"The Potential Renoprotective Effect of Vitamin C and Coenzyme q10 against Cisplatin-Induced Nephrotoxicity in Cancer patients"

Research proposal for the fulfillment of master's degree in clinical pharmacy

Submitted By

Ghada Saied El-Seidy
Teaching assistant of Clinical Pharmacy
Clinical Pharmacy Department
Faculty of Pharmacy
Misr University for Science and Technology

Under supervision of

Dr. Nagwa Ali Sabri
Professor of Clinical Pharmacy
Clinical Pharmacy Department
Faculty of Pharmacy
Ain Shams University

Dr. Rasha Mohamed AbdelMotagalee Aboelhassan
Senior Oncology Consultant
Nasser Institute for Research and Treatment

Dr. Rana Sayed Fouad
Lecturer of Clinical Pharmacy
Clinical Pharmacy Department
Faculty of Pharmacy
Ain Shams University

Faculty of Pharmacy
Ain Shams University
10-9-2025

- **Introduction:**

Cisplatin (Cis) is one of the most effective chemotherapeutic agents, widely used for the treatment of several malignant diseases including head and neck, esophageal, bladder, testicular, ovarian, uterine, cervical, breast, stomach, non-small and small-cell lung cancers[1].

Unfortunately, patients who are receiving cisplatin-based chemotherapy are at risk of severe adverse effects in normal tissues, including neurotoxicity, ototoxicity, nausea and vomiting are liming factors of cisplatin use[2].

Nephrotoxicity is a major factor that negatively impacts their clinical outcomes. Cisplatin is mainly cleared by the kidney through glomerular filtration and tubular excretion, resulting in a higher concentration of this drug in the kidney than in other organs. Cisplatin-induced acute kidney injury (AKI), characterized by rapid deterioration of renal function within days of initiating treatment, occurs in around 30% of patients who are receiving cisplatin chemotherapy [3].

The pathophysiology of cisplatin nephrotoxicity: An important contributor for cisplatin nephrotoxicity is its uptake into kidney cells which is much higher than any tissues, especially in proximal tubules of the kidney where cis concentration can reach up to five folds higher than that of the serum[4],[5].

Cisplatin uptake in renal proximal tubular cells is mediated by membrane transporters such as solute carrier family 22 member 2 (SLC22A2), SLC22A6, SLC22A8, organic cation transporter-2 (OCT2) and copper transporter-1 (Ctr-1). After entering cells, a chloride ion of cisplatin is replaced with a water molecule. Hydrated cisplatin is then metabolically activated to the toxic form by a gamma-glutamyl transpeptidase (GGT) and kynurenine aminotransferase 1 (KYAT1)-dependent pathway [6],[7].

Accumulation of cisplatin in renal proximal tubular cells induces DNA damage, mitochondrial damage, oxidative stress, endoplasmic reticulum (ER) stress, autophagy and cell-cycle regulation. These processes result in renal cell death, inflammation and cell senescence, which lead to acute kidney injury (AKI) and chronic kidney disease (CKD)[3].

The role of oxidative stress in cisplatin nephrotoxicity is well established. Cisplatin additionally represses the antioxidant enzymes including glutathione S-transferase, glutathione peroxidase, and superoxide dismutase, prompting lethal degrees of ROS inside the cell[4].

Three main mechanisms of ROS generation have been proposed: rapid reaction of cisplatin with thiol-containing molecules during its bioactivation depletes cells of glutathione and related antioxidants; cisplatin-injured mitochondria produce excessive ROS and compromise antioxidant enzymes such as SOD and catalase, which in turn exacerbates mitochondrial damage, forming a vicious cycle; cisplatin induces ROS via activating cytochrome P450 enzymes, particularly cytochrome P450 2E1 (CYP2E1) and cytochrome P450 4A11 (CYP4A11)[3].

The consequence of ROS generated is the activation of a transcriptional factor (NF-κB). NF-κB up-regulated the expression of pro-inflammatory cytokines like TNF-α IL-18 and IL-6. Other studies have demonstrated that Cis promotes the intrinsic apoptotic pathway through activation of the proapoptotic gene Bax which binds to the mitochondrial membrane. The consequences of Bax activation are releasing of cytochrome-c from the mitochondria thereby activating cell death. Moreover, Cis induces several signal transduction pathways, such as those involving the p53 protein, that ends in the activation of renal tubular cell apoptosis[8].

