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**ABBREVIATIONS:**

CNI: calcineurin inhibitor

TDDR: Total daily dose ratio

TDD: Total daily dose

**DEFINITIONS:**

Dose-normalized trough: trough (ng/mL) divided by total daily dose

Tacrolimus IR: Immediate-release, or twice-daily, tacrolimus

Total daily dose conversion ratio: Total daily dose prior to conversion divided by total daily dose post-conversion

CYP3A5 expresser: CYP3A5 \*1 genotype, either homozygous or heterozygous

**Title:** Dosing requirements of Astagraf XL® in African American kidney transplant recipients converted from twice-daily tacrolimus

**I. Clinical Section**

**a. Background and Rationale**

Pharmacokinetics from prospective clinical studies demonstrated similar drug exposure (AUC) and correlation between trough (C<sub>0</sub>) and AUC between twice daily tacrolimus and Astagraf XL, which led to 1mg:1mg dose-conversion recommendations; however more recent studies have shown a decrease in tacrolimus exposure after conversion, necessitating increased dosing requirements in 25-50% of patients (1-4). Variability in results from studies may be, in part, due to the type of assay used (LC-MS vs. immunoassays), time after transplant, CYP3A5 alleles (expressers vs. non-expressers), and ethnicity (4-6).

In one study, Niioka, et.al. demonstrated that patients with the CYP3A5 expresser allele had a 25% lower dose-adjusted AUC in the daily tacrolimus group compared to the twice-daily tacrolimus group, while still maintaining good correlation between C<sub>0</sub> and AUC (6). These results are contradictory to Wehland, et.al.'s results that demonstrated a significant difference in CYP3A5 non-expressers after conversion, a study that was limited by small numbers of patients with the CYP3A5\*1 allele (5).

In terms of ethnicity, African American kidney transplant recipients have shown decreased absorption of twice-daily tacrolimus, achieving lower peak concentrations (C<sub>max</sub>) and AUC compared to Caucasian kidney transplant recipients, necessitating a higher total daily dose to achieve adequate C<sub>0</sub> levels (7,8). Additionally, de novo dosing of the extended-release formulation Astagraf XL has revealed that African Americans require approximately 20-30% higher doses than Caucasians from 1month to 12months after transplant to achieve similar C<sub>0</sub> levels(9).

One of the reasons for the alterations of tacrolimus absorption in African Americans is believed to be the much higher incidence of the CYP3A5\*1 expresser allele compared to other ethnicities. Because of the variability in conversion dosing based off of CYP3A5 alleles and the underrepresentation of African Americans in conversion studies, further study is needed so that appropriate conversion dosing can be provided to this at-risk population.

**b. Objective**

Compare the difference in dose-normalized trough and total daily dose necessary to reach the steady state therapeutic goal after conversion from tacrolimus IR to Astagraf XL® in African American kidney transplant recipients.

**c. Study Design**

Single-center, prospective, open-label pilot study

Study duration:

Estimated 12 month enrollment period, with a 90 day follow-up period.



**i. Primary Endpoints**

1. Difference in dose-normalized trough at steady state before and after conversion from tacrolimus IR to Astagraf XL®
  - a. Subcategorized by CYP3A5 expressers vs non-expressers

**ii. Secondary Endpoints**

1. Difference in TDD necessary for steady state therapeutic goal
  - a. Subcategorized by CYP3A5 expressers vs non-expressers
2. TDDR necessary to reach steady state therapeutic goal between CYP3A5 expressers vs. non-expressers
3. Proportion of patients with a TDDR of 1mg:1mg
  - a. Subcategorized by CYP3A5 expressers vs non-expressers
4. Weight-based dose requirements to reach therapeutic goal pre- and post-conversion
  - a. Subcategorized by CYP3A5 expressers vs. non-expressers
5. Days to reach therapeutic goal after conversion
6. Number of dose modifications in the follow-up period
7. Morisky Medication Adherence Scale (MMAS-8) at the time of conversion compared to 90 days after conversion (Appendix II)
8. SF-36 survey at the time of conversion compared to 90 days after conversion (Appendix IV)

