Whittington Health NHS

Malaria in Children:
Investigation and Treatment

Subject:	Malaria in children
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Policy Executive Owner:	Dr Ben Killingley, Dr Trupti Patel
Name and Designation of Author:	Dr Ben Killingley, Acute Medicine Consultant Dr Trupti Patel, Microbiology Registrar Dr Joseph Raine, Paediatric Consultant
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Version Control Sheet

Version	Date	Author	Status	Comment
1.0	April 2012	Dr R Jennings, Dr J Raine, Dr A Smith	In-active	New guideline
2.0	Nov 2015	Dr Ben Killingley, Dr Trupti Patel, Dr Joseph Raine	Active	• Intravenous artesunate replaces intravenous quinine as first line treatment of severe malaria and uncomplicated falciparum malaria if not able to tolerate oral therapy • Intravenous artesunate replaces intravenous quinine in the treatment of severe malaria from SE Asia in all stages of pregnancy • Artemether-lumefantrine replaces quinine and doxycycline or clindamycin as first line treatment of uncomplicated falciparum malaria • Artemether-lumefantrine replaces chloroquine for the treatment of *Plasmodium vivax* malaria from regions of known chloroquine resistance • Advice can be sought from Dr Ben Killingley and Dr Richard Jennings, Consultants in Acute Medicine and Infectious Diseases, at the Whittington Hospital

➢ Criteria for use

This guideline applies to all children (i.e. under 17 years old) known to have malaria or suspected of having malaria.

➢ Background/ introduction

In the UK from 2005 to 2010, there were approximately 1600 cases of imported malaria each year, of which 10-15% of cases were in children [1]. Most cases (~80%) were caused by *Plasmodium falciparum*; the remainder were caused by *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* [1,2]. *P. knowlesi* has increasingly been shown to cause infection in children but remains rare and sporadic [3].

Cases of mixed infection occur, in which *Plasmodium falciparum* is usually one of the two species present. *Plasmodium falciparum* may cause the rapid onset of severe disease, organ failure and death. *Plasmodium falciparum* causes around ten deaths a year in the UK [4]. A disproportionate number of malaria cases occur in London, among whom patients of Nigerian or Ghanaian origin are prominently represented.

Children are over-represented in imported malaria cases in the UK, probably because completely susceptible children accompany their parents on visits to malaria-endemic countries. Malaria in children may present with misleading symptoms such as gastrointestinal upset, sore throat or lower respiratory symptoms.

Any feverish or very sick child who has been to a malaria-endemic country must be investigated for possible malaria.

Malaria has no specific symptoms or signs, and the diagnosis is not proven through inadvertent discovery on routine blood tests; it can only be demonstrated through a specific blood examination, deliberately requested. A high degree of clinical awareness and vigilance is therefore essential both to make the diagnosis, and to identify cases that are clinically severe or likely to become so.

Over the past decade, the choice of therapy for both severe and uncomplicated malaria has changed considerably with the introduction of artemisinin derivatives (see Appendix 1 for drug information). Two large well-designed studies, the SEAQUAMAT (2005) and subsequent AQUAMAT (2010) trials have demonstrated a clear survival advantage of using intravenous artesunate over quinine for severe falciparum malaria in both adult and paediatric populations respectively [5,6]. The AQUAMAT trial of African children also demonstrated a significant reduction in clinical complications (development of coma, convulsions and deterioration of coma score).

WHO guidelines (2015) now recommend that intravenous artesunate be used preferentially over quinine as the drug of choice in children (and adults) **with severe falciparum malaria** [7].

Although there are no studies directly comparing the efficacy of intravenous artesunate to quinine for severe malaria caused by non-falciparum species, artemisinins have demonstrated higher activity against *P. vivax* than *P. falciparum*, and faster parasitic clearance times against *P. vivax* than chloroquine or quinine [8]. In addition, artesunate has been used successfully to treat multiple cases of severe *P. vivax* and *P. knowlesi* in children

[9]. For these reasons, **parenteral artesunate is now recommended as the first-line treatment of all cases of severe malaria regardless of causative species** [7].

In the Whittington Hospital, all cases of malaria must be managed with the involvement of the Whittington microbiology department and/or Dr Ben Killingley or Dr Richard Jennings (Consultant Infectious Diseases Physicians). Cases of severe malaria must always be managed in conjunction with a tertiary Paediatric infectious diseases (ID) unit such as Great Ormond Street Hospital (GOSH) or St Mary's Hospital.

➢ Inclusion/ exclusion criteria

Inclusion criteria: All children known to have malaria or suspected of having malaria.

Exclusion criteria: None.