Cisplatin nephrotoxicity is classified according to severity defined as creatinine increased as follows:

Grade 1: >ULN - 1.5 x ULN **Grade 2** :>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN

Grade 3: >3.0 x baseline; >3.0 - 6.0 x ULN **Grade 4** : >6.0 x ULN

Grade 5 :Death

based on common terminology criteria for adverse events (CTCAE) version 5.0[7].

Traditional **biomarkers** such as serum creatinine and blood urea nitrogen (BUN) often fail to detect early renal damage, necessitating the use of novel biomarkers for timely diagnosis and intervention. The Food and Drug Administration **FDA** and European Medicines Agency **(EMEA)** approved seven new biomarkers used for nephrotoxicity detection that may influence clinical decision making: **KIM-1**, albumin, B2-microglobulin, cystatin C, total protein clusterin, and trefoil factor-3[9].

Kidney injury molecule-1 (KIM-1) is a proximal tubule apical transmembrane protein. KIM-1 downregulates proximal tubular cell PTC cytokine secretion, modulates translational changes through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and interaction with phosphatidylinositol3 PI3 kinase subunit p85 . Experimentally, KIM-1 gene expression reflects ongoing damage in various tubulointerstitial segments and in the renal cortex[10] .

For these reasons, authors began considering KIM-1 as a biomarker capable of identifying early AKI and may even hold a possible predictive role . interestingly, KIM-1 has a

phosphatidylserine receptor which enhances apoptotic bodies and necrotic debris phagocytosis[9].

Vitamin C (ascorbic acid) is a potent antioxidant often supplemented in high amounts to make up for such deficiencies, it is used in the prevention and treatment of a broad spectrum of conditions, including diabetes, atherosclerosis, the common cold, cataracts, glaucoma, macular degeneration, stroke, heart disease, COVID-19, and cancer[11]. Although there is some toxicity reported with vitamin c with higher doses as nausea, vomiting, diarrhea, flushing of the face, headache, fatigue, osmotic diarrhea and disturbed sleep[12].

It is capable of scavenging a wide range of reactive oxygen species and reacting with free radicals in aqueous environments. It forms the first line of defense against oxidant radicals in plasma prevents their damaging effect to macromolecules such as lipids, DNA, and proteins. It has been reported to have the lowest toxicity of all vitamins[13],[14].

In an animal study, the rats which were killed 7 days after cisplatin administration, it was observed that the treatment with vitamin C prevented the depletion of renal glutathione caused by cisplatin, resulting in values close to those observed in the control group. These results suggest the possible involvement of vitamin C-mediated protection against cisplatin induced depletion of renal glutathione [15].

Coenzyme Q10 (CoQ10) as a redox-active lipophilic ROS scavenger was found in various cellular organelles such as mitochondria, lysosomes and Golgi vesicles. It is used as a dietary supplementation and as a cotherapy in conjunction with medication in a number of conditions, including cardiovascular diseases, cancer, muscular neurodegenerative disorders, and diabetes[8]. Although CoQ10 is present naturally in the human body and should therefore be well tolerated, a variety of adverse reactions have been reported, although infrequent and generally mild. These include decreased appetite, diarrhea, dizziness, dyspepsia, and nausea/vomiting[16].

It participates in aerobic cellular respiration working as an electron carrier in the process creating energy through the formation of ATP (adenosine triphosphate).
Not only can it recycle and regenerate other antioxidants such as vitamins E and C, but it can also uniquely affect the initiation and propagation of ROS[9].

It was reported that cisplatin administration caused NF-κB activation with subsequent inflammatory reactions responsible for renal injury . Elevated TNF-α is known as an important step for activation of the NF-κB signaling pathway . Studies revealed that CoQ10

treatment significantly suppressed lipid peroxidation, restored the antioxidant defense mechanisms, attenuated the overproduction TNF-α and NO, and reduced the expression of NF-κB and iNOS in the kidneys of mice exposed to acute cisplatin nephrotoxicity.
The nephroprotective effect of CoQ10 can be attributed to its ability to inhibit the activation of NF-κB signaling pathway which promotes the transcription of NADPH oxidase, TNF-α and iNOS genes [8],[17].

