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# Developing an Effective Health Supplement for the Prevention of Osteoporosis

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## ABSTRACT

This study was carried out to investigate the effects of a bone health supporting medicinal herb formula, Herba Epimedii (E), Fructus Ligustri Lucidi (L) and Fructus Psoraleae (L)-(ELP), in maintaining bone mineral density. Laboratory models and a clinical trial were set up to study the mechanistic actions and clinical effectiveness of the herbal formula -ELP. In the *in vitro* studies, ELP on bone metabolism were accessed by three cell lines (UMR-106, MSCs, RAW264.7). In the *in vivo* studies, ovariectomised and calcium deficiency-induced osteoporotic rats were used to test the bone mineral density changes with ELP. A randomized placebo-controlled clinical trial was conducted to measure the mineral density change in post-menopausal women at the spine, femoral and tibial regions, quality of life and safety. *In vitro* tests using different cell lines yielded positive bone supporting results. *In vivo* tests using ovariectomised rats gave good evidences of bone protection. In the clinical trial, one hundred and fifty postmenopausal osteoporosis women were recruited, randomised and allocated to a herbal group (ELP) or placebo group. After 12 months of treatment using the herbal formula, there was a clear trend of BMD increase in the ELP groups although there was no statistical significance. A subgroup of women having more than 10 years' menopause gave the best results ($p<0.05$). The distal tibia peripheral quantitative computed tomography (pQCT) was also measured and showed a decrease of 2.43% in the herbal group compared with 3.67% in the placebo group ($p = 0.05$). No significant adverse effects were found. While laboratory tests demonstrated positive effects on bone metabolism in both *in vitro* and *in vivo* platforms, the clinical trial also showed the ELP help to maintain a BMD balance. ELP could be recommended as a safe preventive agent against osteoporosis.

**Key words:** Traditional Chinese medicine, osteoporosis, health supplement, bone mineral density, tomography

## INTRODUCTION

Osteoporosis is a major health issue worldwide, it is defined as a condition characterized by low Bone Mineral Density (BMD) and micro-architectural deterioration of bone tissues leading to enhanced bone fragility and a consequent increase in fracture risk (Riggs and Melton, 1995; Dambacher *et al*., 2004). Postmenopausal osteoporosis typically affects women within 15-20 years

after menopause. It is complicated with fractures occurring at sites that contain relatively large amounts of cancellous bone (Dambacher *et al*., 2004). The prevalence of osteoporotic fracture is extremely high. Data from US National Health and Nutrition Examination Survey 2005-2008, showed that 9% of adults aged 50 years and over had osteoporosis at either femur neck or lumbar spine. About one-half had low bone mass at either site. The prevalence was higher in women and increased with age (Looker *et al*., 2012).

In China, epidemiological studies have shown that the incidence of osteoporosis in the population over the age of 40 years was 16.1%, over 60 years 22.6% and over 80 years as high as 50% (Li *et al*., 2002). Osteoporosis in the spine not only leads to fractures but would also produce pain and back deformities, which seriously affect patients' quality of life (Cummings *et al*., 1995).

Estrogen plays an important role in coordinating activities of the bone-forming osteoblasts and bone-resorbing osteoclasts in bone homeostasis. Ovarian hormonal deficiency is one of the most important factors leading to postmenopausal osteoporosis, so that Hormonal Replacement Therapy (HRT) has been popular in the prevention of bone loss in postmenopausal women (Christiansen, 1993; Anonymous, 1993). However, treatment with oestrogen has well-known side effects such as breast soreness and nausea and in the long-term, may have increased risks of breast and uterine cancer development and also venous thrombosis (Lindsay *et al*., 1976).