➢ Clinical management

1) Who to test for malaria (see Appendix 2)

Malaria should be suspected and tested for if:

- The child has been to a malaria-endemic region in the past twelve months **AND** has **ANY** of the following:
- Fever
- Reported symptoms of fever
- A systemic illness not otherwise explained

Most, but not all, falciparum malaria will present within one month of returning from an endemic area. Symptoms and signs are often very non-specific. Gastrointestinal symptoms are common. Hepatosplenomegaly and jaundice are often absent. **Fever is often absent at first assessment and may be absent at any stage of disease.**

2) How to test for malaria

Venous blood in an EDTA (full blood count) tube must be sent to haematology IMMEDIATELY after the suspicion of malaria is raised. The timing of the blood sample does not have to coincide with a fever. The patient's travel history (countries and dates) should be stated on the form. This first malaria test request (first sample) must be marked URGENT. All such first samples will be processed by haematology urgently, regardless of the time of day. The haematology laboratory will do a thick and thin blood film and antigen test. If the film shows *Plasmodium falciparum* ring forms (the pathogenic blood stage) then a percentage parasitaemia will always be reported urgently. Percentage parasitaemias will not be given for non-falciparum positive films, as this information does not influence treatment.

Further investigations required may include blood gas, lactate, liver function, bone biochemistry, urea and electrolytes, coagulation screen, blood culture and clean-catch urine dipstick + MC&S. Unwell children may also need chest X-ray and LP depending on symptoms.

Patients whose initial malaria test is positive should be treated IMMEDIATELY (see below).

Patients whose initial malaria test is negative, and who continue to have fever, should have a daily malaria test until three tests have been negative on three successive days. If the fever resolves, or an alternative diagnosis is made, further testing may not be required. Empirical treatment for malaria despite a negative malaria test should NOT be given without specialist advice.

Patients whose initial malaria test shows a negative blood film but a positive antigen test should be discussed with the Whittington Microbiology Department and/or Dr Ben Killingley / Dr Richard Jennings. If these people are not available then discuss with the registrar in paediatric infectious diseases at St Mary's or Great Ormond Street Hospital.

Any malaria chemoprophylaxis should be stopped while a patient is being investigated in hospital for malaria, and should normally be resumed once malaria has been excluded.

3) How to recognise severe malaria

Severe malaria can cause rapid-onset organ failure and death. This is almost always due to *Plasmodium falciparum* infection, although may rarely be due to other plasmodia species eg *P. vivax*. Even patients who might be expected to have a degree of natural immunity are at risk of severe deterioration. A case of malaria must be regarded as severe if any of the following are present:

- Percentage *P. falciparum* parasitaemia greater than 2%
- Any compromise of conscious level
- Prostration
- Multiple convulsions – more than two episodes in 24 h
- Respiratory distress or hypoxia
- Shock: in children, assess for shock/potential circulatory failure using heart rate, capillary refill time, blood pressure (expected systolic BP ≈ 80 + (2 x age in years)), and end-organ perfusion (including oliguria- see below) [10]
- Clinical jaundice plus evidence of other vital organ dysfunction
- Pulmonary oedema (radiological)
- Metabolic acidosis (pH < 7.3 or plasma bicarbonate < 15mmol/l)
- Hyperlactaemia (lactate > 5mmol/l)
- Hypoglycaemia (blood glucose < 2.2mmol/L)
- Severe normocytic anaemia (haemoglobin < 7.0g/dl)
- Abnormal spontaneous bleeding or laboratory evidence of disseminated intravascular coagulation (DIC)
- Haemoglobinuria
- Renal impairment: oliguria (<1ml/kg/hour in children, <2ml/kg/hour in infants, or a history of oliguria/anuria) or significantly elevated creatinine (unusual in children)

Cerebral malaria, hypoglycaemia, severe anaemia and respiratory distress/acidosis are the commonest manifestations of severe malaria in children. Cerebral malaria is a diffuse disturbance of CNS function, characterised by altered consciousness, commonly accompanied by convulsions.

Remember that children with severe malaria may be afebrile.

Percentage parasitaemia is only loosely correlated with the severity of illness in falciparum malaria. The illness may be life-threatening at parasitaemias of <2%, or may be without clinical complications at parasitaemias >2%.

It is important to consider other causes of an acute febrile illness (including bacterial sepsis and other common causes of fever, in addition to tropical illnesses such as typhoid, hepatitis and tuberculosis) as differential diagnoses, depending on symptoms and signs, and to investigate for these whilst instigating appropriate initial treatment for malaria. Children from areas where malaria is endemic may have malarial parasites detectable in their blood (parasitaemia) without having clinical malaria, and these parasites may be detected during a concurrent illness.

4) Treatment of severe malaria – any (or mixed) *Plasmodium* species: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi* (see Appendix 3)

Treatment must begin IMMEDIATELY once the diagnosis is made; diligent attention to "door-to-needle" time may be life-saving.
In addition, once the diagnosis of severe malaria is made, the following people must be notified immediately:

- The paediatric registrar and consultant on-call for the Whittington

Once the patient has been stabilised and their treatment started, consider contacting:

- The PICU retrieval team (if necessary)
- The on call registrar or consultant in paediatric infectious diseases at GOSH or St Mary's
- The Whittington Infectious Diseases consultants (Drs Ben Killingley or Richard Jennings) or Microbiology consultant, during normal working hours Monday – Friday

1st line treatment

Children weighing less than 20kg:
Initial treatment is with **intravenous (IV) artesunate 3mg/kg given as a bolus at 0, 12 and 24 hours, then once daily until oral therapy is tolerated.**

Children weighing over 20kg:
Initial treatment is with **intravenous (IV) artesunate 2.4mg/kg given as a bolus at 0, 12 and 24 hours, then once daily until oral therapy is tolerated.**

Artesunate has few side effects and there is no need to adjust for renal impairment or to monitor for cardiac toxicity. It does not promote hypoglycaemia. See Appendix 1 for safety profile.

