongue features such as the appearance of a thin whitish coating, atypical thickness, and uncharacteristic teeth marks on the side. The individual's face often lacks gloss. Notably, these manifestations are mild, may happen to many people and, from the perspective of western medicine, may not in fact warrant diagnosis of an individual as being sick. If left untreated however, TCM indicates that a worsening of symptoms may ensue, such as the onset of coughing, fever, headache, delirium, bleeding, etc. In this regard, the identification of an individual with PQD is viewed as an aspect of disease prevention in TCM.

TCM has developed a number of methods to strengthen the PQi. Among these is the use of Reishi, either alone or in combination with other TCM remedies. Although there is no definitive data on the treatment duration of Reishi or Reishi-containing formulas needed for improving PQi, anecdotal reports are available that claim significant improvement within days. Notably, Western medicine has identified immune-boosting properties of Reishi, which may explain the PQi enhancing effects of this plant. Specifically, β-glucan – a component of Reishi - has been shown to activate macrophages (1-3), neutrophils (4, 5) and other immunocytes (6-8), and may exhibit particular benefits among macrophage-rich organs such as the lung, liver and spleen. In fact, β-glucans from sources other than Reishi, such as the baker's yeast, are able to initiate similar immune responses and clinical benefits (9).

A notable feature of TCM is that the diagnosis of sickness and disease is made based upon the signs and symptoms observed by doctors and reported by patients. As such, the diagnostic criteria used in the identification of sickness and disease are largely qualitative in nature; there are few established standards that quantitatively evaluate an individual's health status. Hence, there is a need to develop diagnostic

methods that incorporate the principles of TCM, but which also incorporate standardized, quantifiable evaluations. Such evaluations would measure the magnitude of signs and symptoms, thereby providing a more consistent diagnostic tool that would be less subject to the biases and subjectivity of individual clinicians, and could be more uniformly applied across large populations.

The overlap of TCM and western medicine concerning the beneficial effects of Reishi for its Qi enhancing and immune-modulating effects, respectively, has prompted us to investigate whether or not Reishi, in conjunction with other natural products used in TCM, can enhance an individual's PQi. More specifically, if a commercially available dietary supplement (Proglucamune, USANA Health Sciences) containing powdered Reshi and Shitake mushrooms as well as Baker's yeast extract, and which is comprised of 25% β-glucans by weight, will improve an individual's PQi.

The aim of this preliminary study is to provide proof-of-principle of the effect β-glucan on PQD in adults. The secondary objective is to explore the feasibility of studying β-glucan's effect on improving Generic Qi (GQi) via the standardized method and via conventional method

2. Methods and analysis

2.1 Study design

This proof-of-concept and feasibility study is a non-randomized study, and will employ a one-group pretest posttest design. The participants will receive the β-glucan intervention. The study will follow guidelines of the Declaration of Helsinki and Tokyo for human subjects, and reported using Standard Protocol Items: Recommendations for Pilot or Feasibility Trials reporting template (CONSORT 2020) [10]. Throughout the study, all participants will be accessed by a single TCM practitioner, who had been practicing TCM for over 25 years and had received Good Clinical Practice (GCP) training (https://gcp.nidatraining.org) prior to the study.

2.2 Participants

The number of recruited participants is determined with reference to previous β-glucan studies that reported a significant effect on UTRI [11-14].

2.2.1 Inclusion criteria

1. Male or females aged 18 to 65 years (inclusive) without regard to race or ethnic background
2. Provide a signed Informed Consent prior to entry in the study.
3. Willing to follow all study instructions and consume the assigned investigational product for 12 weeks.

4. Not currently taking a β-glucan containing supplement or any other supplement that might interfere with the study design.
5. Ability to swallow tablets and pills.
6. Diagnosed as having Qi deficiency based on the following criteria:
    - exhibit a history of susceptibility to cold*
    - exhibit a shortness of breath
    - exhibit a lack of energy or excessive fatigue
    - susceptible to spontaneous perspiration
    - exhibit a corpulent tongue with or without white fur
    - unwillingness to speak
    - weak or powerless pulse
    - pale complexion

2.2.2 Exclusion criteria

1. Persons diagnosed by TCM as having medical conditions other than low Qi.
2. Significant acute or chronic illness or other medical conditions that will prevent or interfere with giving an informed consent, or with participation in the study.
3. Persons with insulin-dependent and orally controlled diabetes will also be excluded from the study
4. Scheduling difficulties or lack of transportation that will prevent or interfere with their ability to attend all of the necessary study visits.
5. Persons medically diagnosed with depression or anxiety disorders.
6. Persons with a history of alcohol abuse or other substance abuse within the previous 2 years.
7. Females who are attempting to become pregnant, pregnant, lactating or who have given birth within 1 year.
8. Persons who have had a medical surgery in the past 4 weeks or have scheduled a surgery during the study period.
9. Persons currently enrolled in a clinical trial, or who have completed a clinical trial within the last 4 weeks.
10. Allergies to mushrooms or other fungi.
11. Significant problems with constipation or diarrhea.

