Supplementary Submission to the Senate Inquiry 'Investigation into the use of the quinoline antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force.'

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Major Stuart McCarthy (Rtd)

The Australian Quinoline Veterans and Families Association

Please accept this supplementary submission in response to questions posed by the Committee at the Senate Inquiry hearings in Brisbane on 30 August 2018.

Questions were asked of one witness to the Inquiry with regard to documents relating to the protocols of the studies undertaken in East Timor by the ADF Army Malaria Institute for which many ADF members were trial participants. Although the witness questioned did not appear to be willing to offer a direct answer to the Senators questions, it is likely that these protocols are held by the AMI as part of their clinical trial records. In addition to this potential source of the information requested, an FOI request undertaken by the QVFA included information that could address the question posed by the Senators. This information is discussed in this supplementary submission.

In this regard, please find attached the minutes and ethics protocols (Annexes 1 & 2) sourced as part of this FOI that include various documents submitted to the Australian Defence Human Research Ethics Committee (ADHREC) in regard to the human research ethics application for the trial entitlesd **Protocol 249/01 – Evaluation safety and adverse effects of mefloquine in the prophylaxis of malaria in non-immune Australia soldiers.** This protocol related to the mefloquine / doxycycline trial undertaken by the ADF Army Malarial Institute in East Timor in 2001-2002 in which 1,157 RAR soldiers were given mefloquine as the trial drug.

This submission will consider various information provided in the human research ethics application for Protocol 249/01. This trial compared safety and efficacy of two antimalarial prophylaxis regimens – daily treatment with doxycycline (the ADF first-

line antimalarial) and mefloquine which was at that time the second choice antimalarial for deployed troops.

Information within these documents, as well as articulating the rationale and procedures of the trial, also raise a number of important issues:

1. **The rationale for the study 249/01 has been repeatedly misrepresented by the ADF.**

In Section 2 of Annexe 1 (p13). 'Justification for Investigation', the investigators state that '***There is clear evidence of non-compliance and adverse events related to MQ (mefloquine) in smaller studies, however, no larger studies conduction on Australian soldiers or under field conditions define the adverse event profile.***'

ADF has suggested, on multiple occasions, that this study was carried due to the need to find an alternative antimalarial drug to doxycycline with a better, weekly, dosing regimen to improve compliance. This is clearly not the rationale that was presented to ADHREC as the reason for carrying out this study, which was to determine a previously identified adverse event profile in deployed Australian soldiers.

In addition, the text presented for justification in the multiple iterations of the ADHREC protocol contained in Annexe 1 change over time. The justification appears to be slightly different in each iteration of the protocol presented to ADHREC for approval without this ever being noted by the Committee.

This is further confirmed in the 'Objectives' for this trial identified in Section 3 (Annexe 1, p13), that are clearly stated as '***The objective of this study is to define the adverse events of mefloquine and compare them to doxycycline. A secondary objective is comparing the effectiveness of these medications.***'

This document clearly states that determine the rate and range of adverse events was the primary motivation for carrying out this trial. This is a highly inappropriate use of troops deployed under peace-keeping or war-like conditions.

2. **Identification of those soldiers who were not given mefloquine but remained on doxycycline – not a group that declined to participate but one that was never included.**

The Senators asked several witnesses questions about the 400 individuals who had not been part of the mefloquine trial but had 'chosen' to remain on doxycycline, inferring that these individuals had 'consented' not to be included in the trial cohort.

This document identifies that (Annexe 1, page 15, Section 5 – Study population) that the trial cohort would include *'Core elements of the forward elements of the core battle groups deploying to East Timor under Operation Tanagar'…… The core elements of the Battalion group include Rifle Company and attachments.'*

What is clearly noted is that *'Headquarter elements, Administration Company and Support Company groups with other Battallion group attachments will remain on chemoprophylaxis on in accordance with HPD215* and will monitored with existing surveillance systems'.*

*HPD215 equals 100mg doxycycline daily. This detail is included in version 1.5 of the study design, Section 4, Annexe 1 p39).

It is therefore highly likely that this is the 400 individuals who remained on doxycycline and were not included in the trials, and that these individuals **were not people who had declined to participate but simply a group that had never been included in the study cohort**.

3. **The exclusion criteria for study 249/01 did not include people with pre-existing mental health disorders.**

In Annexe 1, Section 5b, page 14, identifies those criteria requiring exclusion from the trial.

These are stated as:

i) They are pregnanct, or are unwilling or unable to comply with recognised contraception methods for 30 days after administration of the study drugs;
ii) They have a known hypersensitivity to any component of the study drugs;
iii) They are unwilling / unable to give blood collections as required within the study;
iv) They are taking any other investigation drug, during or within, 30 days of taking the study drugs for this study.