When the patient is well enough to tolerate oral therapy, give artemether + lumefantrine (Riamet®) – full course of 6 doses (for simplicity, full course irrespective of the number of IV doses) beginning when the next IV dose is due:

1 tablet = 20mg artemether / 120mg lumefantrine
5-14kg: 1 tablet
15-24 kg: 2 tablets
25-34 kg: 3 tablets
>34 kg: 4 tablets (adult dose)

At 0, 8, 24, 36, 48 and 60 h

Riamet® should be taken with fatty foods or milk. If children are unable to swallow tablets whole, they can be crushed.

NB. There are a number of drugs which interact with Riamet® – see Appendix 1 for list.

2nd line treatment

If artesunate is not available, or there is a delay in obtaining it, the alternative is **IV quinine dihydrochloride 20mg/kg (maximum 1.4 grams) in 5% dextrose or dextrose saline, infused over 4 hours**. This is called the "loading dose". The maximum concentration of the infusion should not exceed 2mg/ml [11]. Treatment using quinine should not be delayed pending arrival of artesunate.

NB This loading dose is not required if the patient has received:

- 3 or more doses of quinine or quinidine in the previous 48 h
- Mefloquine prophylaxis in the previous 24 h
- Mefloquine treatment dose within the previous 3 days

Close monitoring is vital during IV quinine administration, especially the loading dose, as the risk of cardiovascular instability, hypotension and hypoglycaemia rises with faster or higher volume infusions. Appropriate monitoring should include cardiac monitoring, saturation monitoring, plus hourly blood pressure and blood glucose measurements. Send blood for U&E, creatinine and G6PD (quinine is a possible cause of haemolysis in G6PD deficient patients. Treatment is urgent and quinine should be administered prior to the result being known. In patients with known G6PD deficiency quinine should still be given) prior to quinine administration, in addition to checking electrolytes on a blood gas.

The initial loading dose should be followed by further (reduced) doses of intravenous quinine dihydrochloride 10mg/kg (maximum 700mg [11]) in 5% dextrose or dextrose saline, infused over 4 hours, given every 8 hours (so if the loading dose begins at time 0 hours and finishes at time 4 hours, the next dose will begin at time 8 hours). The maximum concentration of the infusion should not exceed 2mg/ml [12].

After 48 hours, the intravenous quinine dose should be reduced to 10mg/kg (maximum 700mg [2]) every 12 hours.

When the patient is well enough to take oral medication, oral quinine sulphate should be substituted (10 mg/kg (maximum 600mg) 3 times a day) to complete a total course of 7 days. This should be given together with a second agent: oral clindamycin 7-13 mg/kg (maximum 450mg), 3 times a day or doxycycline 200 mg daily (if over 12 years old – **doxycycline must NOT be used in children younger than 12 years**) for a total of 7 days (clindamycin and doxycycline are used as additive and synergistic drugs to reduce treatment duration with quinine).

Children with severe malaria must be treated with empirical broad spectrum antibiotic cover e.g. ceftriaxone, until concomitant bacterial sepsis has been excluded. Other adjunctive treatments include mechanical ventilation for a low Glasgow Coma Scale (GCS) or respiratory distress and haemofiltration for severe acidosis. Thrombocytopaenia is common in non-immune children with severe malaria but does not usually require platelet transfusion – discuss with specialist team [2]. Exchange transfusion may be considered for very high parasitaemias, particularly in the context of organ failure, but only after consultation with a malaria specialist.

5) Quinine or chloroquine "allergy"

Genuine allergic (anaphylactic) reactions to quinine are extremely rare. In contrast, itching is a very common reaction to chloroquine, particularly in people of West African origin, and is

often mis-reported by the patient as an “allergy”. Chloroquine itch is readily prevented or treated with antihistamines, and is not a contraindication to the use of chloroquine or quinine. If there is a clear history of a previous severe allergic reaction to quinine or chloroquine, and there is no alternative treatment available, the case must be discussed immediately with a malaria specialist at GOSH or St. Mary’s Hospital.

6) Indications for intravenous malaria treatment

- Severe malaria (see criteria above, Section 3)
- Inability to take oral medication (e.g. through vomiting) – these children will usually not require a loading dose of IV quinine, but discuss if unsure

7) Treatment of uncomplicated falciparum malaria (see Appendix 4)

1st line treatment
Oral artemether + lumefantrine (Riamet®):

1 tablet = 20mg artemether / 120mg lumefantrine
5-14kg: 1 tablet
15-24 kg: 2 tablets
25-34 kg: 3 tablets
>34 kg: 4 tablets (adult dose)

At 0, 8, 24, 36, 48 and 60 h

Riamet® should be taken with fatty foods or milk. If children are unable to swallow tablets whole, they can be crushed.
NB. There are a number of drugs which interact with Riamet® – see Appendix 1 for list.