Subsequently, when other therapeutic measures are developed to correct the loss of BMD, the same concept of quick correction, i.e., treatment, is adopted. This concept is acceptable when the loss of BMD is sharp and severe, under which circumstance, effective treatment is required. However, when the BMD is only starting to decline, there is no necessity of artificially bringing it up. Under such situation, maintaining the BMD at a steady level, i.e., adopting a preventive approach, would be the advisable strategy. The treatment philosophy and evaluation criteria will then require modifications. Maintenance of a quality BMD would need the basic requirements of nutrition with adequate calcium and vitamin D intake, exercises and sunlight but if effective agents are available as additional supplements to further support a balanced bone metabolism, it would be a great blessing. Therefore, the specific objective of the study was to investigate the effects of a bone health supporting medicinal herb formula, Herba Epimedii (E), Fructus Ligustri Lucidi (L) and Fructus Psoraleae (L)-(ELP), in maintaining bone mineral density.

## MATERIALS AND METHODS

**Creating an effective herbal formula:** Traditional Chinese Medicine is built on the principle of maintaining the physiological balance. Since pathological processes are not known during its development, Chinese Medicine aims, not at the pathological target but at the maintenance of normal physiological balance. The well known theory of "yin and yang" is a philosophical expression of excess and deficiency which need to be balanced. In the case of osteoporosis prevention, when Chinese herbs are used, the rationale would be one of balanced bone formation and bone resorption. On a cellular level, it would be a balance between osteoblastic construction and osteoclastic destruction. The expected responses would be a steady BMD and not a rapidly increasing one. When we plan a protocol on an osteoporosis prevention program using Chinese herbs, the assessment target would need to follow accordingly, viz., good results would mean a BMD level that is not decreasing but remains steady or rises slowly.

In Traditional Chinese Medicine (TCM) 'osteoporosis', has not been described. However syndromes with back pain, back deformities, loosening teeth etc., have been classified as "Kidney deficiency" which could be manifestations of osteoporosis (Leung, 2003). Chinese herbs have been

widely used in orthopedic practice in ancient history. Their therapeutic effects in treating skeletal problems have been studied and reported in recent years (Yang *et al.*, 2005; PCMPH, 2005; Liang, 1991). Some other Chinese herbs have potential effects on promoting fracture healing (Yu *et al.*, 1999). All these herbs are suitable agents for research on the prevention of osteoporosis.

Three medicinal herbs classically known to have potential of supporting bone health, viz. Herba Epimedii, Fructus Ligustri Lucidi and Fructus Psoraleae are selected to make up a herbal formula (ELP) for the research. The ELP extract is put on laboratory platforms to investigate its mechanism of action. And a clinical trial is conducted to investigate ELP in prevention of osteoporosis among post-menopausal women.

***In vitro* and *in vivo* studies:** The anabolic effects of the formula ELP water extract on bone formation were evaluated using cultured rat osteoblast-like osteosarcoma cell line UMR-106 and rat mesenchymal stem cells (MSCs).

The dosing effects (1, 0.5 and 0.175 g $day^{-1}$) of the antiosteoporosis function of the water extract of ELP formula were tested in ovariectomised rats fed with calcium deficient diet (0.2% calcium, 0.3% phosphorus) and the dosages followed previous experiments completed (Qin *et al.*, 2005; Zhang *et al.*, 2006). Eleven weeks of herbal treatment demonstrated beneficial effects on the preservation of bone mineral density at the proximal femur in a dose-dependent manner with the preference for higher dosage (Sun *et al.*, 2008).

The component herbs of ELP had all been tested and found non-toxic. The ratio of the three herbs in ratio 5:4:1. No significant increase in uterus weight was observed in the herbal formula treated rats. In addition, microarray data of kidney tissue revealed that this herbal formula was able to down-regulate the expression of phase II drug metabolizing enzymes, similar to the effects of estrogens (Ko *et al.*, 2010, 2011; Siu *et al.*, 2010).

**Clinical trial: Use of the triple herb formula ELP for the maintenance of bone mineral density among the post-menopausal women:** Now that we gained basic information about the effectiveness of ELP in the laboratory, we were ready to conduct a clinical trial.

The study design was not for treating osteoporosis which already developed and was under the obvious threat of fractures. Neither was it meant for those who had strong disease background which predisposed to rapidly developing osteoporosis. Post-menopausal women not under the immediate threat and yet have not developed osteoporosis would be a suitable vulnerable group. This group is usually among the "osteopenic".