No mention is made of screening for pre-existing mental health conditions, or indeed, any health condition prior to entry to the trial.

The only reference to a prior history of neuropsychiatric disorders is presented in the participant consent form under 'Precautions' (see Annexe 1, p22, Protocol V1.6 as an example). In this case, the precautions state:

'If you have had any anxiety attacks or depression in the past you may not be able to use mefloquine.' (Annexe 1, p22, lines 3-4).

The precautions only suggest discussing an adverse reaction, or possible pregnancy with the study medical officer, not a history or past neuropsychiatric disease.

4. **Benefits for the individual were misrepresented.**

In Annexe 1, Section 9 (page 15) identifies the benefits to the individual as '*is convenience in that MQ is a weekly medication and DX (doxycycline) is a daily, in addition to potentially fewer adverse events associated with DX…'*

This is a spurious statement given that the neuropsychiatric side effect profile of mefloquine was already well known and the likelihood that this would be a reduced rate of adverse events was unknown, and was clearly an outcome of the study not a pre-determined fact.

5. **Adverse events were not fully investigated or recorded, despite this being part of the trial protocol.**

In Annexe 1, Section 14, page 18 - Personnel Responsibilities, the study protocol indicates that *'The principle investigator and co-investigator shall…….. c) investigate all adverse events'.*

Given that the study team was not co-located to all individuals who had been given the trial drugs, in fact, witness reports to this inquiry suggest that there was the barest oversight of the majority of troops in the study, **it would be simply impossible for this study requirement to be followed in practice.**

Minutes from the ADHREC meeting on 26 February (undated presumably 2001, see Annexe 2, page 2 section b) also clearly identify that the full side effect profile had not been clearly communicated to the Institutional Ethics Committee. This caused some consternation and additional information was requested to be inserted into the consent form for the trial to address this shortfall in participant information.

In addition, the Committee made the recommendation that the study title be amended to identify that the study was examining 'safety' as a clear part of the protocol (Annexe 2, p3, Decision b.). They also indicated that 6 doses of mefloquine should be administered prior to deployment, this would be the three loading doses plus 3 weekly doses. It is unclear if this requirement was followed in all individuals enrolled in the study.

6. **Coercion was likely and therefore informed consent was not given in the majority of cases.**

Section 20 Volunteer Consent on page 19 of Annexe 1, the documents states *'Volunteers will be recruited using non-coercive means.'*

Multiple, independent witness reports, given both during and prior to this Inquiry have indicated that troops were coerced to participate by the threat of non-deployment. This must no longer be suggested to be a disputed fact but the truth of their experience. **Serving ADF members, as vulnerable subjects, were coerced to participate in this trial and therefore their participation was not truly consensual.**

7. Follow-up procedures were only loosely followed and determination of the endpoint of adverse health events was not determined by necessary clinical surveillance.

Very little information is included in this ADHREC submission regarding follow-up of individuals within the trials.

The study protocol states:

'Investigators should follow-up subjects with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the subject's subsequent course must be submitted to the clinical study monitor.'

(Annexe 1, p24, last paragraph)

This inadequate description certainly allowed for lack of clear adverse event monitoring in the study cohort, and subject who were excluded from the trial due to adverse events, or removed from the Area of Operations after moderate to severe adverse events appear to have experienced little or no follow-up from the study team at all.

8. **Soldiers were recruited into the trial prior to approval of the full, amended protocol by ADHREC.**

There are some inconsistencies in the timeline for ADHREC approval of the Protocol. Multiple versions of the trial protocol were submitted for review by the committee. A letter dated 26 April 2001 (Annexe 1, p32) from the Committee to the Primary Investigator, the Committee states that certain amendments to the protocol were considered and reviewed by the Committee at a meeting on the 30th March, and that the Committee had now approved this protocol and that the Investigator cleared to proceed with the protocol with these amendments in place.

However, the Primary Investigator had written letter to the Committee with a dated 30 March 2001 (Annexe 1 p33) stating that 600 participants had already been recruited and begun a loading dose of mefloquine. Of these 600, 5% had already been withdrawn from the trial due to adverse reactions to the study medications (see Minutes, Annexe 1, p3, point 1 and 2) and had been moved to mefloquine, and one soldier who was given malarone. Approval of the original protocol was accepted in January 2001. **It is therefore possible that those individuals recruited into the trials had received incomplete participation information, and therefore their ability to give fully informed consent will have been compromised.**

What is also an interesting statement in this letter is that ‘requests to continue the trial had been received from 2RAR. This suggests that recruitment outside the original cohorts was being considered and that therefore the risks presenting to operational effectiveness were, or possibly were not, being communicated across the chain of command. It would be interesting to know exactly what information was being communicated to the Commanding Officers of each RAR Battalion regarding the adverse event profile of mefloquine and any potential effects this might have on ground operations for these troops. The sample size was increased to take these incoming Battalions into account with a modification requested to increase the sample size, from an original sample size of 800 to 1500 troops.

