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Improving the radical cure of vivax malaria (IMPROV)

Submission date
30/06/2016

Recruitment status
No longer recruiting

Registration date
18/07/2016

Overall study status
Completed

Last Edited
31/12/2021

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims:
Malaria is an infectious disease which is common in tropical and subtropical countries, caused by a microscopic parasite which is spread from person to person by mosquitos. It can be serious disease if it is not treated quickly and effectively. One type, called vivax malaria, can hide in the liver and reenter the blood to cause repeated illness (relapse). Repeated relapse is particularly damaging to the health and development of children. The usual medicines given for vivax malaria can only kill the parasites in the blood. There is one medicine, called primaquine, which can be taken to kill the vivax malaria parasite in the liver and so will reduce the risk of relapses. Some individuals may have weak red cells. Red cells need enzymes to work properly and weak red cells have low amounts of an enzyme called glucose 6 phosphate dehydrogenase (G6PD). People with G6PD deficiency (G6PDd) can be at risk if they take primaquine because it can destroy their red cells. This study aims to find out how best to use primaquine in patients with normal or weak (G6PD deficient) red cells so that we can introduce better treatments for vivax malaria around the world.

Who can participate?
Patients presenting to a participating treatment centre with uncomplicated vivax malaria are eligible to enrol provided they are over 6 months of age, not pregnant, and not suffering from any other medical condition.

What does the study involve?
Participants are randomly allocated to one of three groups. Participants in all groups undertake standard antimalarial treatment (in pill form) as per standard practice in their country. In addition, those in the first group receive 14 days treatment of low dose primaquine). Those in the second group receive seven days treatment of high dose primaquine followed by seven days of placebo (dummy pill). Those in the third group receive 14 days treatment with a placebo (dummy pill). Patients in all groups are followed up daily for two weeks, then weekly until week 8, and then monthly until 12 months to see if their malaria has come back.

What are the possible benefits and risks of participating?
All patients benefit from receiving treatment against vivax malaria. Patients also receive the results of their G6PD test which can be useful to them if they need malaria treatment in the

future. The main potential risks are side-effects from primaquine but patients are tested for G6PDd, enrolled to a different treatment if found to have G6PDd and monitored closely.

Where is the study run from?
The study is run by Oxford University (UK) and takes place in health centres in Vietnam, Indonesia and Afghanistan

When is study starting and how long is it expected to run for?
January 2013 to February 2018

Who is funding the study?
1. Medical Research Council (UK)
2. Bill and Melinda Gates Foundation (USA)

Who is the main contact?
Professor Ric Price
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Contact information

Type(s)
Scientific

Contact name
Prof Ric Price

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT01814683

Secondary identifying numbers
MR/K007424/1

Study information

Scientific Title
Improving the Radical Cure of Vivax Malaria: A Multicentre Randomised Comparison of Short and Long Course Primaquine Regimen (IMPROV)

Acronym
IMPROV

Study objectives
Due to the long duration of standard primaquine treatment regimens, courses are difficult to supervise, are poorly adhered to and lack effectiveness. Our proposed multicentre randomised clinical trial will provide evidence across a variety of endemic settings on the safety and efficacy of high dose-short course primaquine in G6PD normal patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC), 16/06/2013, ref: 2013-1991
2. Oxford Tropical Research Ethics Committee (OxTREC), 04/06/2013, ref: 1014-13

Study design
Double-blind three-arm randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
P. vivax malaria

Interventions
Patients will be randomly assigned to one of the three treatment arms below:

Intervention group 1: Standard blood schizonticidal therapy plus 14 days of supervised primaquine (7mg/kg total dose) administered once per day (0.5 mg/kg) orally

Intervention group 2: Standard blood schizonticidal therapy plus 7 days of supervised primaquine (7mg/kg total dose) administered once per day (1.0 mg/kg OD) followed by 7 days of placebo orally
Control group: Standard blood schizintocidal therapy plus 14 days placebo orally

The schizintocidal consists of Chloroquine in Vietnam and Afghanistan, and Dihydroartemisinin-piperaquine in Indonesia.

For all study arms, follow up is daily for 2 weeks, then weekly till week 8 and then monthly until 12 months.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
1. Chloroquine 2. DHA-piperaquine plus primaquine

Primary outcome measure
1. Incidence rate (per person-year) of symptomatic recurrent P. vivax is measured within 12 months
2. Incidence rate (per person-year) of symptomatic recurrent P. vivax parasitaemia (detected by microscopy) over 12 months of follow-up in the 7 versus 14-day primaquine groups for all sites combined and stratified by site