**Manufacture of herbal capsules (ELP) and placebo for the clinical trial:** Herba Epimedii (voucher No. ICM-2004-2547, main *Epimedium leptorrhizum* Stearn), Fructus Ligustri Lucidi (voucher No. ICM-2004-2566, *Ligustrum lucidum*) and Fructus Psoraleae (voucher No. ICM-2004-2568, *Psoralea corylifolia* L.) were authenticated by and were deposited in the Institute of Chinese Medicine, The Chinese University of Hong Kong. Subsequently the same herbs were prepared into capsules through aqueous extraction processes in a GMP laboratory in a ratio of 10:8:2. All the products passed the heavy metal, toxicity, microbial and pesticides residue test. A properly designed evidence-based, randomised, placebo-controlled clinical was designed. Ethical approval obtained from the Ethics Committee of the Chinese University of Hong Kong.

**Preparation of the medication**

**Herbal capsule:** These contain the herbal extracts. The subjects will take six capsules per day for 12 months.

**Placebo capsule:** These are filled with starch and coloured to imitate the herbal extract. Subjects in the placebo group take six capsules per day for 12 months. Both groups received 1500 mg Calcium carbonate as a supplement daily.

**Subjects:** One hundred and fifty subjects are allocated in block randomization scheme into herbal and placebo groups in equal proportion. Written consents were obtained from subjects prior to the study enrollment.

Inclusion criteria included age between 45 and 60, at least one year post-menopausal according to individual patient's own experience and lumber spine Bone Mineral Density (BMD) lower than 0.891 g $cm^{-2}$, i.e., osteopenia.

Exclusion criteria exclude those on active treatment on bone pathology; subjects with serious concomitant diseases or addictive disorders and those pregnant.

**Data collection:** The primary endpoint was taken as the BMD changes. Secondary end points include quality of life and adverse effects. The BMD at the spine (L1-L4), proximal femoral and proximal tibial regions are determined at baseline, then 4, 8, 12 months using a Hologic 4500 DEXA bone densitometer. A questionnaire for the quality of life (SF-36, Appendix) was completed and follow-up at 4, 8 and 12 months. Fasting blood for liver and renal functions were collected at the same time points as part of the adverse effects analysis.

This design had been accepted as a standard approach in many of the completed drug trials for osteoporosis. The results of our herbal formula, therefore should offer comparative value to the previously completed trials.

**Statistical analysis:** The sample size calculation was based on the assumption of a mean annual decrease in spinal BMD of approximately 1.9% in untreated women (NIH, 2000). The actual SD in our previous study was 3.6%. To detect 1% difference in spinal BMD using a two-sided 0.05 $\alpha$-level test with 90% power required a sample size of 150 postmenopausal osteoporosis patients.

The main efficacy analysis of this intervention study was planned to be performed in a full analysis set according to the intent-to-treat (ITT) principle which was defined as randomized into the study. A baseline evaluation and at least one post-baseline bone density measurement was required. For the continuous variables, means were compared using analysis of variance. The baseline characteristics of the herbal and placebo groups would be compared by chi-square test, two samples t test or Mann-Whitney test. The percentage changes from baseline for each variable were assessed by a two-way analysis of variance (ANOVA) at both 6 and 12 months. The factors tested in the ANOVA model were treatment groups, postmenopausal strata and the interaction between these two factors. All statistical analyses were performed with SPSS 16.0 version. Student t-test and non-parameter test ($\chi^2$-test) were also used to assess treatment effects.

