IND Protocol: Intravenous Artesunate for

Treatment of Severe Malaria in the United States

IND Sponsor: Centers for Disease Control and Prevention (CDC)

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PROGRAM CONTACT INFORMATION

Principal Investigators:
Paul Arguin, M.D.
Captain, USPHS
Chief, Domestic Malaria Unit
Division of Parasitic Diseases and Malaria
Centers for Disease Control and Prevention
1600 Clifton Road NE, MS A-06
Atlanta, GA 30333
Phone: 404.718.4703
Fax: 404.718.4815

S. Patrick Kachur, M.D.
Captain, USPHS
Chief, Malaria Branch
Division of Parasitic Diseases and Malaria
Centers for Disease Control and Prevention
1600 Clifton Road NE, MS A-06
Atlanta, GA 30333
Phone: 404.718.4764
Fax: 404.718.4815

Clinical Project Manager:
Paul Arguin, M.D.

Medical Monitor:
Paul Arguin, M.D.

1.0 SUMMARY:

Currently, intravenous quinidine gluconate is the only parenteral drug available in the United States (US) for the treatment of severe malaria. This situation is, to our knowledge, unique to the US and is problematic. Quinidine has cardiotoxic effects and has become less and less available in US hospitals with the advent of newer antiarrhythmic drugs. There is currently no alternative parenteral antimalarial drug available to those patients with severe malaria who do not have access to quinidine, who do not tolerate the drug, or whose infection does not respond to quinidine treatment. A well proven alternate treatment, recommended by the World Health Organization (WHO) in preference to quinidine and used worldwide for the treatment for severe malaria, is artesunate. Artesunate, however, has not yet been approved by the Food and Drug Administration (FDA) for use in the US. The Walter Reed Army Institute of Research (WRAIR) is currently conducting studies in several countries using cGMP (Current Good Manufacturing Practices)-produced intravenous (IV) artesunate. We propose to make this intravenous GMP IV artesunate available to malaria patients hospitalized in the US who need IV treatment because of severe disease, high parasitemia, or inability to take oral medications, and who either do not have timely access to intravenous quinidine, do not tolerate quinidine, have contraindications to quinidine, or in whom quinidine treatment has proven ineffective. The drug will be provided to the hospitals, upon request and on an emergency basis, by the CDC Drug Service or by one of the 18 CDC Quarantine Stations nationwide. The IV artesunate will be followed by oral treatment with atovaquone-proguanil (Malarone), doxycycline, clindamycin, or mefloquine to ensure maximal curative effect. The receiving physicians will be requested to notify CDC of any adverse event following administration of the drug.

2. 0 BACKGROUND

2.1 Severe malaria

Severe malaria is a major global health problem. An estimated 1 million deaths are caused annually by severe malaria, especially in Africa, with the majority of deaths occurring in young children. Severe malaria is a medical emergency whose treatment has become increasingly difficult due to the advent and spread of drug-resistant parasites. This situation has been improved by the introduction of artemisinin derivatives, whose life saving properties reside in their rapid action and their efficacy against multidrug-resistant parasites.

Severe malaria results from the infection of a large number of red blood cells by malaria parasites. Of the four species of malaria parasites that infect humans (*Plasmodium falciparum, P. vivax, P. ovale,* and *P. malariae*), almost all cases of severe malaria are due to *P. falciparum*. There have been rare case reports of severe manifestations of disease associated with *P. vivax* infection (Kochar 2005).

The large-scale destruction of parasitized red blood cells releases biologic products harmful to the infected host. The sequestration of infected red blood cells in the small vessels of vital organs such as the brain or kidneys leads to end-organ dysfunction. The resulting manifestations of severe malaria include (WHO 2000):

Table 1: Clinical and laboratory features of severe malaria
Cerebral malaria
Generalized convulsions
Severe anemia
Hypoglycemia
Metabolic acidosis
Acute renal failure
Acute pulmonary edema, acute respiratory distress syndrome (ARDS)
Circulatory shock
Abnormal bleeding
Disseminated intravascular coagulation
Jaundice
Hemoglobinuria
High fever
Hyperparasitaemia

Despite appropriate therapy and medical care, mortality from severe malaria remains high. Case fatality rates were 7.3% - 17.7% in children admitted with severe malaria to a Kenya hospital (Marsh 1995), and 3-15% in European patients admitted in European hospitals (Mühlberger 2003, Krause 2006). The case fatality rate in the United States is estimated to be 1% (Newman 2004).

2.2 Severe malaria in the United States

In the United States malaria is now a rare disease; for this reason it is not always recognized, diagnosed and treated in time and correctly. Since 1996 there have been at least 1,200 annual cases of malaria diagnosed in the US reported to the CDC (CDC 2006). Almost all of these cases occur in persons who, after acquiring the infection in a malaria endemic area abroad, are diagnosed after return to the US ("imported malaria"). Most of these patients are US residents who have no acquired immunity to malaria and are, therefore, at risk of developing severe disease. A major contributing factor to continued malaria-associated mortality in the United States is delay in initiation of appropriate treatment (Newman 2004). In the five-year period between1999-2004, there were 41 deaths from severe malaria in the United States (RD Newman, unpublished).

Based on surveillance data for 2005 and 2006 to date, an estimated 120 cases of complicated malaria requiring parenteral treatment occur every year in the US.

2.3 Diagnosis and treatment of severe malaria in the United States

A provisional diagnosis of severe malaria can be made in a patient who presents any of the features cited in Table 1, and who has malaria parasites demonstrated on microscopic examination of a blood smear. In most cases the parasite will be identified as *P. falciparum*. In some cases the parasites will be identified as *P. vivax, P. ovale,* or *P. malariae,* or a combination of the four species; or the microscopic examination may detect malaria parasites without being able to identify them specifically as being *P. falciparum* (diagnosis: *Plasmodium*, species undetermined). Because microscopic diagnosis is not always accurate (especially in the US, where laboratory personnel are not always familiar with malaria), a patient with the features of

severe malaria (Table 1) and malaria parasites of any species should be treated as if having *P. falciparum*, the species responsible for practically all cases of severe malaria. Treatment for *P. falciparum* will be effective against the blood stage of all four malaria species.

In some patients suspected of having severe malaria based on travel history, clinical findings, and exclusion of other causes of illness, a reliable microscopic diagnosis cannot be secured in a timely manner due to lack of laboratory facilities or trained personnel. Such patients can justifiably be treated presumptively for severe malaria, because the risk of death due to untreated severe malaria outweighs the risk of fatal adverse events caused by a presumptive (and possibly unnecessary) treatment.

Patients with severe malaria in the US are treated specifically with the emergency intravenous administration of a rapidly acting antimalarial drug (quinidine) combined with a slower acting, but more thoroughly parasiticidal drug such as doxycycline or clindamycin (www.cdc.gov/malaria; hereafter will be referred as CDC malaria website 2006). Parenteral treatment aims to rapidly reach parasiticidal blood levels of the antimalarial drug, thus lowering the level of parasitemia and reversing end organ dysfunction and hemolysis. Parenteral therapy is discontinued when the patient is able to tolerate oral medications and the parasite density has reached low levels (i.e. <1% red blood cells infected).

In addition, general supportive care is given which may include infusion of intravenous fluids; correction of metabolic disturbance such as hypoglycemia or acidosis; blood transfusions or exchange transfusion; assisted ventilation; vasopressors; and renal dialysis (WHO 2000; CDC malaria website 2006).

Response to therapy is assessed by clinical observations and measurements of laboratory parameters such as serial blood smears which will document a hoped for decrease in parasitemia and its eventual clearance.

In addition to patients with severe malaria, patients who are unable to ingest drugs orally due to nausea and vomiting (a frequent complication of malaria) should also receive parenteral therapy.

3.0 QUINIDINE

Quinine, a quinolinemethanol that is a component of the bark of cinchona trees, is the oldest known antimalarial drug and remains a key component in the treatment of severe malaria. Parenteral quinine is not commercially available in the United States, where by default severe malaria has been treated since 1991 with the D-isomer of quinine: quinidine (CDC 1991). To our knowledge, the United States is the only country where quinidine is the sole drug available for treatment of severe malaria.

3.1 Quinidine: Administration

Quinidine is a class IA antiarrhythmic agent that exhibits, like quinine, significant antimalarial activity. Quinidine acts rapidly to prevent the maturation of malaria parasites from late rings to schizonts, the basis of its life-saving properties (White 1987).

For treatment of severe malaria, CDC recommends quinidine gluconate given in the following treatment regimen: Initial IV loading dose of 10mg salt per kg infused over 1-2 hours, followed by a continuous maintenance infusion of 0.02 mg salt/kg per minute for 72 hours or until parasitemia is reduced to less than 1% or oral therapy can be started. An alternative regimen is an intravenous loading dose of 24 mg salt/kg infused intravenously over 4 hours, followed by 12 mg/kg salt infused over 4 hours every 8 hours, starting 8 hours after the loading dose.

Due to the potential cardioxicity associated with quinidine, CDC recommends a baseline EKG, continuous cardiac monitoring in an intensive care setting during drug administration, and consultation with a cardiologist (CDC malaria website 2006). Because of these requirements and the need for continuous or daily repeated dosing, the administration of quinidine is relatively cumbersome.

3.2 Quinidine: Decreased availability

Quinidine was widely available in US hospitals but has been progressively replaced by newer, better antiarrhythmic drugs. The decreased availability of quinidine on many hospital formularies has been noted as a contributing factor in deaths from malaria in the United States (CDC 1996) and Canada (Humar 1997). Additional problems potentially affect distribution. In both 2005 and 2006, the drug manufacturer (Lilly) had, for limited periods, only short-dated material (material close to date of expiration) available, which distributors would not accept. Even though during these periods the drug could be obtained directly from the manufacturer, such situations contribute to delays in obtaining the drug if a hospital needing quinidine urgently did not have the drug in stock.

3.3 Quinidine: Resistance

Several studies in Southeast Asia have indicated declining quinine efficacy in that region (Pukrittyakamme 1994). Although CDC has not yet confirmed a case of quinidine failure in patients seen in the US, it is important that US clinicians have access to an alternative antimalarial drug should they encounter such a case.