**iii. Safety endpoints**

1. Incidence of adverse effects related to conversion, including those necessitating a return to the original formulation
2. Memphis Medication Side Effect scale at the time of conversion compared to 90 days after conversion (Appendix III)
3. Incidence of rejection-free graft survival in the 90 days post-conversion
4. Incidence of rejection in the 90 days post-conversion
5. Change in serum creatinine from the time of conversion to 90 days after conversion

**d. Sample Population**

Male or female adult ( $\geq 18$  years old) African American patients with a history of solitary kidney transplant at least 1 month post-transplant. Patients must be on a stable tacrolimus dose for at least 2 weeks prior to randomization. Patients must be capable of understanding the purposes and risks of the study and have the ability to give written informed consent and be willing to participate and comply with the study.

**i. Sample size**

25 subjects from a single-center

**Statistical analysis plan:**

Based off of preliminary data from 7 patients that underwent conversion from tacrolimus IR to Astagraf XL, we utilized no difference in dose-normalized trough as the null hypothesis and a 20% decrease in dose-normalized trough as the alternative hypothesis. Assuming a starting dose-normalized trough of 0.9 and a standard deviation in each group of 0.35, it was determined that 21 patients would be necessary to reach 80% power with an alpha of 0.05, 1-tailed. This should also be sufficient patient data to present a change in mg/kg dosing, which will have a much smaller standard deviation, as well as a percent difference in TDD, assuming a 20% increase in dosage requirements with a standard deviation of 5mg, as evidenced in our preliminary data.

**ii. Inclusion criteria**

1. At least 18 years of age
2. Signed informed consent
3. African American race
4. History of a solitary renal transplant
5. Stable tacrolimus dose for at least 2 weeks prior to randomization

**iii. Exclusion criteria**

1. A condition or disorder that, in the opinion of the investigator, may adversely affect the outcome of the study or the safety of the subject
2. Currently enrolled in an investigational drug trial
3. History of a non-renal organ transplant
4. History of acute cellular rejection within 1 month prior to randomization
5. An increase in serum creatinine by > 20% in the 2 weeks prior to randomization
6. Maintenance immunosuppression that does not consist of tacrolimus IR given twice daily, mycophenolate mofetil or mycophenolate sodium, and prednisone  $\geq$  5mg daily

**e. Study intervention:****i. Intervention, Administration, and Duration**

1. At the time of randomization, subjects will continue their tacrolimus IR orally BID for all scheduled doses that day. The next morning, subjects will begin Astagraf XL® orally daily, with or without food, at a 1mg:1mg total daily dose conversion, with further dose adjustments based off of trough concentrations (goal 5-12ng/mL (using LC-MS)) according to the Schedule of Evaluations (appendix I). The intervention will continue for 90 days post-randomization.
2. Based on the mean daily dose of 11mg in our feasibility patients, we would expect to utilize at least 30,000mg of tacrolimus throughout the study.

**ii. Concomitant Interventions**

1. Mycophenolate mofetil or mycophenolate sodium must be active at the time of randomization. Dose adjustments will be allowed based on side effects or toxicities, at the clinical judgement of the primary investigator. Corticosteroids will be based on institutional protocol and will be continued in all patients at a minimum dose of 5mg daily of prednisone or equal potent exposure if a different corticosteroid is utilized. Antimicrobial and antiviral prophylaxis will be administered based on institutional protocol.

**iii. Prohibited and Precautionary Interventions**

| <b>Drug/Substance Class or Name</b>   | <b>Drug Interaction Effect</b>  | <b>Recommendations</b>   |
|---|---|--|
| Grapefruit or grapefruit juice <sup>b</sup>   | May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) | Avoid grapefruit or grapefruit juice   |
| Alcohol   | May increase the rate of tacrolimus release and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation )              | Avoid alcoholic beverages  |
| Strong CYP3A Inducers <sup>c</sup> :<br>Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenytoin, carbamazepine and phenobarbital), St John's Wort  | May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection  | Increase ASTAGRAF XL dose and monitor tacrolimus whole blood trough concentrations   |
| Strong CYP3A Inhibitors <sup>c</sup> :<br>Protease inhibitors (e.g, nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone, schisandra sphenanthera extracts | May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) | Reduce ASTAGRAF XL dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations |
| Mild or Moderate CYP3A Inhibitors:<br>Clotrimazole, antibiotics (e.g., erythromycin, fluconazole), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole  | May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) | Monitor tacrolimus whole blood trough concentrations and reduce ASTAGRAF XL dose if needed   |