## RESULTS

One hundred and fifty women were enrolled and randomized to either herbal (n = 75) or placebo group (n = 75). The demographic and baseline characteristics of the Intention to Treat (ITT) population (n = 150) are comparable between the two groups. The baseline demographic characteristics and BMD showed no statistically significant differences between the 2 treatment groups. The mean age was 58.4 (3.4) years. The mean time since last menses was 8.2±4.5 years;

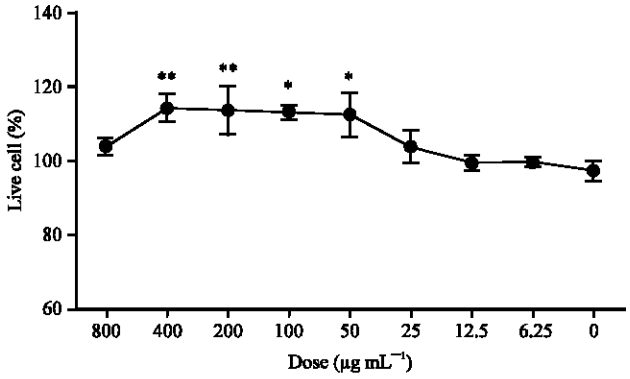


Fig. 1: Effect of ELP water extract on osteoblast-like UMR-106 cells viability for 3 days at different concentrations, Values are the Mean±SEM from three independent experiments in triplicate, **p<0.01; *p<0.05 for significant difference in cell viability from respective baseline culture without treatment

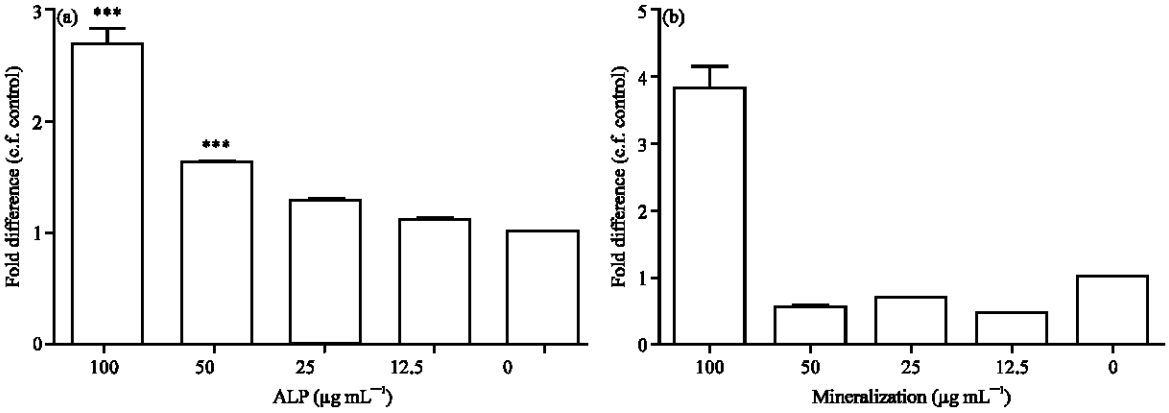


Fig. 2(a-b): Dose effect of ELP on (a) ALP activity and (b) Matrix mineralization in rat MSCs on day 7 and day 14, respectively, Values are the Mean±SEM from three independent experiments in triplicate,***p<0.001 significant difference in ALP activity from respective baseline culture without treatment

the mean age of menopause onset was 50.2±4.0 years. In the intention-to-treat population, the mean compliance rate of the herbal group was 73.7% compared with 81.2% in the placebo group.

***In vitro* study:** ELP significantly increased the proliferation of UMR-106 cells in dose-dependent manner from 50 to 400 μg $mL^{-1}$ (Fig. 1).

In MSCs, ELP stimulated the osteogenic differentiation as indicated by the increase of bone markers such as alkaline phosphatase (ALP) activity and matrix calcium mineralization. ELP elevated the ALP activity significantly at concentrations of 50 and 100 μg $mL^{-1}$ (Fig. 2). The amount of mineralization also increased significantly with ELP (Fig. 2).

On another cell culture platform, ELP significantly inhibited osteoclast formations from RAW264.7 cells upon receptor activation of nuclear factor-κB ligand induction on the fourth day of treatment, at a concentration of 80 and 160 μg $mL^{-1}$. Difference between treated and untreated

cultures of osteoclasts reached statistical significance ($p \leq 0.05$). Our experimental data illustrated that the formula ELP had positive effects on bone metabolism through a double process of osteoblastic activity promotion and osteoclast differentiation inhibition.