Alternative treatments:

Oral quinine sulphate 10 mg/kg (maximum 600mg) 8 hourly for 7 days.

This treatment course of **quinine should be given together with, or followed by, a second anti-malarial drug**, which may be clindamycin or doxycycline as below:

- Oral clindamycin 7-13 mg/kg (maximum 450mg) 3 times daily for 7 days

OR

- Oral doxycycline 200 mg daily for 7 days (if over 12 years old – **doxycycline must NOT be used in children younger than 12 years**).

8) Treatment of uncomplicated non-falciparum malaria (see Appendix 4)

Acute treatment for non-severe *Plasmodium vivax* (except from chloroquine-resistant region), *ovale*, *malariae* or *knowlesi*:

- Chloroquine 10 mg/kg of base (maximum 620mg [2]) single dose orally at 0 h, then
- Chloroquine 5mg/kg of base (maximum 310mg [2]) single dose orally at 6, 24, and 48 h
- Total dose 25 mg base/kg (doses are expressed as mg of base)

Children who are vomiting or who cannot take oral medication must be treated with IV quinine.

If chloroquine-resistant *P. vivax* suspected (as of 2015: Indonesia, Timor-Leste, and the Pacific Island Nations but now increasingly reported throughout Southeast Asia, parts of Africa and South America; for full list of countries where chloroquine resistance has been reported, see http://www.who.int/malaria/areas/drug_resistance/drug_efficacy_database/en/) give:

- Artemether + lumefantrine (Riamet®) as above for uncomplicated *P. falciparum*

Following the above treatment, prevention of relapse due to liver hypnozoites is required if species of *Plasmodium* is *P. vivax*, *P. ovale* or unknown (NB seek specialist advice for children under 6 months of age) with:

- *P. vivax* or species unknown – Primaquine 0.5 mg/kg (maximum 30mg) orally once daily for 14 days
- *P. ovale* – Primaquine 0.25 mg/kg (maximum 15mg) orally once daily for 14 days

P. malariae and *knowlesi* do not require prevention of relapse with primaquine.

Primaquine may cause haemolysis in Glucose-6-Phosphate Dehydrogenase (G6PD) deficient patients. Blood should be taken for G6PD prior to commencing primaquine. Ideally, the result should be available prior to starting treatment. If not, than primaquine can still be started and the haematology lab should be asked to do the test as quickly as they can.
G6PD screening results should be available within 24 hours at the Whittington Hospital, however they may take a few working days.
Patients with known G6PD deficiency requiring prevention of relapse should be discussed with the Infectious Diseases consultant (Dr Killingley or Dr Jennings)/ID registrar at tertiary infectious diseases unit and the haematology consultant.

9) Treatment of mixed infection, or malaria of uncertain species

Treatment should be as for falciparum malaria in the first instance, but specialist advice must be sought thereafter.

10) Admission to hospital, monitoring progress and discharge from hospital

P. falciparum:
Because of the risk of clinical deterioration, all patients with *Plasmodium falciparum* malaria should be admitted for a minimum of 24 hours. If after 24 hours the patient remains well and is tolerating treatment, consideration may be given to discharging the patient for completion of treatment as an outpatient, but such discharges should always be discussed with the consultant first.

Inpatients should have a daily malaria film, including a daily measurement of parasitaemia. It is common for the parasitaemia to rise on the second day of treatment, and this does not represent treatment failure or resistance.

Patients completing treatment for falciparum malaria as an outpatient should return to hospital at least every 24 hours until the parasite count is documented to be falling.

NB. Late haemolysis (10-28 days after treatment) has been observed occasionally in patients treated for severe malaria with artesunate and other artemisinins. Haemoglobin should be checked after 2 weeks.

Non-falciparum malaria:
Patients with non-falciparum malaria can be treated without admission to hospital if they are clinically well, but they are often ill enough on presentation for a brief admission to be appropriate.

11) Advice on future prevention

All parents/guardians of children with malaria should receive advice on future prevention [13], which should highlight the need for:

- Avoidance of mosquito bites through insect repellent use, and through covering up with clothing, particularly in the early morning and evening
- Use of an intact insecticide-impregnated mosquito net
- Use of appropriate chemoprophylaxis

Parents/guardians should be given the details of a travel clinic (e.g. at GP practice, pharmacists or the Hospital for Tropical Diseases or the Royal Free Hospital (latter two are fee paying)) and should be advised to arrange an appointment for specific prophylaxis advice before their next travel.

12) Outpatient follow up

Children with uncomplicated falciparum malaria, and patients with non-falciparum malaria, do not require routine outpatient follow up after discharge. A full discharge summary should be sent to their GP. Children with falciparum malaria managed outside hospital need to re-attend for repeat malaria films every 24 hours until the parasite count is documented to be falling.