|  |   |  |
|--|---|--|
| Other drugs, such as:<br>Magnesium and<br>aluminum hydroxide<br>antacids<br>Metoclopramide | May increase tacrolimus whole<br>blood trough concentrations and<br>increase the risk of serious<br>adverse reactions (e.g.,<br>neurotoxicity, QT prolongation) | Monitor tacrolimus whole<br>blood trough concentrations<br>and reduce<br>ASTAGRAF XL dose if<br>Needed |
|--|---|--|

**f. Clinical and laboratory assessments**

**i. Laboratory assessments**

Laboratory evaluations will be performed at certified laboratories according to the Schedule of Evaluations (appendix I). Required tests are specified in the Schedule of Evaluations. Results will be entered into REDCap.

**ii. Clinical assessments**

All patients will undergo clinical evaluation by the investigator or the investigator's designee at the times specified in the Schedule of Evaluations (appendix I). Results will be entered into REDCap.

**iii. Acute renal dysfunction**

To monitor graft function, serum creatinine will be assessed throughout the study according to the Schedule of Evaluations (appendix I). All episodes of renal dysfunction, defined as an incremental increase in serum creatinine concentration 20% above baseline or  $\geq 0.4\text{mg/dL}$  will be evaluated for rejection by renal biopsy, after the exclusion of other causes of renal graft dysfunction (infection, dehydration, CNI toxicity)

**g. Acute rejection**

- i.** Acute rejection is defined by histologic criteria, showing  $\geq$  grade 1A by Banff Criteria
- ii.** Renal biopsy should be performed in all cases of renal dysfunction (after exclusion of causes other than rejection), to confirm a rejection episode. All subjects must have biopsy confirmation of rejection episodes either before or within 24 hours of onset of treatment for rejection
- iii.** Rejection reversal is defined as return of serum creatinine to within 10% of baseline and/or histologic clearance by Banff criteria
- iv.** Resistant acute rejection is defined as no histologic improvement documented by renal biopsy within 7-10 days after initiation of treatment
- v.** Recurrent acute rejection is defined as rejection recurring more than two weeks after documented rejection reversal

**h. Treatment of acute rejection episode**

- i.** Acute rejection will be treated according to center protocol

**i. Safety monitoring**

Adverse events will be reported in accordance with the FDA Guidelines for Post-marketing Reporting of Adverse Events 21 CFR 310.305 and 314.80

<http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm> and will be recorded in REDCap. Any serious adverse event or a non-serious adverse event that is related to the study and unexpected will be reported to the FDA, per reporting guidelines, as soon as possible, but no later than 15 working days. Any

serious adverse event or a non-serious adverse event that is related to the study and unexpected will be reported to Astellas within 24 hours of occurrence. Adverse events will be graded based upon the Common Terminology Criteria for Adverse Events (CTCAE version 4.03 <http://evs.nci.nih.gov/ftp1/CTCAE/About.html> ). Further, all serious adverse events that are related to the study and are unexpected must be reported to the Medical University of South Carolina IRB within 10 days per The Medical University of South Carolina IRB Unanticipated Problems and Adverse Events Policy and Procedures reporting guidelines.

## Appendix I. Schedule of Evaluations

|                                     |                              | Baseline | Days Post-initiation |      |      |      |      |      |      |      |
|-------------------------------------|------------------------------|----------|----------------------|------|------|------|------|------|------|------|
|                                     |                              |          | 5±3                  | 10±3 | 15±3 | 20±3 | 25±3 | 30±3 | 60±5 | 90±5 |
| History and Physical <sup>1,5</sup> |                              | X        |                      |      |      |      |      |      |      |      |
| Vital Signs                         |                              |          |                      |      | X    |      |      | X    | X    | X    |
| Clinical assessment <sup>4,5</sup>  |                              | X        |                      |      | X    |      |      | X    | X    | X    |
| Laboratory Assessments              | CBC and Chem-7 <sup>2</sup>  | X        | X                    | X    | X    | X    | X    | X    | X    | X    |
|                                     | CYP3A5 genotype <sup>5</sup> | O        | O                    | O    | O    | O    | O    | O    | O    | O    |
|                                     | Tacrolimus C0 <sup>3</sup>   | X        | X                    | X    | X    | X    | X    | X    | X    | X    |