**Primary efficacy end point:** Both herbal and placebo groups showed a decrease in spine BMD over 12 months treatment (herbal group -0.31%, placebo group -0.39%). However, the spine BMD of the herbal group was increased 0.69% in subjects who were more than 10 years after menopause, in contrast, the placebo group of the same stratum decreased by 0.61%. The Hip BMD of the herbal group remained unchanged over 12 month treatment. The overall hip BMD of the placebo group decreased by 0.22%. In the subjects with more than 10 years' duration of menopause hip BMD increased by 0.21%, whereas those treated with placebo decreased by 0.52% (Table 1).

As regards the Spine BMD, subjects over 10 years after menopause showed a 0.7% increased after 12 months herbal treatment. In the placebo group, bone loss over 12 months reached 0.6% ($p = 0.067$). The effects of the herbal treatment appeared to be quite different among three different groups of women stratified according to the duration after onset of menopause.

In the herbal group, the number of women showing gain in spine BMD was higher than that of the placebo group among women over 10 years after menopause ($p = 0.028$). The trends of BMD changes at the Hip were similar to the spine but the difference between herbal and placebo groups did not attain statistical significance. If BMD represents the standard changes in the bone density, peripheral quantitative computed tomography (pQCT) which looks at the distal tibia and distal radius, is more sensitive to early influences and rapid changes. In this study, after 12 months of treatment using the herbal preparation, the distal tibia pQCT decreased 2.43% in the herbal group compared with 3.67% in the placebo group ($p = 0.05$) (Table 2). The tibia (T33%) Strength-strain Index (SSI) was increase 1.94% in the herbal group compared with 0.33% in the placebo group ($p = 0.05$) (Table 2).

Table 1: BMD changes between herbal and placebo group

| | Herbal | Placebo | p-value |
|---|---|---|---|
| **Spine** | | | |
| Baseline (g $cm^{-2}$) | 0.7994±0.1089 | 0.7949±0.1011 | 0.794 |
| Change from baseline (%) | | | |
| At month 6 | -0.0100 | 0.3500 | 0.432 |
| At month 12 | -0.3100 | -0.3900 | 0.839 |
| **Subgroup: Menopausal duration >10 years** | | | |
| Baseline | 0.7996±0.1123 | 0.7547±0.1102 | 0.176 |
| Change from baseline (%) | | | |
| At month 6 | 0.1300 | 0.1800 | 0.984 |
| At month 12 | 0.6900 | -0.6100 | 0.067 |
| **Total hip** | | | |
| Baseline (g $cm^{-2}$) | 0.7573±0.0736 | 0.7592±0.0904 | 0.885 |
| Change from baseline (%) | | | |
| At month 6 | 0.1900 | 0.4400 | 0.379 |
| At month 12 | 0.0300 | -0.2200 | 0.438 |
| **Subgroup: Menopausal duration >10 years** | | | |
| Baseline | 0.7492±0.0909 | 0.7296±0.0936 | 0.473 |
| Change from baseline (%) | | | |
| At month 6 | 0.6300 | 0.3000 | 0.516 |
| At month 12 | 0.2100 | -0.5200 | 0.155 |

Table 2: Bone mineral density (BMD) changes at different anatomic sites measured by peripheral quantitative computed tomography (pQCT)

| | Radius 4% from distal end (%) | | | Tibia 4% from distal end (%) | | | Tibia 33% from distal end (%) |
|---|---|---|---|---|---|---|---|
| Group | Total BMD | Trabecular BMD | Cortical BMD | Total BMD | Trabecular BMD | Cortical BMD | Strength strain index |
| Herbal | 6.65 | -1.99 | 3.57 | 6.15 | -2.43 | 3.03 | 1.94 |
| Placebo | 2.03 | 0.95 | -0.28 | 12.17 | -3.67 | 6.41 | 0.33 |
| p-value | | | | | 0.052 | | 0.047 |

**Quality of life (QoL):** The SF 36 quality of life questionnaire was used (Appendix). Eight domains listed as Physical Function (PF), physical role (RP), Bodily Pain (BP), General Health (GH), Vitality (V), Social Function (SF), Emotional Role (ER) and Mental Health (MH). Only the first four domains were evaluated. PF was remarkably improved compared with the baseline and less remarkable compared with the placebo group. Likewise the physical role (RP) was also improved.