All parents/guardians of children with malaria should be advised to re-attend ED to request a malaria test promptly if the child's fever recurs in the 12 months following their discharge.

➢ Contacts (inside and outside the Trust including out-of-hours contacts)

- Microbiology SpR via switchboard
- Dr Ben Killingley or Dr Richard Jennings, Consultants in Infectious Diseases – mobile, via switchboard
- Dr Michael Kelsey, Consultant Microbiologist, via switchboard
- Dr Julie Andrews, Consultant Microbiologist, via switchboard
- Haematology laboratory scientist on call
- Haematology SpR via switchboard
- Paediatric SpR – bleep 3111
- Paediatric Consultant – via switchboard
- Infectious Diseases paediatric SpR on call via switchboard (GOSH or St Mary's)
- Travel Clinic, Hospital for Tropical Diseases, University College London Hospitals
- Travel Clinic, Royal Free Hospital
- Malaria reference laboratory is available at London School of Hygiene & Tropical Medicine (LSHTM)

➢ References (evidence upon which the guideline is based)

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To be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval

		Yes/No	Comments
1.	**Does the procedural document affect one group less or more favourably than another on the basis of:**		
	• Race	No	
	• Ethnic origins (including gypsies and travellers)	No	
	• Nationality	No	
	• Gender	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Age	No	
	• Disability - learning disabilities, physical disability, sensory impairment and mental health problems	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	No	
4.	**Is the impact of the procedural document likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the procedural document without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	

If you have identified a potential discriminatory impact of this procedural document, please refer it to the Director of Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact the Director of Human Resources.

Checklist for the Review and Approval of Procedural Document

To be completed and attached to any procedural document when submitted to the relevant committee for consideration and approval.

	Title of document being reviewed:	Yes/No	Comments
1.	**Title**		
	Is the title clear and unambiguous?	Yes	
	Is it clear whether the document is a guideline, policy, protocol or standard?	Yes	
2.	**Rationale**		
	Are reasons for development of the document stated?	Yes	
3.	**Development Process**		
	Is it clear that the relevant people/groups have been involved in the development of the document?	Yes	
	Are people involved in the development?	Yes	
	Is there evidence of consultation with stakeholders and users?	Yes	
4.	**Content**		
	Is the objective of the document clear?	Yes	
	Is the target population clear and unambiguous?	Yes	
	Are the intended outcomes described?	Yes	
5.	**Evidence Base**		
	Are key references cited in full?	N/A	
	Are supporting documents referenced?	N/A	
6.	**Approval**		
	Does the document identify which committee/ group will approve it?	Yes	
7.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	Yes	
8.	**Document Control**		
	Does the document identify where it will be held?	Yes	
9.	**Process to Monitor Compliance and Effectiveness**		

	Title of document being reviewed:	Yes/No	Comments
	Are there measurable standards or KPIs to support the monitoring of compliance with and effectiveness of the document?	Yes	
	Is there a plan to review or audit compliance with the document?	Yes	
10.	**Review Date**		
	Is the review date identified?	Yes	
	Is the frequency of review identified? If so is it acceptable?	Yes	
11.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for co-ordinating the dissemination, implementation and review of the document?	Yes	

Executive Sponsor Approval			
If you approve the document, please sign and date it and forward to the author. Procedural documents will not be forwarded for ratification without Executive Sponsor Approval			
Name		Date	
Signature			
Relevant Committee Approval			
The Director of Nursing and Patient Experience's signature below confirms that this procedural document was ratified by the appropriate Governance Committee.			
Name		Date	
Signature			
Responsible Committee Approval – only applies to reviewed procedural documents with minor changes			
The Committee Chair's signature below confirms that this procedural document was ratified by the responsible Committee			
Name		Date	
Name of Committee		Name & role of Committee Chair	
Signature			

Tool to Develop Monitoring Arrangements for Policies and guidelines

What key element(s) need(s) monitoring as per local approved policy or guidance?	Who will lead on this aspect of monitoring? Name the lead and what is the role of the multidisciplinary team or others if any.	What tool will be used to monitor/check/observe/Assess/inspect/ authenticate that everything is working according to this key element from the approved policy?	How often is the need to monitor each element? How often is the need complete a report ? How often is the need to share the report?	What committee will the completed report go to?
Element to be monitored	**Lead**	**Tool**	**Frequency**	**Reporting arrangements**
Appropriate assessment of severity based on guideline	Dr M C Kelsey	Audit	Annual	Pathology Audit Meeting
Appropriate management according to severity	Dr M C Kelsey	Audit	Annual	Pathology Audit Meeting

Appendix 1: Artemisinin derivatives used in this guideline

Artemisinin derivatives, including artesunate and artemether, undergo conversion to dihydroartemesinin, the active metabolite, after injection or ingestion. Dihydroartemesinin has a broad spectrum of activity against the blood stage asexual *Plasmodium* parasites.