Safety assesment of Coenzyme q10: A large portion of the available published data on CoQ10 clinical trials at doses ranging from 30 to 3000 mg/day including the clinical safety study on healthy volunteers by Ikematsu et al. was reviewed. No systematic pattern of adverse effects was found; reports of nausea and other adverse gastrointestinal effects of CoQ10 cannot be causally related to the active ingredient because there is no dose-response relationship. In these clinical studies, 300 to 1200 mg/day of CoQ10 has been studied in a relatively large cohort (n = 80) of early Parkinson's disease patients in a double-blind, placebo-controlled designed clinical trial of 16 months duration, and no adverse effects were found in any dose groups . This trial provides strong evidence of the lack of adverse effects at this dose level of CoQ10. Overall, they concluded that the observed safe level (OSL) for CoQ10 was 1200 mg/day[18-20].

Aim of the work :

This study aims to evaluate the protective effects of (Vitamin C and Coenzyme q10) against cisplatin-induced nephrotoxicity in chemotherapy-naïve cancer patients.

Primary Outcome

To evaluate the patients' glomerular filtration rate, incidence and severity of cisplatin-induced nephrotoxicity using serum creatinine (graded by CTCAE v5.0)

Secondary Outcomes

* KIM-1 biomarker levels in serum in patients receiving cisplatin as an early indicator of acute cisplatin induced kidney injury.

*Assesment of the quality of life through The EORTC QLQ-C30 questionnaire at baseline and by the end of the third cycle.

*Adverse Effects from Antioxidants: Documented through structured case report forms, patient diaries, and adverse event reporting per CTCAE guidelines.

*Time to Onset of Nephrotoxicity: Monitored through serial serum creatinine measurements across defined intervals.

Patients and Methods:

Study design:

-It`s a three-arms, prospective, randomized, open label, parallel study of 75 adult cancer patients. Upon recruitment, Patients will be randomly assigned by permuted block randomization to one of the 3 study groups.

Duration:3 cycles (21 days each)

Study setting:

Patients will be recruited from the oncology department of Nasser Institute for Research and Treatment.

Patients:

Adult patients admitted to the internal medicine department of Nasser Institute for Research and Treatment with proven different types of cancer mainly (lung, pancreatic and bladder cancers) will be assessed for eligibility. Patients who fulfilled the following inclusion and exclusion criteria will be included in the study and will be asked to sign an informed consent to be enrolled in the study.

Eligible patients will be selected according to the following inclusion and exclusion criteria:

- **Inclusion Criteria:**

  - Chemotherapy-naïve patients diagnosed with different types of cancer.
  - Age :adult patients (aged 18-65 years)
  - Candidates eligible for induction chemotherapy (cisplatin+gemcitabine).
  - Baseline estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2.
  - Eastern Cooperative Oncology Group (ECOG) performance status <2.
  - Hematologic parameters (WBC count ≥ 3,000/mm^3 -- Platelet count ≥ 75,000/mm^3-- Hb level ≥ 8.0 g/dL)
  - Alanine aminotransferase (ALT) ≤3× upper limit of normal (ULN).

➢ **Exclusion Criteria:**

- Prior chemotherapy.
- Uncontrolled Diabetes mellitus, active infection, heart failure, or liver impairment.
- Patients with gastritis and G-6-P deficiency
- History of nephrotoxic drugs use over the past 3 months prior to recruitment (e.g., aminoglycosides, amphotericin B or vancomycin).
- Known allergy to any study drugs.

Sample size calculation:

Based on a previous study of vitamin C to prevent vancomycin-induced nephrotoxicity, the expected effect size in GFR would be f= 0.4768[11] . To detect a similar effect size in a balanced ANOVA with 80% power while keeping alpha level of 0.05, a sample size of 16 patients per group would be required. Accordingly, 25 patients will be recruited in each group to account for drop out.

Study groups

Standard of care will be given to all patients.
The chemotherapy regimen consists of ; cisplatin+gemcitabine.
day 1: gemcitabine+ cisplatin: 75 mg/m2 IV , **or** gemcitabine +fractionated cisplatin: 35 mg /m2 on **day 1 and day 8** .This regimen will be repeated every 3 weeks for 3 cycles[7],[21].
All patients should receive a hydration protocol based on the chemotherapy protocol .