Quinidine therapy may be considered to have failed if, at 48 hours after the start of intravenous quinidine therapy, the parasitemia has decreased by less than 90% (i.e., the parasitemia is greater than 10% of its admission value). This estimate is derived from the typical parasite clearance times with intravenous quinidine treatment in a review of the literature (Phillips 1985, Miller 1989, Molyneux 1991, van Hensbroek 1996, Newton 2003).

3.4 Quinidine: Adverse events and cardiotoxicity

Quinidine can cause numerous adverse events including cinchonism, a toxicity syndrome that includes tinnitus, headache, deafness, and occasionally anaphylactic shock. Hypersensitivity reactions, including thrombocytopenic purpura, acute hemolytic anemia, hepatitis, and a systemic lupus erythematous-like syndrome also occur rarely (Kim 1990).

Cardiotoxicity is the adverse reaction to IV quinidine that is of greatest concern. Severe cardiotoxic side effects that can occur during IV therapy may manifest as:

1. Widening of QRS interval
2. Prolongation of QT interval
3. Persistent hypotension unresponsive to fluid resuscitation

Of note, persistent hypotension may also be a consequence of severe malaria.

When a patient with severe malaria develops cardiotoxicity attributable to the parenteral quinidine treatment, the only option currently available is to temporarily discontinue the infusion or reduce its rate which may well contribute to poorer outcomes due to severe malaria.

The evidence-based 2006 publication by the World Health Organization (WHO), "Guidelines for treatment of malaria," states that quinidine is considered more toxic than quinine and should only be used if none of the other effective parenteral drugs are available (WHO 2006).

3.5 Quinidine: Contraindications

Contraindications to quinidine include:

1. Known allergy or hypersensitivity to quinidine or cinchona alkaloids
2. Development of thrombocytopenic purpura with previous quinidine therapy
3. AV junctional or idioventricular pacemaker with no atrial activity or complete AV block
4. Left bundle-branch block or other severe intraventricular conduction defects
5. Cardiac glycoside-induced AV conduction disorders (digitalis toxicity)
6. Myasthenia gravis

If a patient with heart block has a pacemaker, then conduction defects can be considered relative rather than absolute contraindications.

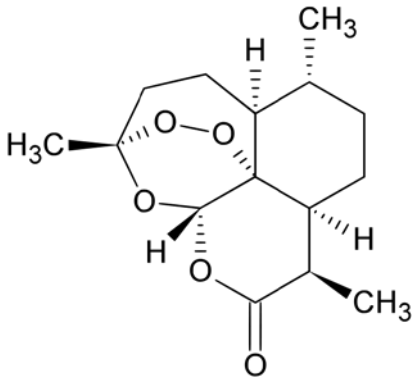
4.0 ARTESUNATE

Other compounds with excellent safety and efficacy data for the treatment of severe malaria are artemisinin derivatives, such as artesunate. The WHO Guidelines for Treatment of Malaria (2006) recommend artemisinin derivatives as an essential component in the treatment of malaria (including severe malaria) worldwide (WHO 2006). While artemisinin derivatives have wide global availability, they have not yet been approved by the FDA for use in the United States. However, artesunate produced under GMP is currently being tested in trials conducted by WRAIR (IND 64,769).

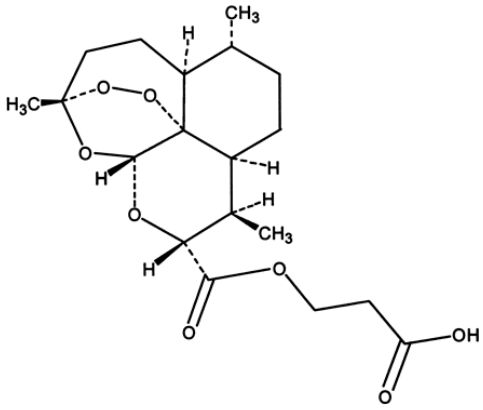
4.1 Artemisinin and its derivatives

Artemisinin is extracted from the "quinghaosu" or sweet wormwood plant (*Artemisia annua* L.) which has been part of traditional Chinese herbal medicine for centuries. Artemisinin was rediscovered and isolated in 1972 by Chinese scientists seeking new treatments for drug-resistant malaria, and was first reported in the medical literature in 1979. It is a sesquiterpene lactone with an internal peroxide linkage (Klayman 1985). The mechanism of antimalarial action of artemisinin has been hypothesized to involve an iron-mediated cleavage of the endoperoxide bridge, which produces oxygen radicals, which then react with nearby molecules, interfering with parasite function (Meshnick 1994). Various derivatives of artemisinin differ by the substituent at position #10. They include dihydroartemisinin, artemether, arteether, and

artesunate. Artesunate is the hemisuccinate of the ester of dihydroartemisinin. It is water based, and rapidly biotransforms to its active metabolite, dihydroartemisinin, which has a short half-life of approximately 1 hour. Artemisinin derivatives have been used for more than two decades and are now a key component of treatment of malaria worldwide. They are available in formulations that allow administration by different routes (oral, parenteral, rectal). WHO supports their use as first-line antimalarial drugs, in combination with other antimalarial agents, in most malaria-endemic areas of the world. Such artemisinin-based combination therapies (ACT) aim to treat drug-resistant *P. falciparum* malaria rapidly and successfully, while at the same time slowing the emergence of resistance to artemisinin (WHO 2006).



Artemisinin



Artesunate

4.2 Artesunate: Efficacy

Experimental studies have demonstrated the efficacy of artesunate against malaria parasites cultured *in vitro*, and against malaria parasites in experimental animal models (rodent and non-human primates).

Artesunate has been used extensively to treat malaria for more than two decades outside the US. Given intravenously, it has been highly effective, and has the advantage of a reliable and rapid pharmacokinetic profile. Studies on the treatment of severe malaria have been conducted in China, India, Thailand, Burma, Vietnam, Brazil, Ghana, Sudan, Gabon, and Malawi. These studies have utilized artesunate intravenously, intramuscularly, and rectally, alone and in combination with other drugs. Trials up to 1999 were summarized in the Cochrane Review Series (McIntosh and Olliaro, 2000). For the purposes of this protocol, only trials that employed intravenous artesunate for treatment of severe malaria are summarized below.

A study of 79 Vietnamese adults compared IV artesunate plus mefloquine, artemisinin suppositories plus mefloquine, and IV quinine. It demonstrated that IV artesunate cleared parasitemia and fever significantly faster than IV quinine, but no significant differences were found in duration of coma or mortality (Hien, 1992). Earlier unpublished studies (TK Anh, 1989) comparing artesunate to IV quinine in 41Vietnamese adults, and follow-up unpublished studies by the same author (TK Anh) in 190 Vietnamese adults from 1992 to 1995 showed statistically significant differences in mortality favoring artesunate. A study in Myanmar among 141 Burmese adults with cerebral malaria showed significantly less mortality in the artemisinin-

derivative arms (which included an arm with IV artesunate plus mefloquine) when compared with the IV quinine plus tetracycline arm (Win 1992).

A randomized, open-label trial compared IV artesunate and IV quinine in 113 adults with severe malaria in two centers in Thailand (Newton 2003). Mortality was 12% in the artesunate arm and 22% in the quinine arm (relative risk 0.53; p=0.22), suggesting that artesunate is at least as effective as quinine. Importantly, parasite clearance times were shorter and fewer patients developed hypoglycemia on artesunate therapy.

In the largest and most definitive trial to date, the South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group performed a multicenter, open-label randomized controlled trial among 1,461 patients with severe malaria in Bangladesh, India, Indonesia and Myanmar (SEAQUAMAT 2005). The trial was stopped early as researchers witnessed a significant reduction in mortality in the artesunate arm (15%) compared to the quinine arm (22%) with a relative risk of 0.69 (95% CI 0.54-0.83). The number of patients needed to receive treatment with artesunate to save one life, in comparison to patients treated with quinine, ranged from 11.1 to 20.2, depending on the countries. Artesunate was well tolerated while quinine was significantly associated with hypoglycemia. These authors recommended that artesunate become the treatment of choice for severe *P. falciparu*m malaria. To complement these studies conducted mainly in Asian adults, similar studies are ongoing on young children in Africa.

The evidence-based 2006 WHO Guidelines for Treatment of Malaria consider artemisinin derivatives to be an essential component in the treatment of severe malaria (WHO 2006).

4.3 Artesunate: Toxicity

Clinical and animal studies suggest that artemisinin derivatives are much less toxic than the quinolines, the group that includes quinine and quinidine (Price 2000). While formal human toxicity studies on artesunate or the artemisinins in general are few, substantial clinical evidence and surveillance in Thailand all suggest that this drug class is relatively well-tolerated in adults and children

4.3.1 Preclinical studies

Animal preclinical data suggest that the most common side effects of artemisinin derivatives might be reversible reticulocytopenia and mild hemolysis, of unknown mechanism (RS Miller, WRAIR, 2004 unpublished data). Neutropenia and diarrhea were seen in primates, but not in dogs. At high doses in non-human primates (>32 mg/kg), transient ataxia and hypersalivation have been observed. Toxicity studies of IV artesunate given for 14 days to beagle dogs detected no adverse effects except for a decrease in red blood cell parameters, including reticulocytes. Toxicity studies of beagle dogs given escalating doses of IV artesunate detected no cardiovascular or respiratory adverse effects. Toxicity studies in experimental animals (including rodents, monkeys, and dogs) demonstrated neurotoxic effects affecting mostly the brain stem (Miller and Blanchard, 2003). Such neurotoxicity has not been found in humans, which suggests that their occurrence in experimental animals were due to the high doses administered or the formulation used (Gordi and Lepist 2004).

The most important concern about this drug class has been the neurotoxicity reported in animals with the long-acting intramuscular oil-based artemisinins, such as arthemeter and arteether (Brewer 1998, Gordi and Lepist2004). All the artemisinins, including artesunate are metabolized to dihydroartemisinin. Most experiments on artemisinins contain too many confounding variables to definitively determine the cause and mechanism of neurotoxicity, particularly since severe malaria may itself cause decreased neurologic function. Li et al (2002) concluded from studies with rats that prolonged drug exposure at low levels was related to a greater likelihood of severe neurotoxicity of artemisinin derivatives.