In conclusion

The information provided in these documents indicate that:

- The rationale and justification of trial Protocol 240/01 was to determine the adverse event profile of mefloquine in Australian soldiers, with efficacy as a secondary concern;
- Troops were recruited into the trial prior to the final participation documents being finalised, and therefore without fully informed consent;

- The procedures for adverse event reporting appear not to have been followed according to the study documentation;
- Follow-up of troops given the study drugs and suffering adverse reactions or being withdrawn from the trial was not adequately undertaken, and particularly not in those individuals returned to country after major medical events.

The evidence presented in these ADHREC documents clearly identifies that the full adverse event profile of mefloquine was not disclosed to the Committee prior to the start of the trials (Annexe 2, p2-3), and that consent documents needed to be amended to include additional information about the known neuropsychiatric adverse event profile. Why this critical information had been originally excluded from the ADHREC application, and to what extent those in the Chain of Command of troops participating in these trials were informed of the full potential risk to operations, are important questions that should be raised to the appropriate individuals as part of this Senate Inquiry.

ANNEXE 1

Protocols and amendments of Protocol 240/01 Evaluation safety and adverse effects of mefloquine in the prophylaxis of malaria in non-immune Australia soldiers.

Modification V1.5 05 June 2001 (C)

Modification V1.5 30 March 2001 (B)

APPROVED APPLICATION Protocol 249/01 (A)
21 MARCH 2001

DEFENCE PERSONNEL EXECUTIVE
DEFENCE HEALTH SERVICE BRANCH
CP2-7-66 Department of Defence CANBERRA ACT 2600

FOI/C
14

2001/5344
ADHREC 249/01
DHSB [illegible] /2001

Major S. Kitchener
Officer In Charge Clinical Trials
Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Major Kitchener

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADMEC) PROTOCOL 249/01: EVALUATION OF MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS

1. Thankyou for submitting for protocol modification version 1.5 dated 5 June 2001. The proposed amendments were considered by The Australian Defence Human Research Ethics Committee on Monday the 18th of June 2001.

2. ADHREC has considered your protocol and has approved the amendment. As such the protocol is now cleared to proceed with these modifications in place.

3. Please contact me if you would like to discuss this further.

Yours sincerely,

s22 [redacted]

R.A. LANDY
Major
Executive Secretary
Australian Defence Human Research Ethics Committee

02 July 2001

Department of Defence

MINUTE

13

548-7-45

Executive Secretary (Attention: Australian Defence Force Medical ethics Committee) (CP2-7-66)

REPORT AND AMENDMENTS TO MEFLOQUINE TRIAL – ADMEC 249/01

1. The Mefloquine trial (ADMEC 249/01) with 4RAR Battalion Group was launched in April following ADMEC approval in January.

2. Initial concerns regarding the potential adverse events from mefloquine used in accordance with the Health Policy Directive may be dispelled to a degree as approximately 5% of all volunteers (n=30/596) have been transferred to doxycycline through possible intolerance of the medication. There has been one SAE involving a young soldiers spraining his ankle in East Timor. Another soldier was determined to have developed early insulin dependent diabetes following removal from the trial. In the (open-label) control group taking doxycycline, approximately 5% (7/131) have also been changed to alternative antimalarials due to intolerance. All of the latter are now taking mefloquine except one soldier now using Malarone.

3. This is an encouraging result. Consequently, requests to continue the trial have been received from the following Battalion Group. 2RAR. It is proposed to alter the protocol slightly to accommodate this request. Changes to the previous protocol have been included below, however, a full amended protocol follows.

a. moving haematology, biochemistry and pharmacology investigations to coincide with relief out of country leave, for logistic reasons, (identified in "Overview of Study"),

b. an additional investigation to determine carriers of malaria prior to relief out of country leave (identified in "Overview of Study"),

c. including a minimum time prior to deployment for recruiting to allow opportunity education and information with pre-deployment medical preparation (identified in "Overview of Study"), and

d. **"7. Sample Size**
The core elements of an ADF Battalion groups in Operation Tanager approximate 1500 in number."