12. Person exhibiting symptom of cold*(*as defined by TCM) within the past 7 days
13. A lifestyle or schedule incompatible with the study protocol.
14. Persons who are allergic to yeast products, have autoimmune disease/an immune disorder, or take antidepressants, blood thinners (anticoagulants, acetylsalicylic acid), or immunosuppressant medication

2.3 Recruitment and consent process

Subjects will be recruited through advertisement and referral from other TCM practitioners. Subjects will be documented by the referral practitioners and will not be referred without prior consent. Subjects that meet the criteria for inclusion will be enrolled. At the enrollment visit, the practitioner will independently assess the participants' PQD status: 1) via the standardized method using the PQD scoring parameters (Table 1 and 2), and 2) via conventional method using traditional TCM diagnosis of PQD status on a binary outcome (Yes/No). For each participant, the standardized and conventional assessments will be successively made at the same visit. The enrollment will start in March and concluded in April 2018.

2.4 Intervention

After the subjects are consented, a TCM practitioner will evaluate patients in a clinical setting with the objective of identifying subjects with PQD based upon the traditional, qualitative measures of TCM. Simultaneously, we will administer the Subject Record at Screening/1st visit and quantitate the participants' PQD status by employing the Standardized Diagnostic Questionnaire (Appendix I) of PQD. Subjects diagnosed as having PQD based on conventional method will be asked to return to the clinic for a second visit in which a basic physical exam (Appendix II), include that of the head, ears, eyes, nose, throat, etc., will be conducted by the PI to ensure the general health condition of subjects are compliant with the inclusion/exclusion criteria. The qualified subjects will then be re-evaluated for PQD and treated with the dietary supplement Proglucamune for 8 weeks.

Following screening, participants with PQD will begin treatment immediately. All participants will be provided with a bottle containing 60 treatment tablets in a sealed bottle and instructed to consume 2 tablets/day for the next 4 weeks. More specifically, subjects will be asked to consume 2 tablets/day of Proglucamune, a supplement currently marketed by USANA Health Sciences as a supplement that supports robust immune function. If any subjects are taking medications, they will be instructed to take the product at least 3 hours before or after the medication. Written instructions concerning how to consume the treatment, as well as information regarding treatment storage conditions and the contact information of the investigators, will be included with the dietary supplement.

Following treatment, participants will return to the clinic every 2 weeks for a period of 8 weeks for a follow-up assessment of their Protective Qi status (Figure 1). At each clinic visit, subjects will be required to undergo a TCM diagnostic work-up to assess their Protective Qi status and to complete the Subject Record at Follow-up (Appendix III). On day 28 (interim clinic visit #3), participants will return any unused treatment tablets that were provided during the first clinic visit. In addition, they will be provided with an additional allotment of 60 treatment tablets in a sealed bottle, and again instructed to consume 2 tablets/day of Proglucamune for the next 4 weeks. This will provide enough tablets for each subject to complete the study.