4.3.2 Human data

Artemisinin derivatives appear to be safe and have been used to treat several millions of cases of malaria without reported serious adverse events. Price (1999) combined findings from studies conducted in western Thailand during which 3,276 patients were treated orally with artesunate, of whom 2,646 also received mefloquine; 386 were treated with arthemether, of whom 180 also received mefloquine; and 1,303 were treated with mefloquine alone. Symptomatic side effects in the pooled group of patients treated with artesunate or artemether monotherapy ranged from 34% (anorexia on Day 1-2), to 15-16% (dizziness-nausea on Day 1-2), to 1% (diarrhea on Day 1-2), and were generally less than the incidence of side effects in the mefloquine monotherapy group (54%, 54%-46%, and 3%, respectively). There was no evidence of neurotoxicity, cardiotoxicity, or allergic reactions attributable to the artemisinin derivatives. Adverse events (AEs) were noted in 17 patients, all of whom had received mefloquine either as monotherapy (2), in combination with artesunate (13) or with artemether (2). No AEs were noted in patients who had received artesunate monotherapy. The AEs consisted of urticaria, hemoglobinuria, seizures, neuropsychiatric reactions, and reversible neurologic changes, and could have resulted from malaria, mefloquine, or the artemisinin-based drugs.

Phase I-II data for IV administration of artesunate from a WHO summary by Dr. Melba Gomes indicate the following:

- Phase I trial: 2-4 mg/kg IV artesunate resulted in a reversible decrease in reticulocyte counts [section 14 i of WHO summary].

- Phase II trial: Approximately 15 mg/kg IV artesunate was administered over 3 days. Reversible increases in liver function tests were seen. Bradycardia was seen in the artesunate group and also in the simultaneous quinine group. [section 14 ii of WHO summary].

- Phase II trial: Approximately 6 mg/kg IV artesunate to patients with cerebral malaria resulted in SGPT elevations and BUN elevations that persisted until Day 6, the last day of observation. [section 14 vi of WHO summary].

- Intrarectal (IR), intramuscular (IM), and IV administration for severe malaria: IR administration resulted in "no major adverse effects" in 30 patients, other than dizziness, nausea, vomiting, and abdominal pain, which are components of acute malaria infection; 5 patients had tenesmus or extruded their suppositories, and had to have them reinserted; tenesmus was also recorded in African patients. IM administration resulted in a

reticulocyte count that did not change by Day 5 of treatment, in spite of pretreatment hematocrits averaging 24%, compared to a reticulocyte count in the quinine comparator group that increased by 1%. IV artesunate was used in a severe malaria study in Vietnam and in a Tanzanian study of 25 patients with uncomplicated malaria. In the Vietnamese patients with severe malaria, there were no apparent side effects; in the Tanzanian patients with uncomplicated malaria, EKGs did not become abnormal as a result of artesunate treatment. The mean creatinine, BUN, SGOT, and bilirubin levels fell between pretreatment measurements and Day 5 measurements.

Severe allergic reactions have been reported in case reports. Two out of 17,000 patients treated with artemisinin derivatives in Thailand developed pruritus and urticarial rashes, and dyspnea following oral artesunate (Leonardi 2001). Among 59 patients with severe malaria treated with IV artesunate in western Thailand, one patient developed an urticarial rash (Newton 2003).

4.3.3 Particulates in artesunate produced for clinical use

Small amounts of dihydroartemisinin may be present as particulates in the 10 to 25 micron range in the currently available clinical lot of artesunate produced for clinical use. The U.S. Pharmacopeia (USP) has established acceptable levels of particulates present at the ≥ 10 micron range. USP <788> sets these limits of acceptability for particle counts for vials less than 25 mL at less than 6000 particles/vial for the ≥ 10 micron range. Although all tests for particulates to date have been within the acceptable range, on January 18, 2008, CDC received particulate results that were in the upper range of the acceptable limits. All currently available laboratory evidence to date suggests that these particles are dihydroartemisinin, the active metabolite of artesunate which is less soluble in water than artesunate. When this product is administered through a 0.8 micron hydrophilic polyethersulfone filter, particulate counts are reduced to an essentially particulate free solution. While the Artesunate Integrated Product team at Walter Reed believes the presence of these particles do not necessarily pose a risk to patients receiving the product, use of the filter negates the possibility of effect without influencing the efficacy of the product. Thus, CDC is now recommending that artesunate should be administered using an in-line 0.8 micron hydrophilic polyethersulfone filter.

4.3.4 Delayed hemolytic anemia after treatment for severe malaria with artesunate

Between 2010 and 2012, 19 instances of delayed hemolytic anemia have been reported in the published literature following treatment of severe malaria with artesunate in other non-endemic countries (Kano 2010; Zoller, Junghanss et al. 2011; Caramello, Balbiano et al. 2012; Kreeftmeijer-Vegter, van Genderen et al. 2012; Rolling, Schmiedel et al. 2012). As of September 2012, CDC recommended that persons treated for severe malaria with artesunate be evaluated for up to 4 weeks after that treatment for evidence of hemolytic anemia. Two cases of delayed hemolytic anemia have been identified in the United States after the use of artesunate for the treatment of severe malaria under this IND protocol. Artesunate kills the intraerythrocytic malaria parasites which are then removed from the red blood cells by the spleen. The leading hypothesis for the occurrence of delayed hemolytic anemia is that the previously infected red blood cells have a decreased life span compared to red blood cells that were never infected. So rather than being lysed by the parasites at the time of the severe malaria episode, the red blood

cells are cleared by the spleen about 7-14 days after the treatment with artesunate in a self-limited hemolytic event. Persons with higher parasitemias seem to have a higher likelihood of delayed hemolytic anemia after treatment with artesunate. Depending on the amount of hemolysis, transfusion may be needed. Any instances of hemolytic anemia after treatment with artesunate should be reported immediately to the principal investigator, Dr. Paul Arguin at parguin@cdc.gov or (404)718-4703.

4.4. Artesunate and pregnancy

The information below is referenced from IND 64, 769, "The Summary of studies on the adverse effects of AS on pregnancy of humans and animals: studies reported in literature and conducted in house" which summarizes the literature and current studies at WRAIR:

- Artesunate causes fetal toxicity in rats and rabbits resulting in fetal resorption and abortion, as well as a low incidence of cardiac malformations and skeletal defects.

- Studies in rats at WRAIR indicate that artesunate crosses the placental barrier and accumulates in the placenta and fetus, which may explain the observed fetal toxicity.

- From 1999 to 2006, a total of 2,045 pregnant women participating in clinical trials in Thailand, the Gambia, and Sudan were treated with artesunate alone or in combination with other antimalarial drugs (such as quinine, mefloquine, atovaquone-proguanil and sulfadoxine-pyrimethamine). Most of these patients were in the second and third trimesters of pregnancy. The investigations found no significant differences from community rates in birth weight, duration of gestation, placenta weights, or congenital abnormality rates in newborns at delivery or in growth and developmental parameters of infants monitored for one year.

McGready (2001) assessed artesunate safety in western Thailand, where 461 pregnant women were treated with artemisin derivatives (predominantly artesunate) with no evidence of adverse effects. In 414 women with known pregnancy outcomes, the rates of abortion (4.8%), stillbirth (1.8%), congenital abnormalities (0.8%), and low birth weight (19.0%) did not differ significantly from rates found in the community. The vast majority of study participants were in their second or third trimesters of pregnancy. In 44 women who received artemisinin derivatives during the first trimester of pregnancy, the abortion rate was not significantly different from the community rate.

Moore (2016) conducted an observational study of 55,636 pregnancies on the Thai-Burma border between 1994 and 2013, assessing the effects of instances of malaria during the first trimester as well as the effects of different malaria medicines on rates of miscarriage and major congenital malformations. There was no difference in those rates for women treated with artemisinins compared to those treated with quinine. The conclusion from this article is that artemisinins including artesunate appear to be safe for use during the 1st trimester of pregnancy

Thus, while animal studies indicate that artesunate can have harmful effects on pregnancy, no such effects have been documented in humans. Ongoing studies continue to demonstrate the safety of artemisinins during pregnancy. Considering that severe malaria represents a substantial

risk for pregnant women and their fetuses, WHO recommends that pregnant women with severe malaria be treated with artesunate or quinine in the first trimester, and with artesunate preferentially to quinine in the second and third trimesters (WHO 2006).

5.0 ARTESUNATE: PRODUCT SOURCE AND DESCRIPTION

5.1 Product

The investigational product to be used in this protocol is the WRAIR's formulation of IV artesunate, WR256283. The product will be provided as a sterile dry-filled powder with a diluent for reconstitution, phosphate buffer. Once reconstituted, the drug should be administered through a 0.8 micron polyethersulfone in-line filter as a precautionary safety measure regarding any potential precipitation of the product.

The bulk drug was purchased from Knoll Pharmaceuticals, and manufactured by SRI International, Menlo Park, CA, US, Batch # 14462-16 (Bottle # BR 29487). It was produced in September – October 2004. Scheduled stability and degradation studies will be conducted at regular interval to ensure the drug's chemical stability. Only drug products with a current certificate of analysis will be used. . No expired drug will be used. The drug label will also contain the following: Store at 2 – 10 degrees Celsius. CAUTION: INVESTIGATIONAL NEW DRUG LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE.

The phosphate buffer (USP), also manufactured by SRI International, Menlo Park, CA, US, Lot #: 090403-B, will be used as diluent for artesunate in this trial. The phosphate buffer will be stored at 2° to 30° Celsius.

IV Artesunate (WR256283) will be supplied with a certificate of analysis and a statement of the expiration or re-test date. CDC will provide the investigational product that has been packaged to prevent contamination or deterioration during transport and storage.