- Group I (Control Group): 25 patients will receive only the standard of care.
- Group II (Vitamin C): 25 patients will receive Vitamin C 500 mg administered orally once daily for 10 days. (for 2 days before day 1 for each cycle)[7],[13].
- Group III (Coenzyme q10): 25 patients will receive Coenzyme q10 30 mg administered orally once daily for 10 days. (for 2 days before day 1 for each cycle) [22-24].

Ethical approval:

The study is designed and will be carried out in accordance with the declaration of Helsinki. The study protocol will be submitted to the ethics committee of the Faculty of Pharmacy, Ain Shams University (ACUC-FP-ASU) for approval before starting the study. Moreover, the study will be registered on clinicaltrials.gov registry. Patients will be educated about the study protocol and an approval will be taken from the patient responsible physician. patients will be required to sign a written informed consent to be recruited in the study.

Methodology:

After consent, all the studied patients will be subjected to complete history taking, thorough clinical examination, weight and height measurement, and determination of ideal body weight (IBW) and body surface area (BSA). The chemotherapy dose will be calculated using the Mosteller body surface area (BSA) formula.

- **Sample Collection and Analysis**

Data Collection and Timeline:

Baseline demographic data:

age, gender, social history, medical and medication history.

*Baseline labs: Serum creatinine, eGFR and KIM-1 markers.

Baseline assessment of quality of life: EORTC QLQ-30

*Follow-ups:

-KIM-1 :At the 3rd day of the third cycle by using double-antibody sandwich ELISA.

-Assesment of the quality of life through The EORTC QLQ-C30 questionnaire by the end of the third cycle.

-Calculation of eGFR will be done at each two cycles.

-Serum creatinine measurements: by the end of each cycle by autoanalyzer.

1. Primary Efficacy Parameter:

- **Incidence of cisplatin-induced nephrotoxicity:**

There are many side effects of cisplatin . However, nephrotoxicity is the main dose-limiting side effect. About 20–30% of patients experience nephrotoxicity following a single dose of cisplatin.

*Measure the serum creatinine levels at baseline before administration of the first cycle then by the end of each cycle by calculating GFR using serum creatinine (graded by CTCAE v5.0)

Serum creatinine is a standard marker for kidney function, and a lower increase or stabilization in creatinine levels would suggest renal protection.

A lower incidence of AKI in the intervention groups (Group II and Group III) compared to the control group (Group I) would indicate efficacy.

2. Secondary Efficacy Parameters:

- **Change in Serum KIM-1 Levels:**

Measure the change in (KIM-1) levels at the baseline and then at the third day of the third cycle of chemotherapy.

KIM-1 is a biomarker for kidney injury, and a reduction in its levels would indicate a protective effect of the interventions (Vitamin C, Coenzyme q10, or both) against cisplatin-induced nephrotoxicity.

*Assesment of the quality of life through The EORTC QLQ-C30 questionnaire at baseline and by the end of the third cycle.

*Adverse Effects from Antioxidants: Documented during weekly phone calls through structured case report forms, patient diaries, and adverse event reporting per CTCAE guidelines.

*Time to Onset of Nephrotoxicity: Monitored through serial serum creatinine measurements across defined intervals.

Patients' compliance to study drugs will be assessed every cycle by pill count method. Patients not adhering to at least 80% of their treatment regimen would be considered non-compliant

3. Exploratory Efficacy Parameters:

- **Biomarker Correlation:**

Explore the correlation between changes in KIM-1 levels and serum creatinine levels to understand the relationship between these biomarkers in predicting kidney injury.

Safety&Tolerability:

Evaluate the tolerability of the chemotherapy regimen with and without the interventions, including the ability to complete all three cycles of chemotherapy. It will be followed up for 21 days until day 1 of the fourth cycle by weekly phone calls and to assess compliance using pill count method .

as the possible toxicities of Cisplatin:

1. Renal Toxicity
2. Gastrointestinal Toxicity (Severe nausea and vomiting -highly emetogenic)
3. Ototoxicity
4. Neurotoxicity

In addition to the GIT side effects of vitamin C and Coenzyme q10 drugs.