Foot notes:

1. Includes vital signs, weight, height, medication dosing
2. Includes sodium, potassium, chloride, CO<sub>2</sub>, BUN, SrCr, glucose, calcium, WBC, HgB, Hct, platelets
3. Tacrolimus concentrations will be 24-hour levels, drawn in the morning of each assessment
4. Includes assessments of adverse events, study drug doses, study drug dose modifications, allograft rejection, need for hospitalization, other immunosuppressant medications, MMAS-8, SF-36, and Memphis Medication Side Effect scale at the Baseline and Day 90 visit
5. Not current standard of care, can be drawn at any time during the study

**Appendix II. Morisky Medication Adherence Score**

| <b>MMAS-8</b>  | <b>Points</b> |
|--|---------------|
| Do you sometimes forget to take your pills?  | 1             |
| People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine? | 1             |
| Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?  | 1             |
| When you travel or leave home, do you sometimes forget to bring along your medicine  | 1             |
| Did you take all your medicine yesterday?  | 1             |
| When you feel like your symptoms are under control, do you sometimes stop taking your medicine?  | 1             |
| Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?   | 1             |
| How often do you have difficulty remembering to take all of your medicine?<br><br>A. Never/rarely<br>B. Once in a while<br>C. Sometimes<br>D. Usually<br>E. All the time     | 0-5           |

| <b>Adherence</b> | <b>MMAS-8 Score</b> |
|------------------|---------------------|
| High Adherence   | 0                   |
| Medium Adherence | 1-2                 |
| Low Adherence    | 3-8                 |

**Appendix III. Memphis Medication Side Effect Scale**

**The Memphis Survey**  
**SIDE EFFECTS BECAUSE OF TRANSPLANT MEDICINES**

The following questions describe problems you might be having because of the transplant or the medicine you are taking. For each problem, you will be asked how frequently you experience it (the first row) and how troubling it is (the second row). Please answer every question.

|                           | Not<br>at all            | Very<br>little           | Sometimes<br>or<br>Moderately<br>troubling | Often<br>or<br>Very troubling | All the time<br>or<br>Extremely<br>troubling |
|---------------------------|--------------------------|--------------------------|--|-------------------------------|--|
|                           | ▼                        | ▼                        | ▼  | ▼                             | ▼  |
| Enlarged gums             |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Increased hunger          |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Staying asleep            |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Weight gain               |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Increased hair growth     |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Infections                |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Trembling hands           |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |

|                           |                          |                          |                          |                          |                          |
|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| High blood pressure       |                          |                          |                          |                          |                          |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Easy bruising             |                          |                          |                          |                          |                          |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Loss of interest in sex   |                          |                          |                          |                          |                          |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Sexual performance        |                          |                          |                          |                          |                          |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Diabetes                  |                          |                          |                          |                          |                          |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Hair Loss                 |                          |                          |                          |                          |                          |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

|                           | Not<br>at all            | Very<br>little           | Sometimes<br>or<br>Moderately<br>troubling | Often<br>or<br>Very troubling | All the time<br>or<br>Extremely<br>troubling |
|---------------------------|--------------------------|--------------------------|--|-------------------------------|--|
|                           | ▼                        | ▼                        | ▼  | ▼                             | ▼  |
| Stomach pain              |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Nausea                    |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Diarrhea                  |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Vomiting                  |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Stomach gas               |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Indigestion               |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
|                           | ▼                        | ▼                        | ▼  | ▼                             | ▼  |
| Mood Changes              |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Depression                |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Nervousness or anxiety    |                          |                          |  |                               |  |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |