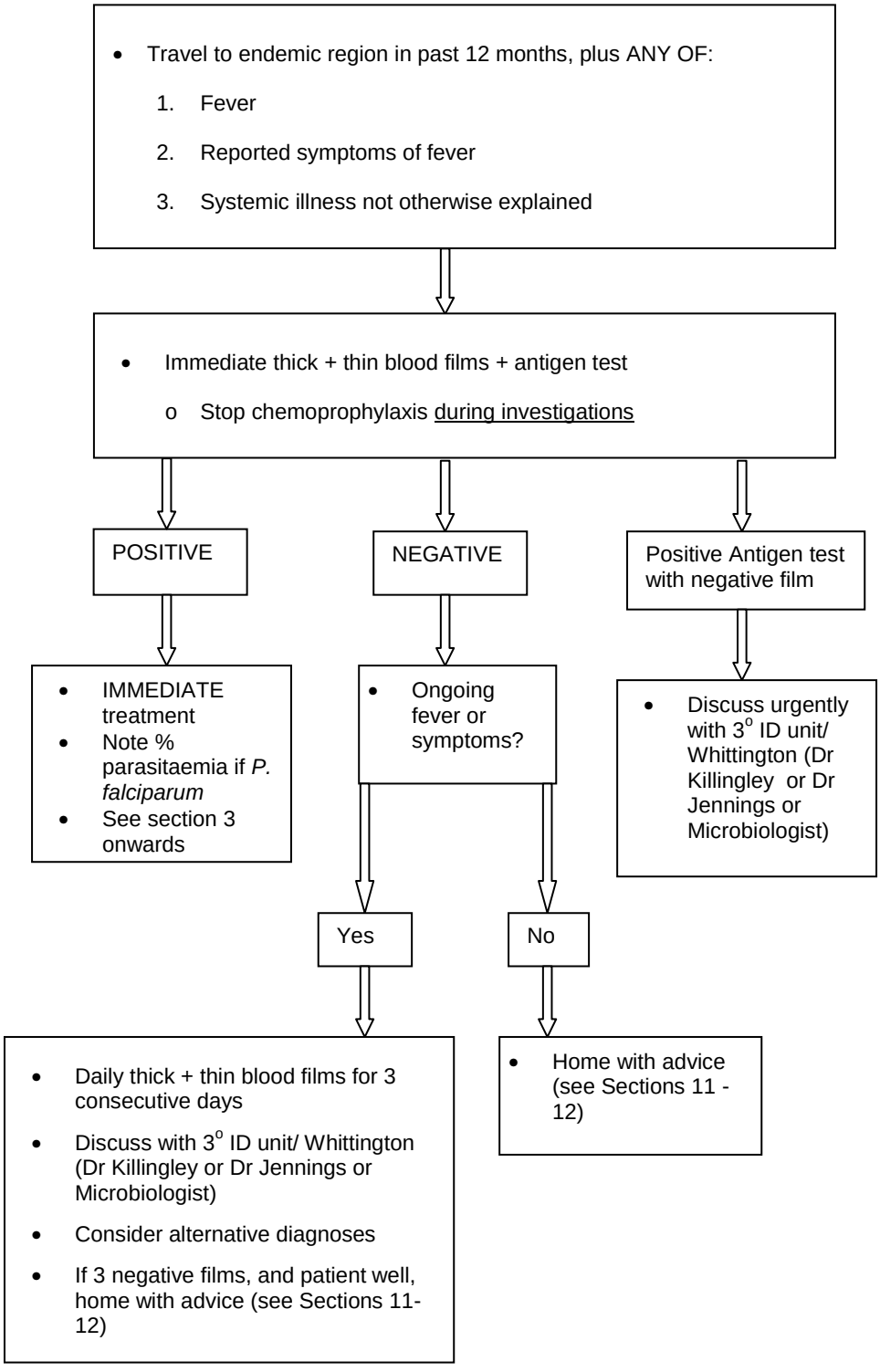
Artesunate is a water soluble intravenous drug used for the treatment of severe malaria (any species) and uncomplicated falciparum malaria if unable to tolerate oral medication.

Riamet® (artemether-lumefantrine) is an oral agent used for follow-on treatment of severe malaria (any species), uncomplicated falciparum malaria and for *P. vivax* from regions with known chloroquine resistance.