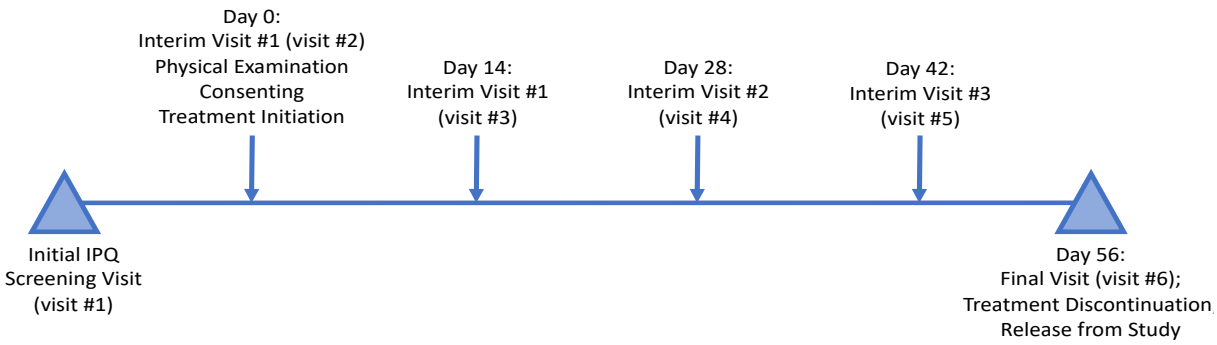

Figure 1 – Clinical Study Design. PQD subjects will begin a 56-day treatment on study Day 0 after initial screening. These successive interim evaluations and a final clinical assessment will be conducted every 14 days thereafter. A final clinical assessment will be performed on Day 56 and mark the end of study for subject participants.

2.5. Outcome measures

2.5.1Primary outcome

The primary outcome will explore the proof-of-principle of β-glucan's effect on improving PQi via conventional method and via standardized method.

2.5.1.1 Change of Protective Qi Score (PQS) assessed by standardized method

Protective Qi of each participant at baseline and each follow-up visit will be measured by an on-site investigator (licensed TCM practitioners) through a standardized quantitative assessment (Table 2). The evaluation includes 3 health conditions relevant to PQD (cold frequency, symptoms, and signs). Each condition will be scored on a 1-10 scale based on a set of standardized criteria (Table 1). The sub-scores will be weighted to arrive at a final PQS. So this PQS will be on a 1-10 scale, with 10 being the most healthy state. The change of the PQS from baseline, indicating the treatment effect, will be calculated and analyzed by statistical means.

2.5.1.2 Change of Protective Qi (PQi) Status assessed by traditional method

Protective Qi status of each participant at baseline and each follow-up visit will be measured by an on-site

investigator (licensed TCM practitioners) through the qualitative traditional assessment. The status was characterized by non-PQD or PQD. The change of PQi status from baseline, indicating the treatment effect, will be calculated and analyzed by categorical statistic.

2.5.2 Secondary outcome

Since PQi is a component of Generic Qi (GQi), we will evaluate the effect of Proglucamune on the secondary outcome Generic Qi Score (GQS) and GQi status.

2.5.2.1 Change of Generic Qi Score (GQS) assessed by standardized method

Generic Qi of each participant at baseline and each follow-up visit will be measured by an on-site investigator (licensed TCM practitioners) through a standardized quantitative assessment (Table 4). The evaluation includes 5 sets of criteria indicative of Generic Qi insufficiency (cold history, symptoms of PQD, symptoms of Lung Qi Deficiency, symptoms of Heart and Spleen Deficiency, and signs of GQD). Each set will be scored on a 1-10 scales, with 10 being the most healthy state (Table 3). The sub-scores will be averaged to arrive at a final GQS. So this GQS will be on a 1-10 scale, with 10 being the most healthy state. The change of the GQS from baseline, indicating the treatment effect, will be calculated and analyzed by statistical means.

2.5.1.2 Change of Generic Qi (GQi) Status assessed by traditional method

Generic Qi status of each participant at baseline and each follow-up visit will be measured by an on-site investigator (licensed TCM practitioners) through qualitative traditional assessment. GQi status was characterized as Generic Qi Deficiency (GQD) or non-GQD. The change of GQi status from baseline, indicating the treatment effect, will be calculated and analyzed by categorical statistic.

2.6 Statistical analysis

We will follow intention-to-treat method to analyze participants' PQi and GQi change. In the case of missing data that resulted from withdrawn participants or missing visits, the PQi and GQi records from the previous visit will be used (Last Observation Carried Forward, or LOCF, imputation).

Baseline data will be imported into RStudio [15] analysis and reported using descriptive statistics.

Changes in the PQS and GQS at follow-up will be assessed using One-Way ANOVA. Change in the PQi status and GQi status will be assessed using repeated measures logistic regression.

All statistics will be conducted using RStudio.

3.0 Data management

Study participants will be assigned a unique code to enable data linkage throughout follow-up. All data will be entered into an electronic management system by research team member. To ensure accurate data

entry, we will check data entry for a random 10% sample records entered after that. Data collection and study conduct will be monitored through weekly meeting with the research team.

4.0 Discussion

This study will explore a novel approach of bridging TCM and WM, i.e., investigating the utility of an established WM therapy for mitigating a condition defined by TCM principle. Specifically, this study will investigate the potential using β-glucan to improve PQi and GQi in participants with PQD. Given the lack of stringent criteria of PQD diagnosis, this study will seek the proof-of-principle of standardized diagnostic PQS and GQS developed by experts' panel, especially on PQS.