|                             |                          |                          |                          |                          |                          |
|-----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Irritability                |                          |                          |                          |                          |                          |
| Do you have this problem?   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Anger                       |                          |                          |                          |                          |                          |
| Do you have this problem?   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Keeping a positive attitude |                          |                          |                          |                          |                          |
| Do you have this problem?   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |



|                                    | Not<br>at all            | Very<br>little           | Sometimes<br>or<br>Moderately<br>troubling | Often<br>or<br>Very troubling | All the time<br>or<br>Extremely<br>troubling |
|------------------------------------|--------------------------|--------------------------|--|-------------------------------|--|
|                                    | ▼                        | ▼                        | ▼  | ▼                             | ▼  |
| Feelings of uselessness            |                          |                          |  |                               |  |
| Do you have this problem?          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Being worried                      |                          |                          |  |                               |  |
| Do you have this problem?          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Worthlessness                      |                          |                          |  |                               |  |
| Do you have this problem?          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Hopelessness                       |                          |                          |  |                               |  |
| Do you have this problem?          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Ability to concentrate             |                          |                          |  |                               |  |
| Do you have this problem?          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
|                                    | ▼                        | ▼                        | ▼  | ▼                             | ▼  |
| Completing daily errands           |                          |                          |  |                               |  |
| Do you have this problem?          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Participating in social activities |                          |                          |  |                               |  |
| Do you have this problem?          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Doing housework                    |                          |                          |  |                               |  |
| Do you have this problem?          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| How troubling is it?               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |
| Doing yardwork                     |                          |                          |  |                               |  |
| Do you have this problem?          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>      | <input type="checkbox"/>                     |

| How troubling is it?                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
|--------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Performing my job                    |                          |                          |                          |                          |                          |
| Do you have this problem?            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Participating in physical activities |                          |                          |                          |                          |                          |
| Do you have this problem?            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Participating in leisure pastimes    |                          |                          |                          |                          |                          |
| Do you have this problem?            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Driving                              |                          |                          |                          |                          |                          |
| Do you have this problem?            | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

|                                | Not<br>at all            | Very<br>little           | Sometimes<br>or<br>Moderately<br>troubling | Often<br>or<br>Very<br>troubling | All the time<br>or<br>Extremely troubling |
|--------------------------------|--------------------------|--------------------------|--|----------------------------------|---|
|                                | ▼                        | ▼                        | ▼  | ▼                                | ▼   |
| Being independent              |                          |                          |  |                                  |   |
| Do you have this problem?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| How troubling is it?           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| Ability to travel on vacations |                          |                          |  |                                  |   |
| Do you have this problem?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| How troubling is it?           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| Reading                        |                          |                          |  |                                  |   |
| Do you have this problem?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| How troubling is it?           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
|                                | ▼                        | ▼                        | ▼  | ▼                                | ▼   |
| Decreased muscle strength      |                          |                          |  |                                  |   |
| Do you have this problem?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| How troubling is it?           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| Climbing stairs                |                          |                          |  |                                  |   |
| Do you have this problem?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| How troubling is it?           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| Walking                        |                          |                          |  |                                  |   |
| Do you have this problem?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| How troubling is it?           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| Bone pain                      |                          |                          |  |                                  |   |
| Do you have this problem?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| How troubling is it?           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| Stiff joints                   |                          |                          |  |                                  |   |
| Do you have this problem?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| How troubling is it?           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>                   | <input type="checkbox"/>         | <input type="checkbox"/>                  |
| Foot pain                      |                          |                          |  |                                  |   |

|                           |                          |                          |                          |                          |                          |
|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Hip pain                  |                          |                          |                          |                          |                          |
| Do you have this problem? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How troubling is it?      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

## Appendix IV. SF-36 Survey

### SF-36

Choose one option for each questionnaire item.

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

- ☐ 1 - Excellent
- ☐ 2 - Very good
- ☐ 3 - Good
- ☐ 4 - Fair
- ☐ 5 - Poor

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

- ☐ 1 - Much better now than one year ago
- ☐ 2 - Somewhat better now than one year ago
- ☐ 3 - About the same
- ☐ 4 - Somewhat worse now than one year ago
- ☐ 5 - Much worse now than one year ago

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?