5.2 Current WRAIR trials with product

The product is currently being used by WRAIR in several ongoing clinical trials under IND 64,769. A single-dose safety studies demonstrated the virtual lack of any measurable side effects in doses approaching currently up to 8 mg/kg, nearly four times the recommended dose. Minor, extremely transient side effects consisted of minor lightheadedness in up to 40% of the participants at the time of infusion and an alteration of taste (metallic taste) in up to 50% of the participants (prior to breaking the code).

An ongoing study using repeated dosing aims to assure that there is no cumulative toxicity, which is not predicted by available information on the pharmacokinetics of artesunate and its metabolites, or by several published observational studies of cumulative toxicity.

In a safety and efficacy study, Kenyan adults with non-complicated *P. falciparum* malaria were treated with this cGMP IV artesunate at the same drug regimen as proposed in this CDC program. No major adverse events have been noted in 30 subjects. The pharmacokinetics and efficacy of the product were comparable to those of previously used (non-ICH cGMP) artesunate preparations.

Currently scheduled trials include: dose optimization trials in uncomplicated malaria in adults in both Kenya and Thailand; safety and efficacy trial in children with severe malaria in Gabon and Malawi; safety, efficacy, and population pharmacokinetics trial in children with uncomplicated malaria in Kenya. The close working relationship of CDC and WRAIR will assure that findings from these trials will be rapidly communicated to improve this CDC program if appropriate. The results of the scheduled trials will also be communicated to the IRB in a timely manner.

6.0 OBJECTIVE

The primary purpose of this program is to make available intravenous artesunate for treatment of severe malaria in US hospitals when parenteral quinidine cannot be used due to unavailability, intolerance, contraindications, or parasite non-response. Adverse events associated with the administration of artesunate will be recorded in accordance with 21CFR312.32.

7.0 TREATMENT DESIGN

7.1 Inclusion Criteria/Eligibility

In order to be eligible for IV artesunate, a patient must meet criteria a, b, and c below:

a. Malaria confirmed by microscopy. It is expected that the great majority of the eligible cases will diagnosed as *P. falciparum*. Patients with other microscopic diagnoses of malaria (*Plasmodium* of undetermined species, or species other than *falciparum*) will also be eligible, taking into account the unfamiliarity of some US laboratories with malaria diagnosis and the importance of timely treatment of severe malaria. In exceptional cases, microscopic diagnosis might be waived, e.g., a patient with strong clinical suspicion of severe malaria, for whom a timely, reliable microscopic diagnosis is not available (current CDC guidelines advise that in such cases, parenteral antimalarial treatment is justified).

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b. Parenteral treatment required due to one or more of the following reasons (1, 2, or 3):
    1. Unable to take oral medications
    2. High density parasitemia (>5%)
    3. Severe malaria based on:
        - *i.* Impaired consciousness
        - *ii.* Seizures
        - *iii.* Circulatory collapse/shock
        - *iv.* Pulmonary edema or acute respiratory distress syndrome (ARDS)
        - *v.* Acidosis
        - *vi.* Acute renal failure
        - *vii.* Abnormal bleeding or disseminated intravascular coagulation (DIC)
        - *viii.* Jaundice
        - *ix.* Severe anemia (Hb < 7 g/dL)

c. Administration of IV artesunate desirable due to one or more of the following:

1. Availability: When IV artesunate would be available more quickly than IV quinidine; if both drugs are equally available, the attending clinicians will decide which drug to use in consultation with CDC.
2. Quinidine failure: Parasitemia greater than 10% of baseline at 48 hours after initiation of intravenous quinidine
3. Quinidine intolerance:
    i. QRS interval is widened by $\geq$ 50%
    ii. QT interval exceeds 0.60 seconds
    iii. QTc interval is prolonged by more than 25% of the baseline value
    iv. Persistent hypotension unresponsive to fluid resuscitation
    v. Development of reaction to quinidine during therapy
4. Contraindications to quinidine
    i. Known allergy or hypersensitivity to quinidine or cinchona alkaloids (quinine)
    ii. Thrombocytopenic purpura with previous quinidine therapy
    iii. AV junctional or idioventricular pacemaker with no atrial activity or complete AV block
    iv. Left bundle-branch heart block or other severe intraventricular conduction defects
    v. Cardiac glycoside-induced AV conduction disorders (digitalis toxicity)
    vi. Myasthenia gravis

7.2 Exclusion Criteria

a. Known allergy to artesunate

7.3 Special considerations: Pregnant Women

For pregnant women, especially in the first trimester of pregnancy: the lack of data regarding potential artesunate teratogenicity must be weighed against the risks of severe malaria in the context of quinidine unavailability or unsuitability. Ultimately, malaria is life threatening for both the pregnant woman and the fetus, and artesunate should not be withheld if quinidine is unavailable, contraindicated, ineffective, and/or not tolerated.

7.4 Procedures

a. Malaria Branch medical epidemiologists who take CDC Malaria Hotline clinical calls from physicians will determine eligibility using the "Eligibility for IV Artesunate" form (Appendix I).
b. If the patient meets eligibility criteria and the attending physicians agree, CDC Malaria Branch staff will fax and/or email the required consent form (Appendix V) and drug administration protocol (Appendices II, III) to the physician or other health care provider.
c. CDC Malaria Branch staff will initiate the procedure for release of IV artesunate from the CDC Drug Service or Quarantine Station to the appropriate treatment facility (Appendix IV).

d. Artesunate will be released from CDC Drug Service or Quarantine Station to the treatment facility as rapidly as possible (ground courier or air), preferably within 2 hours.
e. Artesunate will be administered at the health facility, in consultation with CDC medical epidemiologists as needed.
f. If Serious Adverse Events (SAE) occur, the treatment facility will notify CDC within 24 hours by telephone and send the Serious Adverse Event Report form (Appendix III) 10 calendar days by fax, email, or regular mail.

8.0 ADMINISTRATION OF ARTESUNATE AND FOLLOW-ON TREATMENT

8.1 Artesunate

The investigational product IV artesunate (WR256283) will be provided as a sterile dry-filled powder and will be prepared for administration by reconstitution in the sodium phosphate buffer prior to infusion.

Reconstitution and administration of IV artesunate:

The formulation of artesunate consists of two parts. Part A is a vial filled with base artesunate, the active component; Part B (diluent) is a vial filled with phosphate solution used to dissolve the artesunate in Part A just prior to administration. Specifically, 11 ml of diluent will be withdrawn from the diluent vial (Part B) and injected into the artesunate vial (110 mg of artesunate) (Part A). This mixture will be gently swirled for 5 to 6 minutes (resulting in a concentration of 10 mg/ml) and will be administered within 1 hour. The reconstituted drug will be injected intravenously (through an established intravenous line or needle) pushed over 1-2 minutes through a 0.8 micron hydrophilic polyethersulfone filter.

Schedule and dosage of IV artesunate:

Intravenous artesunate will be administered at the dosage of 2.4 mg/kg at 0 hour, 12 hour, 24 hour, and 48 hour for a total of 4 doses (the same dosage as used in the SEAQUAMAT trial). The dosage may be modified later, to a simpler daily administration for 3 days, depending on the findings of current dose-finding trials by WRAIR in Thailand and Kenya (cf. cross reference with IND 64,760).

8.2 Follow-on treatment

Please note that the follow-on treatment is not part of this program and will not be provided by CDC.

In parts of the world where IV artesunate is used, it is typically followed by an oral medication once the patient is able to tolerate medications by mouth. Although artesunate is a life-saving drug, because of its rapid action, it often fails to eliminate all parasites; therefore necessitating adjunct therapy. This is similar to the current standard of care regimens in the United States in which the rapidly acting drug such as quinine and quinidine is always coupled with a follow-on drug such as doxycycline or clindamycin. Treatment with a follow-on, different drug ensures curative treatment through complete elimination of all remaining malaria parasites. Because IV

artesunate has a short half-life (less than 2 hours), potential drug-drug interactions should not be an issue. The treating physicians should make sure to use an appropriate follow-on drug to complete the treatment of malaria. The choice of which follow-on drug to use is at the discretion of the treating physician. The follow-on oral drug should be initiated on the last day of artesunate treatment, at least 4 hours after the IV dose of artesunate. The treating physicians should choose to use one of the drugs recommended by CDC against chloroquine-resistant *P. falciparum* (CDC malaria website, 2006), by order of preference:

8.2.1 Atovaquone-proguanil (AP, Malarone) is the follow-on drug of first choice, and will be given to most patients. Malarone is also the oral follow-on drug used in the current WRAIR trial in Kenya. AP has been used in combination with oral artesunate for treatment of uncomplicated malaria (Gupta 2005).

Malarone, manufactured by GlaxoSmithKline Corporation in oral tablet forms contain the active ingredients atovaquone and proguanil hydrochloride (referred as AP) are available in two strengths, adult (250 mg atovaquone/100 mg proguanil) and pediatric (62.5 mg atovaquone/25 mg proguanil).

Adults will receive AP 1 g/400 mg (four adult tabs) every day for 3 consecutive days.

Children will receive AP doses based upon body weight as indicated below.

5 – 8 kg:	2 peds tabs po every day for 3 consecutive days
9 – 10 kg:	3 peds tabs po every day for 3 consecutive days
11 – 20 kg:	1 adult tab po every day for 3 consecutive days
21 – 30 kg:	2 adult tabs po every day for 3 consecutive days
31 – 40 kg:	3 adult tabs po every day for 3 consecutive days
> 40 kg:	4 adult tabs po every day for 3 consecutive days

Note: AP is not recommended for infants under 5 kg.

8.2.2. Doxycycline (or clindamycin for children under 8 years and pregnant women) will be the follow-on drug for patient who cannot take AP. Adult dosage of doxycycline: 100 mg po bid for 7 days; pediatric dosage (children 8 years or older) 4 mg/kg/day divided bid for 7 days. Children under 8 years of age should receive instead clindamycin 20 mg base/kg/day divided tid for 7 days.