5.0 Funding

This study and all associated expenses will be financed entirely by the sponsor (USANA Health Sciences, Inc. 3838 West Parkway Blvd., Salt Lake City, UT 84120)

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Table 1. Calculation of Standardized Protective Qi Score (PQS)

Category	Parameter	Weight
Cold History	**TCM Inquiry (Cold frequency)**	25%
Symptoms of PQD	**TCM Inquiry (Spontaneous sweating)**	16.7%
	TCM Inquiry (Aversion to wind & cold)	16.7%
Sign of PQD	**TCM Inspection（Tongue）**	8.3%
	TCM Auscultation（Low voice & apathy）	6.7%
	TCM Palpation (Overall Pulse)	10%
	TCM Palpation (Cun Pulse)	16.7%

The PQS were obtained from the standardized protocol shown in Table 2, and the weighting coefficients were based on TCM investigators' clinical experience.

Table2: Standardized criteria for PQS assessment

Candidate Parameter		Method of measurement and scores	
Cold Frequency	TCM Inquiry (Cold frequency)	No cold in the past 2 months	0
		Once in the past 2 months	1
		Twice in the past 2 months	2
		3 times or more in the past 2 months	3
Symptoms of PQD	TCM Inquiry (Spontaneous sweating)	No spontaneous sweating, sweat only with intense physical activities	0
		Sweat with routine physical activities	1
		Sweat heavily with routine physical activities	2
		Sweat with slight physical activities like walking	3
		Sweat spontaneously	4
	TCM Inquiry (Aversion to wind & cold)	No aversion to wind or cold	0
		Aversion to wind	1
		Aversion to cold, but relieved by adding light clothing	2
		Aversion to both cold (but relieved by light clothing) and wind, or susceptible to cold when exposed to wind or cold	3
		Aversion to cold (only relieved by think clothing that covers whole body); or very easily catch a cold when exposed to wind or cold	4
Sign of PQD	TCM Auscultation（Low voice & apathy）	The participant's voice is loud & clear at a distance of 2m from the investigator	0
		The participant can be heard & understood at 2m from the investigator, but the voice is recognizably weak.	1
		The participant's voice is clearly low at 2m from the investigator & needs much attention to understand.	2
		The participant can be heard from 2m but need repeated clarification.	3
		The participant cannot be heard with a clear understanding at a distance of 2m.	4
	TCM Inspection（Tongue）	The tongue looks light red with thin white coating and is of proper size.	0
		The tongue looks pale in color with white coating; however, the tongue is of proper size & has no tooth mark on the sides.	1
		The tongue looks pale with white coating. This size is slightly larger than normal. Tooth-marks are visible but are limited to part(s) of the tip and sides of the tongue.	2
		The tongue looks pale with white coating. This size is significantly larger than normal. Tooth-marks are visible along the full length of the tip and sides of the tongue.	3
	TCM Palpation (Overall Pulse[1])	Normal pulse	0
		Deficient Pulse is detectable but not apparent	1
		Apparent Deficient Pulse	2
	TCM Palpation (Cun Puls[1])	Normal pulse	0
		The pulse shows characteristics of Floating or Deficient Pulse, but not both.	1
		Floating pulse is present, Deficient Pulse is detectable but not apparent.	2
		Floating pulse is present, Deficient Pulse is apparent.	3

[1]. Overall pulse indicates the overall impression of pulse at the three locations: Cun, Guan, & Chi.

Table 3. Calculation of Standardized Generic Qi Score (GQS)

Category	Parameter	Weight
Cold History	**TCM Inquiry (Cold frequency)**	20%
Symptoms of PQD	**TCM Inquiry (Spontaneous sweating)**	10%
	TCM Inquiry (Aversion to wind & cold)	10%
Symptoms of Lung Qi Deficiency	**TCM Inquiry (Shortness of breath)**	10%
	TCM Inquiry (Unwillingness to talk)	10%
Symptoms of Spleen and Heart Qi Deficiency	**TCM Inquiry (Limb weakness)**	6.67%
	TCM Inquiry (Lack of energy)	6.67%
	TCM Inquiry (Low spirit, fatigue)	6.67%
Signs of GQD	**TCM Inspection（Tongue）**	5%
	TCM Auscultation（Low voice & apathy）	5%
	TCM Palpation (Overall Pulse[1])	5%
	TCM Palpation (Cun Pulse)	5%

The GQS were obtained from the standardized protocol shown in Table 4, and the weighting coefficients were based on TCM investigators' clinical experience.