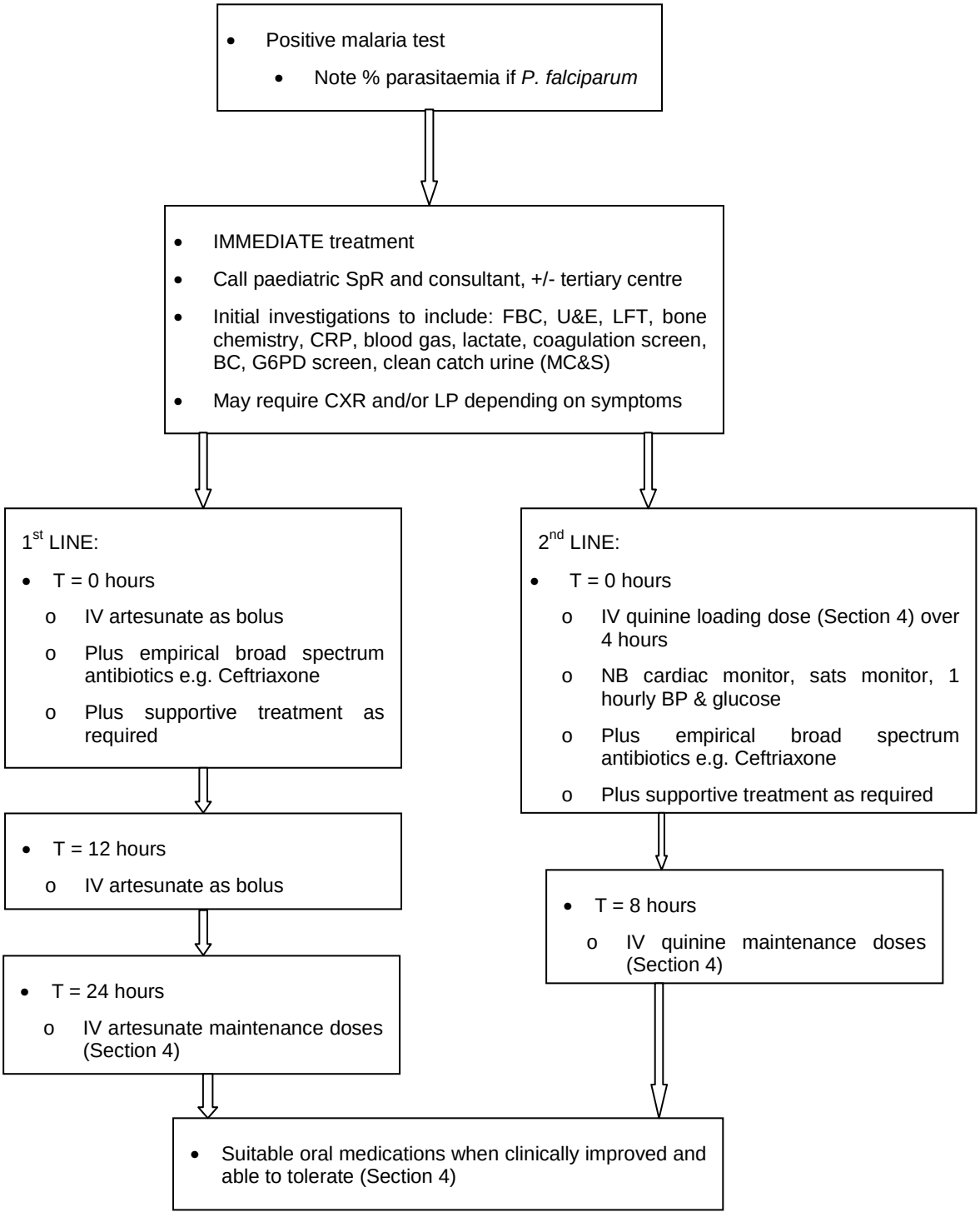
	IV artesunate	**PO artemether- lumefantrine (Riamet®)**
Dose	• Children >20kg and adults: 2.4 mg/kg IV bolus at 0, 12 and 24 hours, then every 24 hours thereafter • Children <20kg: 3.0 mg/kg IV bolus at 0, 12 and 24 hours, then every 24 hours thereafter	1 tablet = 20mg artemether / 120mg lumefantrine Children: 5-14kg: 1 tablet 15-24 kg: 2 tablets 25-34 kg: 3 tablets >34 kg: 4 tablets (adult dose) Adults: 4 tablets At 0, 8, 24, 36, 48 and 60 hours Riamet® should be taken with fatty foods or milk. If children are unable to swallow tablets whole, they can be crushed.
Adjustment in renal impairment	None	None NB: In severe renal impairment monitor ECG and plasma potassium concentration.
Adjustment in liver impairment	None	None
Pregnancy and breast-feeding	• Use for all stages of pregnancy if returning from SE Asia • NOT recommended for first trimester if returning from other countries (use IV quinine) • Minimal data on use in breastfeeding but benefit thought to outweigh theoretical concerns	• In pregnancy, animal studies have also shown adverse effects on the early development of the fetus, but the artemisinin derivatives have not been fully evaluated during early pregnancy in humans • Avoid breast-feeding for at least 1 week after last dose (due to long half-life of lumefantrine; present in milk in animal studies)
Side effects	• Common: o Nausea o Vomiting o Anorexia o Dizziness • Rare:	• Common: o Vomiting o Diarrhoea o Abdominal pain o Anorexia o Cough

	o Neutropenia o Anaemia o Delayed haemolysis o Elevated liver enzymes o Hypersensitivity reactions (1:3000) o ECG abnormalities	o Headache • Uncommon: o Sleep disturbances o Dizziness o Prolonged QT interval o Elevated liver enzymes • Rare: o Myalgia o Arthralgia o Hypersensitivity reactions (1:3000)
Interactions	• Avoid drugs that prolong QT interval if possible • Increased plasma concentration with nevirapine	• Drugs metabolised by CYP2D6 and CYP3A4 (e.g. rifampicin) • Drugs known to prolong the QTc intervals • Anti-retroviral drugs • Other antimalarials • Grapefruit juice
Contraindications	Known hypersensitivity to artesunate or artemisinin derivatives	• Known hypersensitivity to artemether or lumefantrine • Family history of congenital QT interval prolongation • Family history of sudden death • History of arrhythmias • History of clinically relevant bradycardia • History of congestive heart failure accompanied by reduced left ventricular ejection fraction • Acute porphyrias