8.2.3 Mefloquine, although a highly efficacious antimalarial, will be the follow-on drug of last choice because of the relatively high rate of adverse drug reactions in persons who receive treatment doses of mefloquine. Adult dosage: initial dose of 750 mg salt po followed by 500 mg salt 6-12 hours after initial dose; pediatric dosage: 15 mg salt/kg po as initial dose, followed by 10 mg salt/kg po given 6-12 hours after initial dose.

8.3 Patients still not tolerating oral medications after 3 days of IV artesunate:

The vast majority of patients will have recovered after 3 days of treatment with IV artesunate. For those patients who still cannot tolerate oral medications, several treatment options are

available, depending on the patient's clinical and parasitological status. The most suitable course of treatment should be selected by the attending clinicians in consultation with CDC. Potential options include:

1. Continue IV artesunate, not to exceed a total course of 7 days
2. Switch to treatment with IV doxycycline (7 days) or IV clindamycin (7 days).

(These regimens are described more in detail on the CDC website http://www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm).

As soon as the patient can tolerate oral medications, switch to an appropriate oral follow-on treatment.

9.0 SUPPORTIVE CARE AND FOLLOW-UP

It is expected that patients will be treated in intensive care units, and that they will receive appropriate supportive treatment required by their clinical status (e.g., fluid administration, transfusions, assisted ventilation, vasopressors, etc.).

A thin blood smear should be prepared and read by an experienced microscopist to determine baseline parasite density, expressed as a percent of red blood cells infected. Blood smears should be repeated every 12 - 24 hours until at least two consecutive blood smears are negative, and also at the end of treatment.

Any Adverse Events (AE) potentially associated with the administration of artesunate will be treated appropriately.

10.0 SAFETY DATA COLLECTION AND REPORTING

The attending physicians will be responsible for the real-time collection and evaluation of safety data. All Adverse Events (AE) recorded during the treatment, whether or not considered to be related to administration of artesunate, will be included in the data analysis. The outcome of all AEs will be documented to the extent possible. Attending physicians and their designees will be instructed on the importance of recording relevant clinical data and documenting medications prescribed for a participant experiencing an AE during the program.

The Principal Investigators (at the CDC Malaria Branch) will be responsible for collecting safety data. All SAEs noted during artesunate administration should be reported within 24 hours by telephone to the Malaria Branch, and via the Adverse Events Report Form (Appendix III) which should be faxed, emailed, or mailed to the Principal Investigators within 10 days.

Definitions of Adverse Events (AEs)

An ADVERSE EVENT (AE) is any untoward medical occurrence associated with the use of a drug/biologic in humans, whether or not considered drug/biologic related.

SUSPECTED ADVERSE REACTION is any adverse event for which there is a reasonable possibility that the drug/biologic caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship

between the drug/biologic and the adverse event. “Suspected adverse reaction” implies a lesser degree of certainty about causality than “adverse reaction.” CDC must report adverse events as “suspected adverse reactions” only if there is evidence to suggest a causal relationship between the drug/biologic and the adverse event, such as:

a) A single occurrence of an event that is uncommon and known to be strongly associated with the drug/biologic.
b) One or more occurrences of an event that is not commonly associated with the drug/biologic, but is otherwise uncommon in patients who received the drug/biologic.
c) Aggregate analysis of specific events observed in this treatment program that indicates those events occur more frequently in the patients treated with the drug/biologic than observed in patients from outbreak investigations or other historical information in which no drug/biologic treatment was given.

An ADVERSE REACTION is any adverse event caused by the drug/biologic.

A SERIOUS ADVERSE EVENT (SAE)/SERIOUS SUSPECTED ADVERSE REACTION is an adverse event or suspected adverse reaction if, in the view of either the treating physician or CDC, it results in any of the following outcomes:

- death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An UNEXPECTED ADVERSE EVENT/UNEXPECTED SUSPECTED ADVERSE REACTION is an adverse event or suspected adverse reaction that is not listed in this protocol or is not listed at the specificity or severity that has been observed.

CDC Reporting Requirements to FDA and CDC IRB

Upon receipt of reported AEs from treating physicians, CDC will review to determine any suspected adverse reactions that are both serious and unexpected. Upon such determination, CDC will report these AEs to FDA within 15 calendar days. Per 21 CFR 312.32, a suspected adverse reaction is determined based on evidence to suggest a causal relationship between artesunate and the AE, such as:

a) A single occurrence of an event that is uncommon and known to be strongly associated with artesunate.
b) One or more occurrences of an event that is not commonly associated with artesunate, but is otherwise uncommon in patients who received artesunate for treatment.

c) Aggregate analysis of specific events observed in this treatment program that indicates those events occur more frequently in the patients treated with artesunate than in a concurrent or historical control group in which no aretesunate treatment was given.

CDC will also report to FDA within 15 calendar days any clinically important increase in the rate of a serious suspected adverse reaction and any findings from clinical studies or animal studies or in vitro testing that suggest a significant risk in humans exposed to artesunate. Unexpected fatal or life-threatening suspected adverse reactions will be reported to FDA as soon as possible and no later than 7 calendar days after CDC's initial receipt of the information. CDC will also report AEs and incidents to CDC IRB according to CDC IRB's policy and procedures.

AE Follow-Up

All AEs will be followed to resolution to the extent possible. For all individuals who can be followed, outcomes may be classified as recovered, sequellae, death, or lost-to-follow-up. Additional information may be obtained from the treating clinicians, the patient, or the patient's records.

11.0 DATA COLLECTION, HANDLING, AND RECORDKEEPING

As stated in the objectives, the primary purpose of this program is to make intravenous artesunate available for the treatment of severe malaria in the context of quinidine unavailability, failure, intolerance or contraindication. Treating physicians should complete the Demographics and Enrollment forms and submit them to CDC. They can use the additional forms to assist in the management of the patient but they do not have to send these completed forms to CDC unless they need to request additional artesunate doses to extend treatment beyond 3 days or if there has been an SAE. To the extent practicable, safety information will be collected on cases experiencing AEs, and reported to the FDA and CDC IRB as appropriate. Data collection and storage for these cases will be handled by the CDC Drug Service through its secure database. All data from AE cases will be included in the evaluation of safety.

12.0 Program Modifications

Any change or modification to the program that affects participants, objectives, program design, procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be agreed upon and approved by the Principle Investigators and the CDC IRB prior to implementation. The informed consent form (ICF) must be revised to concur with any amendment, as appropriate, and must also be reviewed and approved with the amendment. A participant already enrolled in the program will be informed about the revision and asked to sign the revised ICF if the modification directly affects the participant. A copy of the revised, signed (with date) ICF will be given to the participant. All original versions of the ICF will be retained as part of the participant's permanent record and a copy will be retained at CDC.

Administrative changes to the program are corrections and/or clarifications that have no effect on the way the program is to be conducted. These administrative changes will be agreed upon by the Principle Investigators and will be documented. The CDC IRB will be notified in writing of administrative changes prior to implementation.

13.0 PROGRAM RESPONSIBILITIES

13.1 Principal Investigators

The Principal Investigators will coordinate activities and implementation of the protocol with the Malaria Branch staff and the CDC Drug Service. The Principal Investigators will coordinate the dissemination of information about this new service to health departments and medical practitioners.

13.2 CDC Malaria Branch Medical Officers/Epidemiologists

CDC Malaria Branch Medical Officers/Epidemiologists will respond to clinical calls and will evaluate all severe malaria cases to determine eligibility and, if necessary, initiate the protocol. The Malaria Branch Medical Officers/Epidemiologists will be responsible for initiating drug delivery and conducting follow-up phone calls.

13.3 Clinicians in Healthcare Facilities

Clinicians will be responsible for determining whether the patient fulfills criteria for administration of artesunate; contacting CDC; administering the drugs as described in the protocol that was provided to them by CDC; and reporting to CDC any AEs recorded during the program—whether or not considered to be related to the administration of artesunate.

14.0 ETHICAL, Legal, and Administrative Requirements

14.1 Current Good Clinical Practice (cGCP)

The procedures set forth in this program are designed to ensure that the Sponsor and all program personnel abide by the Code of Federal Regulations (in particular, 21 CFR, Parts 56, 312, 314, and 600) and ICH Guidelines for GCP. The site investigator for each hospital confirms this by signing the Form FDA 1572 (Investigator's Agreement Form).

14.2 Informed Consent

Written informed consent, in compliance with 21 CFR 50, will be obtained before any program-related procedures are initiated. Informed consent will be obtained from each participant or the participant's legal guardian. Informed consent includes the principle that it is critical that the individual be informed about the potential risks and benefits of participating in this program. This information will allow individuals to make a personal risk-versus-benefit decision and understand the following general principles:

1. Participation in this program is entirely voluntary.
2. Participants may withdraw from participation in this program at any time without penalty or loss of benefits to which they are otherwise entitled.
3. Refusal to participate in this program involves no penalty.
4. The individual is free to ask any questions that will allow him/her to understand the nature of this program.

   If a patient is unable to respond and make wishes known about artesunate treatment, and no next-of-kin or legal representative is available, and the patient's illness is life-

threatening, per 21 CFR 50.23 “Exception from General Requirements”, informed consent may be deemed not feasible and the treating physician can make the determination to administer artesunate. Per 21 CFR 50.23, the patient’s treating physician, acting as site investigator, and a physician who is not otherwise participating in this expanded access IND treatment program, will document the following on the consent form and will return a copy of the consent form to CDC. CDC will also report to CDC IRB as required and according to CDC IRB’s policy and procedures.

1. Patient is confronted by a life-threatening situation necessitating the use of artesunate.
2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from, the patient.
3. Time is not sufficient to obtain consent from the patient’s legal representative.
4. There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient.

If immediate use of artesunate is, in the treating physician’s opinion, required to preserve the life of the patient, and time is not sufficient to obtain the independent determination required above in advance of administering artesunate to the patient, the determinations of the treating physician shall be made and, within 2 working days after the use artesunate, be reviewed and evaluated in writing by a physician who is not participating in this treatment protocol.

The consent forms will:

1. Be updated as needed.
2. Be written in language understandable to the participant— readability score 7.6 (Flesch Kincaid). No written translated consent form will be used; however, verbal translation may be used, if necessary.
3. Not include exculpatory language.
4. Be documented in accordance with 21 CFR 50.27.