Statistical analysis:

• Statistical analysis will be done using SPSS statistical software package and a probability value of equal or less than 0.05 will be considered statistically significant.

Statistical Tests:

• Categorical data will be summarized as frequency and percentage.

• Continuous variables will be expressed as the mean±SD for parametric data or as the median {interquartile range(IQR)} for non-parametric data.

• Oneway ANOVA will be used to compare parametric continuous variables between 3 groups while Kruskal Wallis test will be used for non parametric variables

• Chi square test will be used to compare categorical data between the 3 study groups

• Log rank test will be used to compare time to onset of nephropathy in the 3 study groups.

References :

1. Volarevic, V., B. Djokovic, M. G. Jankovic, et al. “Molecular Mechanisms of Cisplatin-Induced Nephrotoxicity: A Balance on the Knife Edge Between Renoprotection and Tumor Toxicity.” Journal of Biomedical Science 26 (2019): 25. https://doi.org/10.1186/s12929-019-0518-9. .

2. Hajian, S., M. Rafieian-Kopaei, and H. Nasri. “Renoprotective Effects of Antioxidants Against Cisplatin Nephrotoxicity.” Journal of Nephropharmacology 3, no. 2 (2014): 39–42. PMID: 28197460; PMCID: PMC5297526.

3. Tang, C., M. J. Livingston, R. Safirstein, et al. “Cisplatin Nephrotoxicity: New Insights and Therapeutic Implications.” Nature Reviews Nephrology 19 (2023): 53–72. https://doi.org/10.1038/s41581-022-00631-7.

4. Hindawi. “International Journal of Inflammation,” vol. 2020, Article ID 5369797, 11 pages. https://doi.org/10.1155/2020/5369797.

5. Tang, C., M. J. Livingston, R. Safirstein, et al. “Cisplatin Nephrotoxicity: New Insights and Therapeutic Implications.” Nature Reviews Nephrology 19 (2023): 53–72. https://doi.org/10.1038/s41581-022-00631-7.

6. Manohar, S., and N. Leung. “Cisplatin Nephrotoxicity: A Review of the Literature.” Journal of Nephrology 31 (2018): 15–25. https://doi.org/10.1007/s40620-017-0392-z.

7. Ghonaim, E., S. El-Haggar, and S. Gohar. “Possible Protective Effect of Pantoprazole Against Cisplatin-Induced Nephrotoxicity in Head and Neck Cancer Patients: A Randomized Controlled Trial.” Medical Oncology 38 (2021): 108. https://doi.org/10.1007/s12032-021-01558-y.

8. Bash, H., and I. Mohammed Ridha. “Coenzyme Q10 Ameliorates Cisplatin-Induced Nephrotoxicity in Rats.” PharmacologyOnline 3 (2018): 49–56. http://pharmacologyonline.silae.it.

9. Tanase, D. M., E. M. Gosav, S. Radu, C. F. Costea, M. Ciocoiu, A. Carauleanu, C. M. Lacatusu, M. A. Maranduca, M. Floria, and C. Rezus. “The Predictive Role of the Biomarker Kidney Molecule-1 (KIM-1) in Acute Kidney Injury (AKI) Cisplatin-Induced Nephrotoxicity.” International Journal of Molecular Sciences 20 (2019): 5238. https://doi.org/10.3390/ijms20205238.

10. Brooks, C. R., and J. V. Bonventre. “KIM-1/TIM-1 in Proximal Tubular Cell Immune Response.” Oncotarget 6 (2015): 44059.

11. Mussa A, Mohd Idris RA, Ahmed N, Ahmad S, Murtadha AH, Tengku Din TADAA, Yean CY, Wan Abdul Rahman WF, Mat Lazim N, Uskoković V, Hajissa K, Mokhtar NF, Mohamud R, Hassan R. High-Dose Vitamin C for Cancer Therapy. Pharmaceuticals (Basel). 2022 Jun 3;15(6):711. doi: 10.3390/ph15060711. PMID: 35745630; PMCID: PMC9231292.