The overall incidence of adverse events was 80 with herbal group and 62 with placebo group ($p = 0.688$). The most common adverse events included common cold, back pain and gastrointestinal upset which were self containing and did not affect the compliance. With regard to liver and renal functions, there were no significant changes in the liver and renal functions in both the treatment and placebo groups.

## DISCUSSION

Much work has been done on the use of Chinese herbs to maintain bone density. Claims have been made that the herbal treatment is effective like using pharmaceutical (Xie *et al.*, 2001). However, in a comprehensive review done in China, collecting all available data, no conclusion could be drawn. The reports on the trials have been defective. The methodology adopted ignored randomization, blinding, case number selection and the terminology used was also not uniform (Xie *et al.*, 2005).

In this randomized controlled clinical trial, using a three herbs formula - ELP, we showed that 12 months of treatment gave a clear trend of BMD increased in the herbal group. A subgroup of women having more than 10 years' menopause gave the best result ($p<0.05$) pQCT of distal tibia also showed better results compared with the placebo group ($p<0.05$). The three herbs were safe to consumption and adverse effects were trivial. The BMD improvements appeared to be slow and not remarkable. The changes appeared more impressive in the pQCT findings of the distal tibia, a site considered to be more responsible to early influences.

If a drug is required for the rapid build-up of the bone density, ELP is not a good choice. The strength of this study lies in the proper choice of methodology basing on evidence based medicine. The application of an appropriate methodology as is required in randomized controlled trials, is inevitable. However comparing the efficacy of herbal supplements with pharmaceuticals with well defined targets like bisphosphonates is inappropriate since herbal supplements are known to be used as support rather than treatment and action is known to be slow and weak. Our clinical trials has therefore supported ELP as an effective bone health supplement, rather than a drug to treat osteoporosis.

Since the issuing of FDA guideline on the production of botanical drug products, which could be equivalent to health supplements for specific needs, hundreds of application have been received but up to the end of 2008, only one item has been approved. The only approval is a topical agent derived from probably a herbal item with the least controversy, viz., green tea. And since the

product is for external use, the safety issue would be of less concern (Chen *et al.*, 2008). The possible reason for the disappointingly slow pace of development, according to US analysts, must include difficulties in quality control and lack of determination from the industry side. Difficulties in quality control make large scale clinical trials (phase 3) difficult. Industry's lukewarm interest originates from the absence of meaningful exclusivity of the botanical product and yet the problematic translation of anecdotal experiences in traditional or alternative medicine (U.S. DHHS, 2004; Wu *et al.*, 2004).

In our viewpoint, anecdotal experiences cannot be taken automatically as evident. Instead, using the modern concept of clinical trial could reveal the efficacy of health supplements with specific indications after completing the trial using the modern methodology of clinical research. Safety is an essential issue that deserves universal emphasis and once safety is definitely assured, we would like to see that clinical trials could be more freely encouraged although the absolute quality of the herbs used would remain a difficult problem. Until good agricultural practice under strict rules and regulations could become a genuine enforceable practice, a reasonable range of quality variations could be considered inevitable. With regard to exclusivity, the use of simple combinations of herbs would help a lot. After all, traditional Chinese medicine treatment believes in multiple target management making combined herbal formulation mandatory.