Before being enrolled in this program, all individuals will sign and date an informed consent form (ICF) prior to undergoing any program-related procedure. The ICF must be dated, witnessed, and retained by the investigator as part of the program records at the medical facility administering the product. Should the program be modified, the ICF may be revised to reflect the changes in the program. Each participant will receive a copy of the signed ICF and any revised ICF. If the signed form is lost, the participant will be required to sign and date a new ICF before receiving subsequent treatment. Because artesunate will be used for a potentially life- threatening illness, the ultimate responsibility for decision making for this product for all minors should be the parent or guardian. Waiver of assent for older children (7-17 years of age) will be requested from the CDC IRB. Parental permission will be sought in accordance 21 CFR 50.55.

14.3 Risks

The risks to the patients include:

1. Accidental disclosure of private identifiable information
2. Risks inherent to the procedures needed for the diagnosis and treatment of severe malaria
3. Risks of AEs and SAEs.

To minimize the risks of disclosure of private information, the patients' records and identifiable databases will be kept under conditions of confidentiality routinely followed in hospitals. At CDC, the participants' records will be kept in locked, secure storage areas at the Drug Service and at the Malaria Branch. To minimize the risks inherent to diagnostic and treatment procedures and the risks of AE and SAEs, all medical personnel and CDC investigators will exercise due care in the management of the patients. These risks are justifiable in relation to the anticipated benefits to the patient, namely treatment of a potentially fatal disease with an effective, rapidly-acting antimalarial drug.

14.4 Inclusion of children

This protocol is greater than minimal risk, but presents the prospect of direct benefit to patients. The risk of adverse drug reaction is far outweighed by the benefit of being treated for severe malaria, a potentially fatal disease. The relation of the anticipated benefit to the risk is more favorable than that of other available treatments, as one of the eligibility criteria for this treatment is that other available treatments are not clinically appropriate.

In accordance with 21 CFR 50.55, permission will be sought from a parent or guardian. Minors who are legally able to give consent under local laws will not be considered children.

14.5 Privacy and Confidentiality

Participant identification number and date of birth will identify participants in a secure CDC database. Participants will be advised that they could be contacted by telephone or by mail at later dates for follow-up through their treating physician. This follow-up includes safety surveillance.

Representatives of the Sponsor, drug manufacturer, and the FDA are eligible to photocopy and review medical and program records related to this program as a part of their responsibility to protect human participants in this program.

No personal data will be used in any external communication or publication.

15.0 FINANCING AND INSURANCE

The CDC is funding this clinical program. Should a participant be injured as a direct result of participating in this program, he/she will receive medical care for that injury. Should a participant require medical treatment, the costs for hospital and medical care will not be covered by the CDC and will need to be paid by the participant, the participant's insurer, Medicare, or Medicaid. The participant should understand that this does not constitute a waiver or release of

legal rights. The investigators or designees will discuss this issue with the participant or legally authorized representative at the clinical site.

16.0 PUBLICATION POLICY

All data collected during the course of this program may be published in the open medical literature with the identity of the participants protected.

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APPENDICES

Artesunate Compassionate Use Participant ID: ☐☐☐☐☐

Study Inclusion

Date Informed Consent form signed *(dd/mon/yyyy)*: __ __/__ __ __/__ __ __ __

Determining eligibility:

A patient is eligible to receive IV artesunate treatment if at least one criterion is satisfied in EACH of sections A, B, and C.

Section A: (Malaria diagnosis). One of the following criteria must be satisfied:

☐ Malaria confirmed by microscopy

☐ Strong clinical suspicion of severe malaria, but timely microscopic confirmation is not possible, and parenteral treatment with antimalarial drug is urgently needed.

Section B: (Need for IV treatment). At least one of the following criteria must be satisfied (Check all that apply):

☐ Unable to take oral medication
☐ Parasitemia > 5% (parasitemia:_____)
☐ Impaired consciousness
☐ Seizures
☐ Circulatory collapse/shock
☐ Pulmonary edema or acute respiratory distress syndrome
☐ Acidosis
☐ Acute renal failure (creatinine: _____)
☐ Abnormal bleeding or disseminated intravascular coagulation (DIC)
☐ Jaundice (bilirubin: _____)
☐ Severe anemia with hemoglobin under 7 gm/dL (hemoglobin: _____)

Section C: (IV artesunate desirable). At least one of the following criteria must be satisfied (check all that apply):

☐ IV artesunate would be obtainable more quickly than quinidine; if both drugs are equally available, the attending clinicians should decide which drug to use*, in consultation with CDC (nearest available known sources of IV quinidine: _____ and IV artesunate:_____)

☐ Quinidine treatment failure: Parasitemia at 48 hours after initiation of intravenous quinidine is more than 10% of baseline parasitemia

Baseline parasitemia (% RBC infected) _____ Date/time_____
Parasitemia at 48 h (or later)_____Date/time_____

Participant ID: ☐☐☐☐☐

☐ Quinidine intolerance (circle all that apply)
   a. QRS interval is widened by ≥ 50% (baseline_____; current_____)
   b. QT interval exceeds 0.60 seconds
   c. QTc interval is prolonged by >25% of the baseline value (baseline_____; current_____)
   d. Persistent hypotension unresponsive to fluid resuscitation

☐ Contraindications to quinidine (circle all that apply):
   a. Known allergy or hypersensitivity to quinidine or cinchona alkaloids (quinine) (describe reaction_____)
   b. Thrombocytopenic purpura with previous quinidine therapy
   c. AV junctional or idioventricular pacemaker with no atrial activity or complete AV block
   d. Left bundle-branch heart block or other severe intraventricular conduction defects (describe_____)
   e. Cardiac glycoside-induced AV conduction disorders (digitalis toxicity) (digoxin level_____)
   f. Myasthenia gravis

DOES THE PATIENT MEET ELIGIBILITY CRITERIA? ☐ YES ☐NO
(At least one criterion in each of the sections A, B, and C)

**: Precautions concerning artesunate:*

-Patients with known allergy to artesunate or other artemisinin derivatives should not receive artesunate

- For pregnant women, especially women in the first trimester of pregnancy: the lack of data regarding potential artesunate teratogenicity must be weighed against the risks of severe malaria in the context of quinine unavailability or unsuitability. Ultimately, malaria is life-threatening for both the pregnant woman and the fetus, and artesunate should not be withheld if quinidine is unavailable or unsuitable.

Date of enrollment *(dd/mon/yyyy)*: __ __/__ __ __/__ __ __ __

Artesunate Compassionate Use Participant ID: ☐☐☐☐☐

Demographics

1. Today's date: _____
2. CDC Epidemiologist: _____
3. Station delivering artesunate _____
4. Patient Participant's Name: _____
5. Patient's Medical Record Number: _____
6. Patient's Date of Birth_____
7. Patient's Gender: ☐ Male ☐ Female
8. Is Patient of Hispanic or Latino ethnicity? ☐ Yes ☐ No
9. Check the *primary* race of the patient. If patient considers him/herself of more than one race, check 'Other' and specify the races:

☐ White	☐ Asian
☐ Black or African American	☐ Native Hawaiian or Other Pacific Islander
☐ American Indian or Alaska Native	☐ Other, specify races: _____

10. Is the patient pregnant: ☐Yes ☐ No ☐ N/A

    If yes, how many weeks? _____

11. Parasite species: ☐Pf ☐ Pv ☐Po ☐Pm (Check all species that apply)
    ☐Unknown ☐Smear not performed ☐Smear not read
12. Parasite density : _____%
13. Physician's Name _____
14. Physician's Phone
    i. Office:_____
    ii. Pager: _____
    iii. Cellular: _____
15. Hospital Name_____
16. Hospital Address _____

    _____

    Hospital Phone: _____

Artesunate Compassionate Use (Appendix II) Participant ID: ☐☐☐☐☐

Treatment Plan

☐ Determine patient's dose of artesunate:

Adults and children:

Artesunate 2.4 mg/kg at 0 hour, 12 hours, and 24 hours, and 48 hours

☐ Reconstitute artesunate

The formulation of artesunate consists of two parts. Part A is a vial filled with base artesunate, the active component; Part B (diluent) is a vial filled with phosphate solution used to dissolve the artesunate in Part A just prior to administration.
Specifically, 11 ml of diluent will be withdrawn from the diluent vial (Part B) and injected into the artesunate vial (110 mg of artesunate)(Part A). This mixture will be gently swirled for 5 to 6 minutes (resulting in a concentration of 10 mg/ml) and will be administered within 1 hour.

Artesunate for injection

Manufactured by SRI International, Menlo Park, CA, US
Lot #: 090403-A, produced in September 2003

Phosphate Buffer USP (diluent), 0.3 Molar, pH 8.1

Manufactured by SRI International, Menlo Park, CA US
Lot #: 090403-B, produced in September 2003

☐ Administer the reconstituted drug intravenously by injection into an established intravenous line or needle over 1-2 minutes through a 0.8 micron hydrophilic polyethersulfone filter.

☐ Watch patient for 30 minutes. Observe any development of allergic symptoms such as itching, redness, swelling, shortness of breath, chest pain, or watery eyes.

If patient develops any allergic reaction manage symptoms accordingly and discontinue treatment.

☐ If the patient experiences any Serious Adverse Events (SAEs), report them to CDC within 24 hours by telephone.

☐ Complete the Serious Adverse Events Report Form. If the patient experiences any Serious Adverse Events regardless of potential relationship to artesunate, it must be reported within 10 days of the SAE.

Follow-on Oral Treatment

The follow-on oral drug will be initiated on the last day of artesunate treatment, at least 4 hours after the IV dose of artesunate. Use ONE of the following, by decreasing order of preference:

Participant ID: ☐☐☐☐☐

☐**1. Atovaquone-proguanil (Malarone)** (first choice)

Adults: Tabs of 250/100 mg: four tabs po daily for 3 consecutive days
Children: Tabs of 62.5/25 mg (peds tabs) or 250/100 mg (adult tabs) po at the following weight-based doses:

5 – 8 kg:	2 peds tabs po daily for 3 consecutive days
9 – 10 kg:	3 peds tabs po daily for 3 consecutive days
11 – 20 kg:	1 adult tab po daily for 3 consecutive days
21 – 30 kg:	2 adult tabs po daily for 3 consecutive days
31 – 40 kg:	3 adult tabs po daily for 3 consecutive days
> 40 kg:	4 adult tabs po daily for 3 consecutive days

Note: Atovaquone-proguanil is not recommended for infants under 5 kg.