12. Korah, M. C., et al. (2017). Adverse effects and side effects on vitamin therapy: A review. Asian Journal of Pharmaceutical and Clinical Research, 10(5), 19–26. https://doi.org/10.22159/ajpcr.2017.v10i5.17014

13. El-Sherazy, N. H., N. S. Bazan, S. S. Shaheen, and N. A. Sabri. “Impact of Ascorbic Acid in Reducing the Incidence of Vancomycin-Associated Nephrotoxicity in Critically Ill Patients: A Preliminary Randomized Controlled Trial.” F1000Research 10 (2021): 929. https://doi.org/10.12688/f1000research.55619.1.

14. Xu, W., Z. Mao, B. Zhao, T. Ni, S. Deng, P. Yu, J. He, and E. Mao. “Vitamin C Attenuates Vancomycin-Induced Nephrotoxicity Through the Reduction of Oxidative Stress and Inflammation in HK-2 Cells.” Annals of Palliative Medicine 10, no. 2 (2021): 1748–1754. https://doi.org/10.21037/apm-20-694.

15. Antunes, L. M. G., Darin, J. D. C., & Bianchi, M. L. P. (2000). Protective effects of vitamin C against cisplatin-induced nephrotoxicity and lipid peroxidation in adult rats: A dose-dependent study. Pharmacological Research, 41(4), 405–411. https://doi.org/10.1006/phrs.1999.0600

16. Raizner, A. E. (2019). Coenzyme Q10. Methodist DeBakey Cardiovascular Journal, 15(3), 185–191. https://doi.org/10.14797/mdcj-15-3-185

17. Fouad, A. A., Al-Sultan, A. I., Refaie, S. M., & Yacoubi, M. T. (2010). Coenzyme Q10 treatment ameliorates acute cisplatin nephrotoxicity in mice. Toxicology, 274(1–3), 49–56. https://doi.org/10.1016/j.tox.2010.05.007

18. Hidaka, T., K. Fujii, I. Funahashi, N. Fukutomi, and K. Hosoe. “Safety Assessment of Coenzyme Q10 (CoQ10).” IUBMB Life 57, no. 12 (2005): 831–838. https://doi.org/10.1002/biof.5520320124.

19. Shults, C. W., D. Oakes, K. Kieburtz, M. F. Beal, R. Haas, S. Plumb, J. L. Juncos, J. Nutt, I. Shoulson, J. Carter, K. Kompoliti, J. S. Perlmutter, S. Reich, M. Stern, R. L. Watts, R. Kurlan, E. Molho, M. Harrison, and M. Lew. "Effects of Coenzyme Q10 in Early Parkinson Disease: Evidence of Slowing of the Functional Decline." Archives of Neurology 59 (2002): 1541–1550.

20. Ikematsu, H., K. Nakamura, S. I. Harashima, K. Fujii, and N. Fukutomi. "Safety Assessment of Coenzyme Q10 (Kaneka Q10) in Healthy Subjects: A Double-Blind, Randomized, Placebo-Control Trial." Regulatory Toxicology and Pharmacology 44 (2006): 212–218.

21. Vermorken, B., E. Remenar, C. van Herpen, et al. "Phase III Study of Cisplatin and Fluorouracil with or without Docetaxel in Advanced Head and Neck Cancer." New England Journal of Medicine. https://doi.org/10.1056/NEJMoa071028 .

22. Maxfield, L., Daley, S. F., & Crane, J. S. (2023, November 12). Vitamin C deficiency. In StatPearls. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK493187/

23. Gillberg, L., Ørskov, A.D., Nasif, A. et al. Oral vitamin C supplementation to patients with myeloid cancer on azacitidine treatment: Normalization of plasma vitamin C induces epigenetic changes. Clin Epigenet 11, 143 (2019). https://doi.org/10.1186/s13148-019-0739-5

24. Gaziano JM, Glynn RJ, Christen WG, et al. Vitamins E and C in the Prevention of Prostate and Total Cancer in Men: The Physicians' Health Study II Randomized Controlled Trial. JAMA. 2009;301(1):52–62. doi:10.1001/jama.2008.862

Appendix

EORTC QLQ-C30 (Version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ☐☐☐☐
Your birthdate (Day, Month, Year): ☐☐☐
Today's date (Day, Month, Year): ☐☐☐

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent