

Genetic Variability in CYP2D6 in U.S Active Duty Population
Protocol WR 2253 Version 2.2, Oct 30, 2015

Appendix 3

Proposed recruitment script for both e-mail and telephonic contacts:

Study Objective: This study is being conducted to find out the genetic differences of a liver enzyme called CYP2D6 that exist in a group of active duty soldiers. All 250 enrolled volunteers (up to 450) will have their CYP2D6 genotype determined, then a subset will be invited to take a dose of the FDA-approved antimalarial drug primaquine so we can measure drug levels in the blood and urine after administration and see how the liver enzyme type affected the breakdown of the drug.

Study Duration: Depends on the phase. Phase 1 only will last one clinic visit. For those enrolled in phase 1 and 2, Phase 1 will still be one clinic visit and phase 2 will be 3 visits. There may be a lag time of up to 3 months between screening/phase 1 visit and phase 2 procedures.

Number of People in the Study: A total of 250 volunteers (up to 450 if necessary) will be enrolled in phase 1 and a subset of 54 will be selected to enroll in phase 2.

Study Background: Everyone has enzymes, which are proteins that help break down medicines, in their livers. Genetic differences in the enzymes of different people can result in the presence of higher or lower levels of medication in the body. One enzyme called CYP2D6 is responsible for breaking down the antimalarial drug primaquine. Those with low levels or no CYP2D6 enzyme may not break down primaquine adequately, which means the medicine may not be able to clear a malaria infection fully from the liver. This could result in those people having recurrences of certain types of malaria. We will perform a genetic test using your blood to determine your CYP2D6 genotype. Based on this we can categorize you on your ability to break down types of medication into "poor", "intermediate", or "extensive (normal)" enzyme activity. Of the 250 people (up to 450), we will ask 54 volunteers to participate in the second phase of the study where we will give you a one-time 30 mg dose of primaquine by mouth then, over a 24-hour period, draw blood and collect urine to measure drug levels. Then the study will be finished.

Brief review of inclusion / Exclusion criteria

Inclusion Phase 1:

- Active duty Service member, (male or female) 18 to 60 years of age (inclusive) at the time of enrollment
- Written informed consent for phase 1 must be obtained from the subject before screening procedures

Inclusion Phase 2

- Written informed consent for phase 2 must be obtained from the subject before additional screening procedures
- Free of significant health problems as established by medical history, laboratory and clinical examination before undergoing primaquine dosing
- If the subject is female, she must be of non-childbearing potential (either surgically sterilized or one year post-menopausal) or, if of childbearing potential, she must be



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capable of preventing pregnancy, have a negative pregnancy test at the time of the administration of primaquine, and must agree to continue such precautions until at least 48 hours after primaquine administration.

- Normal (non-deficient) G6PD phenotype (range: 4.6 to 13.5 units/gm hemoglobin)
- Subjects must obtain approval from his or her supervisor per WRAIR Policy 06-15 in order to participate in the primaquine dosing.

Exclusion Criteria Phase 2 (none for Phase 1)

- Use of any investigational or non-registered drug within 30 days preceding the primaquine dosing.
- Pregnant (positive urine β -HCG) or nursing at screening or plans to become pregnant or nurse from the time of enrollment until at least 48 hours after primaquine dosing.
- Allergy to primaquine
- Use of medications known to cause drug interactions with primaquine or CYP2D6
- Acute or chronic, clinically significant, pulmonary, cardiovascular, hepatic, neurological, or renal functional abnormality, as determined by history, physical examination, and laboratory evaluation
- ALT above normal range
- Glomerular filtration rate (GFR) above normal range for the subject's age and ethnicity
- Hemoglobin below normal range
- Hepatomegaly, right upper quadrant abdominal pain or tenderness
- Suspected or known current alcohol abuse as determined from the medical history or by physical examination
- Use of any drugs that may cause hemolytic anemia and/or bone marrow suppression such as quinacrine, dapsone, rifampin, colchicine, ribavirin, penicillamine and sulfonamides.
- Any other significant finding that in the opinion of the investigator would increase the risk of having an adverse outcome from participating in this study

Study Plan:

Screening Phase 1

A person who wants to enroll in the study will be screened to ensure they are eligible to participate. Screening includes:

- A detailed explanation of the study
- Completion of the informed consent documents
- Phase 1: 5 mL blood draw one time
 - Those who indicate they wish to participate in Phase 2 will sign the ICF and be contacted after Phase 1 genotyping results are available

Screening Phase 2

- Brief medical history and physical exam
- Urine pregnancy test for women
- Blood drawn for safety labs (10 mL)



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Visit 1&2 Phase 2

- A urine pregnancy test will be performed for all women
- 30 mg of primaquine will be given orally
- Blood tests will be drawn over a 24-hour period to determine drug levels
- Investigators will ask you for any adverse effect from the drug

Risks to the Volunteers may include:

- From primaquine: nausea, vomiting, and stomachache. These risks are negligible when primaquine is taken with food.
 - Note: study staff have methods to decrease or limit most, if not all, side effects
- From blood draws: bruising at the site
- From G6PD deficiency: Those volunteers found to be G6PD deficient in Phase 2 will be excluded from Phase 2 since taking the drug primaquine may cause hemolysis and anemia.
- Loss of confidentiality: If you participate in this study, there is a chance that limited information about you may be disclosed to persons outside of this study such as WRAIR and USUHS Institutional Review Board (IRB). These representatives may have access to review research records as part of their responsibility to protect humans in research but they must also maintain confidentiality of your records within the limits of the law.

Payment:

- Payments will be made for blood drawn during the study but not for transportation or other expenses.
- The screening and Phase 1 blood draw will be \$100.00. Active duty personnel will be paid \$50 for the latter draw, unless the visit occurs during off duty hours or they are on leave.
- Phase 2 will be \$100 for screening and blood draw, active duty personnel will be paid \$50 for the blood draw, unless the visit occurs during off duty hours or they are on leave. If enrolled in phase 2, volunteers will receive \$50 per blood draw and a \$50 bonus if they complete all blood draws to include the 24 hour time point for a total of \$450.00.

Study Setting: Outpatient



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Earlier Versions Invalid