☐**2. Doxycycline** (or **clindamycin** for children under 8 years and pregnant women) (second choice; for patients who cannot take atovaquone-proguanil)

Adults: 100 mg po bid for 7 days
Children (8 years or older): 4 mg/kg/day divided bid for 7 days

Children under 8 years and pregnant women: instead of doxycycline, administer clindamycin 20 mg base/kg/day divided tid for 7 days

☐**3. Mefloquine** (third choice, for patients who cannot take atovaquone-proguanil, doxycycline, and clindamycin)

Adults: Initial dose of 750 mg salt po followed by 500 mg salt 6-12 hours after initial dose
Children: Initial dose of 15 mg salt/kg po followed by 10 mg salt/kg po given 6-12 hours after initial dose

☐***Patients still not tolerating oral medications after 3 days of IV artesunate:***
If, after 3 days of treatment with IV artesunate, the patient still cannot tolerate oral medications, several treatment options are available, depending on the patient's clinical and parasitological status. The most suitable course of treatment should be selected by the attending clinicians in consultation with CDC. Potential options include:

1. Continue the IV artesunate, not to exceed a total course of 7 days
2. Switch to treatment with IV doxycycline (7 days) or IV clindamycin (7 days).
   (these regimens are described more in detail on the CDC website http://www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm)

As soon as the patient can tolerate oral medications, switch to an appropriate oral follow-on treatment.

Artesunate Compassionate Use Participant ID: ☐☐☐☐☐

Day 0 Artesunate Dosing

1. Dosing date *(dd/mon/yyyy)*: ____/_____/_____

2. Participant's weight: _____kg

3. Dose ordered: _____ mg

4. Dosing start time *(hh:mm)*: ____:____; Dosing stop time *(hh:mm)*: ____:____

5. Did participant receive the entire dose?
   - ☐ Yes
   - ☐ No; Total amount received:_____ ml
     Record the reason the full dose was not received:_____

12 hour dose

Was participant dosed? ☐ Yes *(complete below)* ☐ No; reason not dosed: _____
(section is complete)

1. Dosing date *(dd/mon/yyyy)*: ____/_____/_____

2. Dose ordered: _____ mg

3. Dosing start time *(hh:mm)*: ____:____; Dosing stop time *(hh:mm)*: ____:____

4. Did participant receive the entire dose?
   - ☐ Yes
   - ☐ No; Total amount received: _____ ml
     Record the reason the full dose was not received:_____

24 hour dose

Was participant dosed? ☐ Yes *(complete below)* ☐ No; reason not dosed: _____
(section is complete)

1. Dosing date *(dd/mon/yyyy)*: ____/_____/_____

2. Dose ordered_____ mg

3. Dosing start time *(hh:mm)*: ____:____; Dosing stop time *(hh:mm)*: ____:____

4. Did participant receive the entire dose?
   - ☐ Yes
   - ☐ No; Total amount received:_____ ml
     Record the reason the full dose was not received:_____

Artesunate Compassionate Use Participant ID: ☐☐☐☐☐

48 hour dose

Was participant dosed? ☐ Yes *(complete below)* ☐ No; reason not dosed: _____
(section is complete)

2. Dosing date *(dd/mon/yyyy)*: ____/_____/_____

2. Dose ordered: _____ mg

3. Dosing start time *(hh:mm)*: ____:____; Dosing stop time *(hh:mm)*: ____:____

5. Did subject receive the entire dose?
   ☐ Yes
   ☐ No; Total amount received: _____ ml
   Record the reason the full dose was not received:_____

Artesunate Compassionate Use Participant ID: ☐☐☐☐☐

Follow-on dosing

1. Was the participant dosed sequentially with an oral agent?
☐Yes *(complete below)* ☐No, reason not dosed: ______________________________
(page is complete)
Check medication given *(check one)*: ☐ Malarone ☐ Doxycycline ☐ Mefloquine
Complete dosing information in table below. Cross through, initial and date any rows not needed.

Date of dosing *(dd/mon/yyyy)*	Time of dosing *(hh:mm)*
__ __/__ __ __/__ __ __ __	__ __:__ __
__ __/__ __ __/__ __ __ __	__ __:__ __
__ __/__ __ __/__ __ __ __	__ __:__ __
__ __/__ __ __/__ __ __ __	__ __:__ __
__ __/__ __ __/__ __ __ __	__ __:__ __
__ __/__ __ __/__ __ __ __	__ __:__ __
__ __/__ __ __/__ __ __ __	__ __:__ __
__ __/__ __ __/__ __ __ __	__ __:__ __
__ __/__ __ __/__ __ __ __	__ __:__ __
__ __/__ __ __/__ __ __ __	__ __:__ __

Artesunate Compassionate Use Participant ID: ☐☐☐☐☐

Malaria Microscopy Results

Record all smears for the participant in the tables below. Cross through, initial and date any portion of the page not needed.
If a smear was performed, do not leave any rows of the table blank - Record '0' for those smears where parasites are not present.

Date drawn:____/______/________; Time drawn:____:____
dd mon yyyy *hh mm*

Parasite Species	**% Parasitemia**
P. falciparum	
P. vivax	
P. ovale	
P. malariae	

Date drawn:____/______/________; Time drawn:____:____
dd mon yyyy *hh mm*

Parasite Species	**% Parasitemia**
P. falciparum	
P. vivax	
P. ovale	
P. malariae	

Date drawn:____/______/________; Time drawn:____:____
dd mon yyyy *hh mm*

Parasite Species	**% Parasitemia**
P. falciparum	
P. vivax	
P. ovale	
P. malariae	

Date drawn:____/______/________; Time drawn:____:____
dd mon yyyy *hh mm*

Parasite Species	**% Parasitemia**
P. falciparum	
P. vivax	
P. ovale	
P. malariae	

Artesunate Compassionate Use Participant ID: ☐☐☐☐☐

End of Trial

1 End date* *(dd/mon/yy)*: ____/_____/_____

2 Did subject complete treatment? ☐Yes ☐No *(complete below)*

Check ***one*** primary reason the participant did not complete the treatment:

- ☐ AE/SAE
- ☐ Death
- ☐ Withdrawal of consent *(check one)* ☐ Investigator request ☐ Participant request
- ☐ Lost to follow-up
- ☐ Other; specify reason: _____

*Complete 'End date' as follows:

If participant	**Record date as**
Completed through day XX	Day XX visit date
Discontinued due to AE/SAE	Date it was determined to discontinue due to AE/SAE
Died	Date of death
Withdrawal of consent	Date of withdrawal (either investigator request or subject request)
Lost to follow-up	Date of last contact with subject (telephone call, office visit, etc)
Other	Date of 'Other' event

I have reviewed all CRFs and attest that the data contained in them is accurate and complete.

_____ ____/_____/_____

Clinician's Signature Date Signed *(dd/mon/yyyy)*

Artesunate Compassionate Use (Appendix III) Participant ID: ☐☐☐☐☐

Serious Adverse Event

Record Serious Adverse Events reported/observed for the participant during participation in the trial **OR** Check if None ☐ *(form is complete)*

SAE Criteria *(check 'Yes' or 'No' for each below)*:

Yes	No		Yes	No	
☐	☐	Death	☐	☐	Congenital anomaly/birth defect
☐	☐	Life-threatening adverse event	☐	☐	Prolongation of hospitalization
☐	☐	Required major medical/surgical intervention	☐	☐	Re-hospitalization (complete below)
☐	☐	Persistent or significant disability/incapacitation			Admission date: ___/____/_____ *(dd/mmm/yyyy)*
					Discharge date: ___/____/_____ *(dd/mmm/yyyy)*
					Or check if not yet discharged ☐

			Comments:
SAE Description			
Date and Time of Onset			
Date and Time of Resolution			
Severity		☐ Mild ☐ Moderate ☐ Severe	
Relationship to:	Artesunate	☐ Not Related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	
	Follow-on drug	☐ Not Related ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	
Action taken with artesunate due to SAE		☐ None ☐ Dosing changed ☐ Artesunate permanently discontinued	
Did SAE require treatment?		☐ Yes ☐ No	
Outcome		☐ Recovered ☐ Ongoing ☐ Resolved with residual effects ☐ Death	

If SAEs occur (events that are life threatening or result in death, prolongation of hospitalization, incapacity or disability, or birth defect): Notify CDC within 24 hours by telephone. Call the CDC Malaria Hotline at 770-488 7788 from 9:00am to 5:00 pm Eastern time; after hours call the CDC Emergency Operations Center at 770-488 7100. Ask to speak with the malaria clinician on call.

Fill out this form and fax or email it to the CDC Malaria Branch (fax: 404.718.4815; email: parguin@cdc.gov) or mail it to the CDC Malaria Branch (Address: 1600 Clifton Road NE, MS A-06, Atlanta, GA 30333) within 10 calendar days.

Appendix IV

List of CDC Quarantine Stations that stock Artesunate

Artesunate will be stored at the CDC Drug Service at CDC Headquarters in Atlanta, as well as in CDC Quarantine Stations. Current Quarantine Stations that stock artesunate are listed below, with their jurisdiction for artesunate delivery.

1. CDC Atlanta Quarantine Station
   Hartsfield International Airport
   Ph: (404) 639-1220;
   Jurisdiction: Georgia, Alabama, Mississippi, North Carolina, South Carolina, and Tennessee.

2. CDC Chicago Quarantine Station
   O'Hare International Airport
   Ph: (773) 894-2960;
   Jurisdiction: Illinois, Indiana, Iowa, Nebraska, South Dakota, North Dakota, Minnesota, Michigan, Ohio, Kentucky, and Wisconsin.