Table 4: Standardized Criteria for Generic Qi diagnosis

Candidate Parameter		Method of measurement and scores	
Cold Frequency	TCM Inquiry (Cold frequency)	No cold in the past 2 months	0
		Once in the past 2 months	1
		Twice in the past 2 months	2
		3 times or more in the past 2 months	3
Symptoms of PQD	TCM Inquiry (Spontaneous sweating)	No spontaneous sweating, sweat only with intense physical activities	0
		Sweat with routine physical activities	1
		Sweat heavily with routine physical activities	2
		Sweat with slight physical activities like walking	3
		Sweat spontaneously	4
	TCM Inquiry (Aversion to wind & cold)	No aversion to wind or cold	0
		Aversion to wind	1
		Aversion to cold, but relieved by adding light clothing	2
		Aversion to both cold (but relieved by light clothing) and wind, or susceptible to cold when exposed to wind or cold	3
		Aversion to cold (only relieved by think clothing that covers whole body); or very easily catch a cold when exposed to wind or cold	4
Symptoms of Lung Qi Deficiency	TCM Inquiry (Shortness of Breath)	1-10 scale, with 1 indicating the most symptomatic	
	TCM Inquiry (Unwilling to talk)		
Symptoms of Spleen and Heart Qi Deficiency	TCM Inquiry (Limb weakness)	1-10 scale, with 1 indicating the most symptomatic	
	TCM Inquiry (Lack of energy)		
	TCM Inquiry (Low spirit, fatigue)		
Sign of GQD	TCM Auscultation （Low voice & apathy）	The participant's voice is loud & clear at a distance of 2m from the investigator	0
		The participant can be heard & understood at 2m from the investigator, but the voice is recognizably weak.	1
		The participant's voice is clearly low at 2m from the investigator & needs much attention to understand.	2
		The participant can be heard from 2m but need repeated clarification.	3
		The participant cannot be heard with a clear understanding at a distance of 2m.	4
	TCM Inspection （Tongue）	The tongue looks light red with thin white coating and is of proper size.	0
		The tongue looks pale in color with white coating; however, the tongue is of proper size & has no tooth mark on the sides.	1
		The tongue looks pale with white coating. This size is slightly larger than normal. Tooth-marks are visible but are limited to part(s) of the tip and sides of the tongue.	2
		The tongue looks pale with white coating. This size is significantly larger than normal. Tooth-marks are visible along the full length of the tip and sides of the tongue.	3
	TCM Palpation (Overall Pulse[1])	Normal pulse	0
		Deficient Pulse is detectable but not apparent	1
		Apparent Deficient Pulse	2
	TCM Palpation (Cun Puls[1])	Normal pulse	0
		The pulse shows characteristics of Floating or Deficient Pulse, but not both.	1
		Floating pulse is present, Deficient Pulse is detectable but not apparent.	2
		Floating pulse is present, Deficient Pulse is apparent.	3

[1]. Overall pulse indicates the overall impression of pulse at the three locations: Cun, Guan, & Chi.

Appendix I

Participant questionnaire (Qi-related information)

Part I

Do you have a history of **catching** a cold* (*, defined by TCM) in the past year? If no, please proceed to Part II of this section; if yes, please fill out the following blanks.

1. How many times did you **catch** a cold* in the **past year**?
   i. Once — duration:

   ii. Twice — duration of cold #1:
   duration of cold #2:

   iii. 3 times or more — duration of cold #1:
   duration of cold #2:
   duration of cold #3:
   duration of other colds:

   iv. During the above colds*, did you experience any of the following symptoms:
   - Sneezing
   - Coughing
   - Sweating
   - Nasal discharge or congestion
   - Itching or painful throat
   - Headache
   - Aversion to wind and cold
   - General pain and malaise
   - High fever (body temperature > 39.1^0C)

2. How many times did you **catch** a cold* **last winter (2017 – 2018)**?
   i. Once — duration:

   ii. Twice — duration of cold #1:

duration of cold #2:

iii. 3 times or more

duration of cold #1:

duration of cold #2:

duration of cold #3:

duration of other colds:

iv. During the above colds*, did you experience any of the following symptoms:

- Sneezing
- Coughing
- Sweating
- Nasal discharge or congestion
- Itching or painful throat
- Headache
- Aversion to wind and cold
- General pain and malaise
- High fever (body temperature > 39.1^0C)

3. How many times did you **catch** a cold* in the **last two months**?

i. Once

duration:

ii. Twice

duration of cold #1:

duration of cold #2:

iii. 3 times or more

duration of cold #1:

duration of cold #2:

duration of cold#3:

duration of other colds:

iv. During the above colds*, did you experience any of the following symptoms:

- Sneezing
- Coughing

- Sweating
- Nasal discharge or congestion
- Itching or painful throat
- Headache
- Aversion to wind and cold
- General pain and malaise
- High fever (body temperature > 39.1^0C)

4. How many days have elapsed since you last experienced symptoms of a cold*? If you currently have an ongoing cold, write "ongoing".