Appendix 2: Management of suspected case of malaria



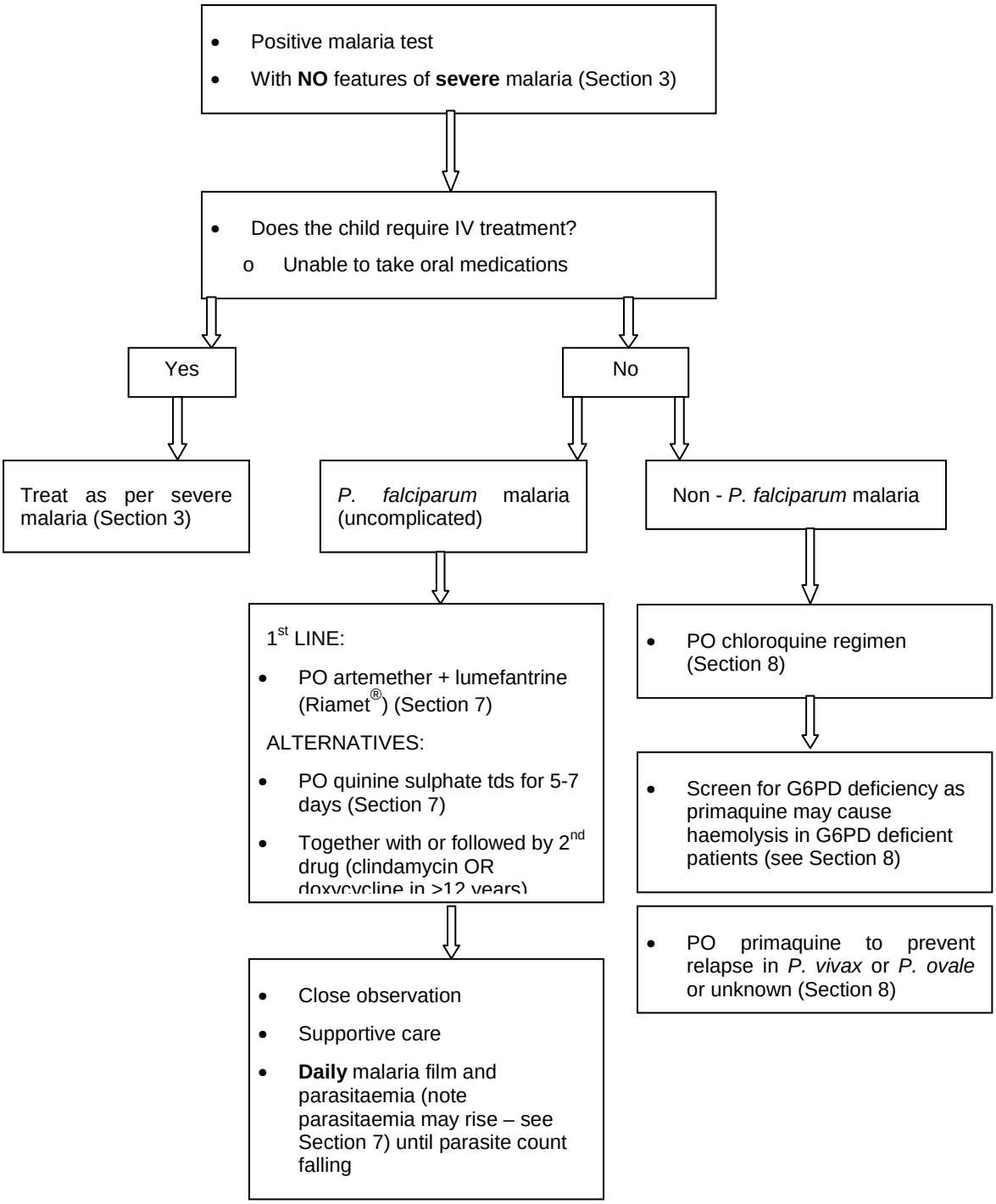
Appendix 3: Management of confirmed case of paediatric malaria - severe



Notes:

- Quinine 'allergy' – Section 5
- Mixed infection/uncertain species – Section 9
- Ongoing care and follow up for all patients – Sections 10-12

Appendix 4: Management of confirmed case of paediatric malaria – non-severe



Notes:

- Quinine 'allergy' – Section 5
- Mixed infection/uncertain species – Section 9
- Ongoing care and follow up for all patients – Section 10-12