3. CDC Honolulu Quarantine Station
   Honolulu International Airport
   Ph: (808) 861-8530;
   Jurisdiction: Hawaii, Guam, and Pacific Trust Territories.

4. CDC Houston Quarantine Station
   George Bush Intercontinental Airport (IAH)
   Ph: (281) 230-3874
   Jurisdiction: Texas, New Mexico, Kansas, Missouri, Arkansas, Louisiana, and Oklahoma.

5. CDC Los Angeles Quarantine Station
   Tom Bradley International Airport
   Ph: (310) 215-2365;
   Jurisdiction: Southern California (Los Angeles, Orange, San Bernardino, Riverside, Ventura, Santa Barbara, and San Luis Obispo counties), Colorado, and Arizona.

6. CDC Miami Quarantine Station
   Miami International Airport
   Ph: (305) 526-2910;
   Jurisdiction: Florida, Puerto Rico and the Virgin Islands.

7. CDC New York Quarantine Station
   JFK International Airport
   Ph: (718) 553-1685;

Jurisdiction: New York, Maine, New Hampshire, Massachusetts, Rhode Island, Connecticut, Pennsylvania, New Jersey, Delaware, Maryland, Virginia, West Virginia, Vermont, and the District of Columbia.

8. CDC San Francisco Quarantine Station
San Francisco International Airport
Ph: (650) 876-2872;
Jurisdiction: Central and Northern California (46 counties), Nevada, Utah, and Wyoming.

9. CDC Seattle Quarantine Station
Seattle-Tacoma International Airport
Ph: (206) 553-4519;
Jurisdiction: Washington, Idaho, Montana, Oregon, and Alaska.

Appendix V

PARTICIPANT CONSENT / PARENTAL PERMISSION FORM

Flesch-Kincaid 7.6 (without title and signature block)

You or your child are being asked to take part in this treatment program because you or your child have severe malaria. Severe malaria is the most serious form of malaria, which one gets through the bite of an infected mosquito. Usually, this type of bite happens while traveling in a part of the world that has the malaria parasite. Severe malaria can lead to many problems including coma, kidney and lung trouble, anemia (low red blood cells), and death.

This treatment program is sponsored by the Centers for Disease Control and Prevention (CDC). This program will use the drug artesunate to treat your severe malaria. Artesunate is an investigational drug. This means that artesunate has not been approved by the Food and Drug Administration (FDA) to treat malaria in the United States (U.S.). You or your child are being asked to take artesunate because:

- you or your child have severe malaria; and
- you or your child cannot take the drug quinidine; or
- Artesunate is available sooner than quinidine might be

Quinidine is used in the US to treat severe malaria. Just like quinidine, artesunate may help people with severe malaria get well sooner. Intravenous (IV) (by vein) artesunate has been used in many other parts of the world to treat severe malaria. Before deciding whether to take part, we want you or your child to know about the program.

This is a consent form. It gives information about this program. The program staff will talk with you or your child about this information. You or your child are free to ask questions at any time. Taking part in this program is voluntary. You or your child may leave this program at any time. If you or your child decide not to take part in or to stop this program, it will not affect the medical care you or your child would normally get. If you or your child agree to take part in this program, you will be asked to sign this consent form. You will get a copy to keep.

WHAT WILL HAPPEN TO ME?
We will take blood for tests to count the number of parasites (germs) in your or your child's blood at the start of treatment and then every 12 hours.

We will ask you or your child about drugs you or your child are taking, any allergies, and your or your child's health.

We will give you or your child artesunate by vein. Then we will watch you or your child for about 30 minutes to make sure that you or your child don't have an allergic reaction to artesunate. If any allergic reactions or other side effects are seen, you or your child will be

treated. Costs for hospital and medical care will not be covered by the CDC and will need to be paid by you, your insurer, Medicare, or Medicaid.

We will give you or your child doses of artesunate by vein every day for 3 days. Then we will switch you or your child to another medicine that you or your child can take by mouth.

If we cannot make the switch from medicine by vein to medicine by mouth because you or your child cannot take medicines by mouth, we will continue giving you or your child medicines by vein as needed; but you or your child will not receive artesunate for more than 7 days.

HOW MANY PEOPLE WILL TAKE PART IN THIS TREATMENT PROGRAM?
We do not know how many people will need artesunate to treat severe malaria.

ARE THERE BENEFITS?
By taking artesunate, you or your child may be cured of severe malaria.

ARE THERE RISKS?
Most people do not have serious problems when they take artesunate. There are rare reports of people developing anemia (low red blood cells) up to one month after they take artesunate. There is a chance that you or your child will have side effects, including an allergic reaction. When we draw blood for tests, or when we inject drugs by vein, there is a chance that this may cause pain, bleeding, or bruises where the needle enters the skin. In rare cases, needle sticks may cause fainting or infection.

WHAT ARE THE OTHER CHOICES BESIDES THIS PROGRAM?
Quinidine is an FDA-approved drug for treating severe malaria. However, if quinidine is not available, or if your or your child's doctor feels that you or your child cannot take quinidine, there are no other FDA-approved IV drugs available for severe malaria.

WHAT IF I AM PREGNANT?
We do not know enough about artesunate to be sure that it will not cause harm to pregnant women and their babies. However, one recent study that included 183 pregnant women with malaria found that artesunate did not seem to cause miscarriages or congenital malformations. Also, malaria in itself can be harmful to the pregnant woman and her baby. You and your doctor will have to weigh the risks and benefits of taking artesunate, for you and your baby, if you are pregnant.

WHAT ABOUT PRIVACY?
We will keep all information about you or your child as private as the law allows. People who work at CDC and FDA may look at your medical records. Your or your child's name and personal information will not be used or listed in reports or articles in magazines or journals. However, FDA rules say that CDC has to follow certain laws and rules to give this drug to you or your child. Your or your child's doctor has to give CDC a report about your or your child's response to treatment with artesunate. This is necessary because CDC has to report to FDA about the safety of artesunate. If more details about your or your child's treatment course are needed, your or your child's doctor might have to give CDC a copy of your or your child's medical records. Your or your child's doctor may contact you in the future to obtain follow up

information that could be shared with CDC. FDA and the company that makes artesunate are allowed to look at CDC's files about participants treated with this drug. Also, CDC is allowed to give your or your child's name to public health or medical people who, for example, need to find out how you or your child got the infection and how to prevent other cases.

VOLUNTARY PARTICIPATION

It is your choice to take artesunate or for your child to be treated under this protocol.

- You may refuse or stop treatment at any time.
- You or your child will not lose any rights to get other health care by being in this program or by not being in this program.

WHAT IS THE COST OF THIS DRUG?

The drug will be given to you or your child free of charge. The other costs of the hospital and medical care are not covered by the CDC and will need to be paid by you, your or your child's insurer, Medicare, or Medicaid.

WHAT HAPPENS IF I AM HARMED?

If you are hurt from being in this program, treatment will be given by the medical staff at your or your child's hospital. CDC does not normally pay for harm done to you or your child as a result of being in a treatment program. Thus, you, your or your child's insurer, Medicare, or Medicaid will have to pay for any care that is needed. However, by signing this consent form and agreeing to be in this program, you or your child are not giving up any of your or your child's rights.

WHO CAN I CALL IF I HAVE PROBLEMS OR QUESTIONS?

If you have any questions about this program, you may talk with your doctor**,** Dr. _____ at the following phone number _____ or with Drs. Paul Arguin (at 404.718.4703) or S. Patrick Kachur (at 404.718.4764). You may talk with the available CDC malaria doctor at either 770-488-7788 or 770-488-7100. If you feel that you or your child have been harmed please contact Drs. Paul Arguin (at 404.718.4703) or S. Patrick Kachur (at 404.718.4764). If you have questions about your or your child's rights as a participant in this program, please contact CDC's Human Research Protection Office at (800)584-8814.Please leave a message that includes your name and telephone number, and refer to CDC protocol # 5032.

CONSENT STATEMENT

I have read the form or it has been read to me. I have been given a chance to ask questions and my questions have been answered. I agree to get or for my child to get intravenous artesunate to help treat severe malaria.

Print Participant/Parent Name:_____

Participant/Parent Signature: _____ Date:_____

Legally Authorized Representative Signature: _____ Date: _____

Witness Signature:_____Date:_____

(If applicable) I have translated this form into the _____ language.

Translator's Signature:_____ Date:_____

NOTE: If participant is unable to sign, next of kin or legal guardian may sign.
NOTE: The participant will be offered a copy of the consent form.

If participant gives verbal consent, but is unable to sign and next of kin or legal guardian is not available, the patient should give his/her mark (either an "X" or a thumbprint), and the consenting physician should complete the following:

I, (Print Physician's Name)_____ certify that the above named participant has read this document or had it read to them, is unable to sign the document, and has verbally consented to participate. I further certify that a next of kin or a legal guardian who could sign for the participant is not readily available.

Physician's Signature:_____ Date:_____

IF OBTAINING INFORMED CONSENT IS NOT FEASIBLE:
In the event that obtaining informed consent is not feasible because the patient is unable to respond and make wishes known about artesunate treatment and no legal guardian or next-of-kin is present the following provides for the treating physician to make a clinical determination to treat with artesunate provided that the treating physician and an independent physician certifies to the following within 2 working days of treating the patient with artesunate:

1. Patient is confronted by a life-threatening situation necessitating the use of artesunate
2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from, the patient.
3. Time is not sufficient to obtain consent from the patient's legal representative.
4. There is no available alternative method of approved or generally recognized

therapy that provides an equal or greater likelihood of saving the life of the patient.

□ Document as such in the patient's medical record and ensure the patient or patient's legally authorized representative is made aware that investigational artesunate was administered.

□ Name & signature of treating physician who made the determination to administer artesunate to patient when informed consent could not be obtained:

_____ _____ ____

Name Signature Date

□ Name & signature of second physician, who is not otherwise participating in this treatment protocol, reviewing and evaluating decision to administer artesunate to patient:

_____ _____ ____

Name Signature Date

□ Return copy of this signed page to CDC