FDA and other regulating bodies' regulations demand that once a disease claim is made, safety, effectiveness and quality assurance become mandatory (Leung and Cheng, 2008). A health supplement can claim a beneficial effect on 'bone health' but not on osteoporosis. Once a claim on osteoporosis improvement is made, it is required to have positive demonstration on improvement of objective data like BMD improvement. Our clinical trial indicated that ELP might not be able to acquire a significant rising BMD which is mandatory for drug treatment. However the trend was there, as long as a herbal supplement maintains the BMD at a steady level, its role as a preventive agent is fulfilled. Our results might support the need of a different concept for the assessment of the efficacy of botanical drugs used for prevention.

## CONCLUSION

In our search for an innovative herbal formula to prevent the development of osteoporosis, we need to organize a randomized control trial. Since we have good laboratory data supporting the pharmacological effects of the three herbs formula ELP, we believe it would support bone health in the osteopenic women. The mechanism of action of the three herbs combined, apparently have both osteoblastic and osteoclast suppression activities. In a further exploration on the molecular basis of the complex nature of the herbs, more refined target orientated studies could be done. We need to be clear about whether the support of BMD is working through a cellular level or indirectly via the increased absorption of calcium or decreased excretion of calcium; and whether Vitamin D plays an important role? The essence of Chinese Medicine is that, since it is not aimed towards a specific target, as long as there is evidence about its safety and efficacy, a practical clinical use as a supplement is justified. Like drug trials for pharmaceuticals, more randomized controlled trials using appropriate groups of vulnerable people will further strengthen the evidence on clinical values.

## ACKNOWLEDGMENTS

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## APPENDIX

SF-36; Questionnaire for quality of life.

**SF-36 questionnaire:**
(1992 -- Medical Outcomes Trust)

Patient Name: _____ Date: _____

1. In general, would you say your health is: (circle one)
   Excellent Very good Good Fair Poor

2. Compared to one year ago, how would you rate your health in general now? (circle one)
   Much better now than one year ago
   Somewhat better now than one year ago
   About the same as one year ago
   Somewhat worse than one year ago
   Much worse than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Mark each answer with an X)

| Activities | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports | | | |
| Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf | | | |
| Lifting or carrying groceries | | | |
| Climbing several flights of stairs | | | |
| Climbing one flight of stairs | | | |
| Bending, kneeling or stooping | | | |
| Walking more than a mile | | | |
| Walking several blocks | | | |
| Walking one block | | | |
| Bathing or dressing yourself | | | |

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Mark each answer with an X)

| | Yes | No |
|---|---|---|
| Cut down on the amount of time you spent on work or other activities | | |
| Accomplished less than you would like | | |
| Were limited in the kind of work or other activities | | |
| Had difficulty performing the work or other activities (for example, it took extra effort) | | |

**Appendix:** Continue

5. During the past 4 weeks, 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)? (Mark each answer with an X)

| | Yes | No |
|---|---|---|
| Cut down the amount of time you spent on work or other activities | | |
| Accomplished less than you would like | | |
| Didn't do work or other activities as carefully as usual | | |

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? (circle one)
   Not at all Slightly Moderately Quite a bit Extremely

7. How much bodily pain have you had during the past 4 weeks? (circle one)
   None Very mild Mild Moderate Severe Very severe

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

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 D (Mark each answer with an X)

| | 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 |
|---|---|---|---|---|---|---|
| Did you feel full of pep? | | | | | | |
| Have you been a very nervous person? | | | | | | |
| Have you felt so down in the dumps that nothing could cheer you up? | | | | | | |
| Have you felt calm and peaceful? | | | | | | |
| Did you have a lot of energy? | | | | | | |
| Have you felt downhearted and blue? | | | | | | |
| Did you feel worn out? | | | | | | |
| Have you been a happy person? | | | | | | |
| Did you feel tired? | | | | | | |

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 with friends, relatives, etc.)? (circle one)

11. How TRUE or FALSE is each of the following statements for you?
   All of the time Most of the time Some of the time A little of the time None of the time

**Appendix:** Continue

| | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
|---|---|---|---|---|---|
| I seem to get sick a little easier than other people | | | | | |
| I am as healthy as anybody I know | | | | | |
| I expect my health to get worse | | | | | |
| My health is excellent | | | | | |

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