- |  | Yes, limited<br>a lot   | Yes, limited<br>a little | No, not<br>limited at all |
|--|-------------------------|--------------------------|---------------------------|
| 3. <b>Vigorous activities</b> , such as running, lifting heavy objects, participating in strenuous sports  | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |
| 4. <b>Moderate activities</b> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |
| 5. Lifting or carrying groceries   | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |

- |  | Yes, limited<br>a lot   | Yes, limited<br>a little | No, not<br>limited at all |
|--|-------------------------|--------------------------|---------------------------|
| 6. Climbing <b>several</b> flights of stairs | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |
| 7. Climbing <b>one</b> flight of stairs      | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |
| 8. Bending, kneeling, or stooping            | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |
| 9. Walking <b>more than a mile</b>           | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |
| 10. Walking <b>several blocks</b>            | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |
| 11. Walking <b>one block</b>                 | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |
| 12. Bathing or dressing yourself             | <input type="radio"/> 1 | <input type="radio"/> 2  | <input type="radio"/> 3   |

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**?

- |   | Yes                     | No                      |
|---|-------------------------|-------------------------|
| 13. Cut down the <b>amount of time</b> you spent on work or other activities                          | <input type="radio"/> 1 | <input type="radio"/> 2 |
| 14. <b>Accomplished less</b> than you would like  | <input type="radio"/> 1 | <input type="radio"/> 2 |
| 15. Were limited in the <b>kind</b> of work or other activities                                       | <input type="radio"/> 1 | <input type="radio"/> 2 |
| 16. Had <b>difficulty</b> performing the work or other activities (for example, it took extra effort) | <input type="radio"/> 1 | <input type="radio"/> 2 |

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)?

- |  | Yes                     | No                      |
|--|-------------------------|-------------------------|
| 17. Cut down the <b>amount of time</b> you spent on work or other activities | <input type="radio"/> 1 | <input type="radio"/> 2 |
| 18. <b>Accomplished less</b> than you would like                             | <input type="radio"/> 1 | <input type="radio"/> 2 |
| 19. Didn't do work or other activities as <b>carefully</b> as usual          | <input type="radio"/> 1 | <input type="radio"/> 2 |

20. 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?

- ☐ 1 - Not at all
- ☐ 2 - Slightly

- ☐ 3 - Moderately
- ☐ 4 - Quite a bit
- ☐ 5 - Extremely

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

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

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

- ☐ 1 - Not at all
- ☐ 2 - A little bit
- ☐ 3 - Moderately
- ☐ 4 - Quite a bit
- ☐ 5 - Extremely

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

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

|   | All of<br>the time      | Most of<br>the time     | A good bit<br>of the time | Some of<br>the time     | A little of<br>the time | None of<br>the time     |
|---|-------------------------|-------------------------|---------------------------|-------------------------|-------------------------|-------------------------|
| 23. Did you feel full of pep?   | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3   | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 |
| 24. Have you been a very nervous person?                                | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3   | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 |
| 25. Have you felt so down in the dumps that nothing could cheer you up? | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3   | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 |
| 26. Have you felt calm and peaceful?                                    | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3   | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 |
| 27. Did you have a lot of energy?                                       | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3   | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 |
| 28. Have you felt downhearted and blue?                                 | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3   | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 |
| 29. Did you feel worn out?  | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3   | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 |
| 30. Have you been a happy person?                                       | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3   | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 |
| 31. Did you feel tired?   | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3   | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 |

32. 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.)?

- ☐ 1 - All of the time
- ☐ 2 - Most of the time
- ☐ 3 - Some of the time
- ☐ 4 - A little of the time
- ☐ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

|  | Definitely<br>true      | Mostly<br>true          | Don't<br>know           | Mostly<br>false         | Definitely<br>false     |
|--|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| 33. I seem to get sick a little easier than other people | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 34. I am as healthy as anybody I know                    | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |
| 35. I expect my health to get worse                      | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |



|                            | Definitely<br>true      | Mostly<br>true          | Don't<br>know           | Mostly<br>false         | Definitely<br>false     |
|----------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| 36. My health is excellent | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 |

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