Secondary outcome measures
1. The incidence rate (per person-year) of any recurrent P. vivax malaria is measured at 12 months
2. The incidence rate (per person-year) of any recurrent (i.e. symptomatic and asymptomatic) P. vivax parasitaemia over 12 months of follow-up in the 7 and 14-day primaquine regimens for all sites combined and stratified by site
3. Incidence risk of any recurrent symptomatic of P. vivax malaria compared to control arm is measured at 12 months
4. The incidence rate (per person-year) of any recurrent symptomatic P. vivax parasitaemia over 12 months of follow-up in either the 7 or the 14-day primaquine regimens compared with the control arm, for all sites combined and stratified by site
5. The Haematological recovery in patients with vivax malaria will be assessed as the incidence risk of severe anaemia (Hb<7g/dl) and/or blood transfusion within the 12 month follow up period, and the mean fall in baseline Hb at day 7 and day 14
6. Proportion of patients with Serious Adverse Drug reactions is measured within 42 days of primary treatment, 6 and 12 months
7. Tolerability of primaquine will be assessed by comparing the proportion of patients with nausea, vomiting, abdominal pain and vomiting of a dose within 1 hour of administration within 12 months
8. Drug tolerability will be assessed by comparing the proportion of patients completing a full course of observed primaquine therapy within 12 months
9. Incidence risk of severe anaemia in G6PD deficient arm and/or requirement for blood transfusion within the 12 month follow up period and the mean fall in baseline Hb at day 7 and day 14

10. Cost effective analysis in the management of P. vivax with respect to the use of G6PD tests, the dosing schedule and the epidemiological context will be conducted at 12 months

Overall study start date
01/01/2013

Completion date
28/02/2018

Eligibility

Key inclusion criteria
Participant (or parent/guardian of children below age of consent) is willing and able to give written informed consent to participate in the trial; verbal consent in the presence of a literate witness is required for illiterate patients. In addition, written assent (or verbal assent in the presence of a literate witness for illiterates) from children 12 to 17 years as per local practice.

1. Monoinfection with P. vivax of any parasitaemia in countries which use Chloroquine (CQ) as blood schizontocidal therapy. Mixed infections with P. vivax and P. falciparum can be enrolled in countries which use an artemisinin combination therapy
2. Diagnosis based on rapid diagnostic tests
3. Over 6 months of age
4. Weight 5 kg or greater
5. Fever (axillary temperature 37.5 degrees C) or history of fever in the last 48 hours
6. Able, in the investigators opinion, and willing to comply with the study requirements and follow-up

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
1875

Total final enrolment
2336

Key exclusion criteria
1. Female participant who is pregnant, lactating or planning pregnancy during the course of the study
2. Inability to tolerate oral treatment
3. Previous episode of haemolysis or severe haemoglobinuria following primaquine
4. Signs/symptoms indicative of severe/complicated malaria or warning signs requiring parenteral treatment- Haemoglobin concentration less than 9 g/dL
5. Known hypersensitivity or allergy to the study drugs

6. Blood transfusion in last 90 days, since this can mask G6PD deficient status
7. A febrile condition due to diseases other than malaria (e.g. measles, acute lower respiratory tract infection, severe diarrhoea with dehydration)
8. Presence of any condition which in the judgment of the investigator would place the participant at undue risk or interfere with the results of the study (e.g. serious underlying cardiac, renal or hepatic disease; severe malnutrition; HIV/AIDS; or severe febrile condition other than malaria); coadministration of other medication known to cause haemolysis or that could interfere with the assessment of antimalarial regimens
9. Currently taking medication known to interfere significantly with the pharmacokinetics of primaquine and the schizontocidal study drugs
10. Prior antimalarial medications in the previous 7 days

Date of first enrolment
01/07/2014

Date of final enrolment
30/11/2017

Locations

Countries of recruitment
Afghanistan

Ethiopia

Indonesia

Viet Nam

Study participating centre
Health Protection and Research Organisation (HPRO)
Laghman
Afghanistan
1001

Study participating centre
Health Care and Social Development Organization (HSDO)
Jalalabad
Afghanistan
2601

Study participating centre

Hanura Health Center
Lampung
Indonesia
35451

Study participating centre
Tanjong Leidong District Health Center
Medan
Indonesia
20231

Study participating centre
Dak O Health Commune
Viet Nam
830000

Study participating centre
Bu Gia Map Health Commune
Viet Nam
830000

Study participating centre
Krong Pa Health Commune
Viet Nam
600000

Study participating centre
Metehara Health Centre
Ethiopia
-

Study participating centre
Arba Minch Hospital
Ethiopia
-

Sponsor information

Organisation
University of Oxford

Sponsor details
NDM Research Building
Nuffield Department of Medicine
University of Oxford
Old Road Campus
Roosevelt Drive
Headington
Oxford
England
United Kingdom
OX3 7FZ

Sponsor type
University/education

Website
http://www.ndm.ox.ac.uk/home

ROR
https://ror.org/052gg0110

Organisation
Menzies School of Health Research

Sponsor details
PO Box 41096
Casuarina NT
Australia
0811

Sponsor type
Research organisation

Website
http://www.menzies.edu.au/

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Publication and dissemination plan
Primary and secondary publications will be published in peer reviewed journals from June 2018.

Intention to publish date
30/06/2018

Individual participant data (IPD) sharing plan
Not provided at registration

IPD sharing plan summary
Data sharing statement to be made available at a later date, Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Protocol article	protocol	07/12/2015		Yes	No
Results article		14/09/2019	31/12/2021	Yes	No