Part II

1. Do you have spontaneous perspiration?
    a. I don't readily sweat, or sweat only with intense physical activities
    b. I sweat with some slight physical activities like walking
    c. I sweat spontaneously
    d. I sweat heavily and instantly with physical activities
    e. I sweat even without any physical activities
2. Aversion to wind or cold
    a. No aversion to wind or cold
    b. Aversion to wind
    c. Aversion to cold, but relieved by adding clothing
    d. Aversion to both cold (but relieved by clothing) and wind, or susceptible to cold* when exposed to wind or cold weather
    e. Aversion to cold (only relieved by clothing that covers whole body), very readily catch a cold* when exposed to wind or cold weather

Part III

1. Do you often feel shortness of breath?
2. Do you often feel unwillingness to talk?

Part IV

1. Do you often feel limb weakness?
2. Do you often feel a lack of energy?
3. Do you often feel in low spirits?

Part V

1. Do you often have cough?
2. Do you often have thin sputum
3. Do you often feel timidity
4. Do you have nasal allergies (stuffy and itchy nose, runny nose with clear drainage)?

Part VI

1. Do you often have poor appetite?
2. Do you have loose stools
3. Do you often have uncomfortable feeling in the abdomen after eating?

Part VII

1. Do you often feel palpitations?
2. Do you often feel depressed?

Part VIII

1. Do you have frequency of urination?
2. Do you often feel soreness of lower back?
3. Do you have cold limbs, especially legs?

Appendix II

Physical Examination

Part I

1. Height:
2. Weight:
3. Blood Pressure:
4. Heart Rate:
5. Respiration Rate:

Part II

1. weak or powerless pulse
2. cun-pulse superficial or weak
3. corpulent tongue or with white fur
4. low voice

Appendix III

Participant questionnaire – Section II (Generic Qi-related information)

Part I

1. Did you ***catch*** any cold* (*as defined by TCM) in the past two weeks?

   a. If no, please proceed to Part II

   b. If yes: how many times, and how long did it last?

      v. Once duration:

      vi. Twice duration of cold #1:
      duration of cold #2:

   c. During the above colds*, did you experience any of the following symptoms:

- Sneezing
- Coughing
- Sweating
- Nasal discharge or congestion
- Itching or painful throat
- Headache
- Aversion to wind and cold
- General pain and malaise
- High fever (body temperature >39.1^{0}C)

   d. How many days have elapsed since you last experienced symptoms of a cold*? If you currently have an ongoing cold, write "ongoing".

Part II

3. Do you have spontaneous perspiration?
   a. I don't readily sweat, or sweat only with intense physical activities
   b. I sweat with some slight physical activities like walking
   c. I sweat spontaneously
   d. I sweat heavily and instantly with physical activities
   e. I sweat even without any physical activities

4. Aversion to wind or cold
   a. No aversion to wind or cold

b. Aversion to wind
c. Aversion to cold, but relieved by adding clothing
d. Aversion to both cold (but relieved by clothing) and wind, or susceptible to cold* when exposed to wind or cold weather
e. Aversion to cold (only relieved by clothing that covers whole body), very readily catch a cold* when exposed to wind or cold weather

Part III

1. Do you often feel shortness of breath?
2. Do you often feel unwillingness to talk?

Part IV

1. Do you often feel limb weakness?
2. Do you often feel a lack of energy?
3. Do you often feel in low spirits?

Part V

1. Do you often have a cough?
2. Do you often have thin sputum
3. Do you often feel timidity

Part VI

1. Do you often have poor appetite?
2. Do you have loose stools
3. Do you often have uncomfortable feeling in the abdomen after eating?

Part VII

1. Do you often feel palpitations?
2. Do you often feel depressed?

Part VIII

1. Do you have frequency of urination?
2. Do you often feel soreness of lower back?
3. Do you have cold limbs, especially legs?