4. These amendments also attempt to coincide with investigations associated with other (logistics) elements of the Battalion Group undertaking trials of Malarone and doxycycline (AMI/MAL 3.0).

5. The "Overview of the Study" is included as an additional enclosure for ready reference to this trial and the amendments forwarded for ADMEC approval.

Original signed

S J KITCHENER
MAJ
OC CLINICAL FIELD

ARMY MALARIA INSTITUTE

05 Jun 01

Enclosure 1: Overview of Study MQ 1.6

Enclosure 2: Complete AMI Protocol MQ 1.6

Enclosure 1:Overview of MQ 1.6

	Screening	4. Loading Safety	5. Field Safety	6. Followup [1]
Study Visit	1	2	3	As required
Day	**Prior to deployment** **D-25 (days) min.**	D-7	**Variable** **ROCL**	As required
Written informed consent	*			
Inclusion/exclusion Criteria	*			
Physical Examination				*
Medical history/ Demography	*		*	*
Medication issued	*			Supply by RAP in field conditions
Malaria blood smears / tests			*	*
Haematology/ Biochemistry			*	*
Pharmacology			*	*
Pregnancy test	*			• (if female)
Adverse event review		*	*	*
Concomitant medicine review	*	*	*	*

Notes:

1. Followup initiated by treating medical facility in cooperation with AMI Investigators once diagnosis of malaria has been made.

ROCL = relief out of country leave

Amendments shaded

CLINICAL TRIAL PROTOCOL

PROTOCOL NO. MQ001
Version 1.5 (ADMEC amended)

PROTOCOL TITLE:

Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers

Principal Investigator:

MAJ Scott Kitchener MBBS MPH
OC Clinical Field AMI

CAPT John Cunningham BSc (Hon) MBBS
RMO 4RAR

Co-Investigators:

LTCOL Mike Edstein PhD
Deputy Director AMI

LTCOL Peter Nasveld MBBS BSc Med (Hons)
RO Clinical Studies AMI

CAPT Anne Jensen
RO Clinical Studies AMI

LT Michael Reid
RO Clinical Studies AMI

Study Coordinator:

Professor Karl Rieckmann MD
Director AMI

[redacted]

Version 1.6

Summary of Protocol:

TITLE	Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers
SPONSOR	Australian Army Malaria Institute
PLANNED STUDY START	April 2001
INDICATION	Malaria prophylaxis
INVESTIGATOR	Major Scott Kitchener – Australian Army Malaria Institute
OBJECTIVES	The objective of the study is primarily to define the safety and tolerability of mefloquine under operational conditions. Secondary objectives are to assess the effectiveness of mefloquine under operational conditions.
STUDY DESIGN	Active reporting of adverse events / side effects to medication using a questionnaire system, pharmacokinetics (on a core group of one Company), log returns for compliance review and active surveillance for malaria cases.
SAMPLE SIZE	800 volunteers.
SELECTION CRITERIA	Volunteers recruited from exposed groups of troops serving in East Timor (4RAR and 2RAR Battalion group core elements).
FORMULATIONS	1. Mefloquine 250mg, second daily for 3 doses, then weekly, 2. Primaquine 15mg bd for 14 days on RTA. 3. All volunteers on primaquine continue with mefloquine weekly as per current ADF policy
ROUTE OF ADMINISTRATION	Oral
OUTCOME VARIABLES: SAFETY AND TOLERABILITY **EFFECTIVENESS**	Clinical adverse events Changes of laboratory values (haematology, biochemistry, plasma drug levels Compliance Protection from malaria infections

Overview of Study

	Screening	Loading Safety	Field Safety	Followup[1]
Study Visit	1	2	3	As required
Day	Prior to deployment D-25 (days) min	D-7	Variable ROCL	As required
Written informed consent	*			
Inclusion/exclusion criteria	*			
Physical Examination				*
Medical history/ demography	*		*	*
Medication issued	*			Supply by RAP in field conditions
Malaria blood smears / tests			*	*
Haematology/ Biochemistry			*	*
Pharmacology			*	*
Pregnancy test	*			* (if female)
Adverse event review		*	*	*
Concomitant medicine review	*	*	*	*

Notes:

1. Followup initiated by treating medical facility in cooperation with AMI Investigators once diagnosis of malaria has been made.

ROCL = relief out of country leave

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2. Adverse Experience Form

3. Severe Adverse Experience Form

1. Background

Mefloquine (MQ) is presently included as an alternative malaria chemoprophylaxis agent in the Health Policy Directive 215, however a cloud has existed over the adverse events arising. No definitive prospective study under field conditions has been conducted to determine these outcomes. The drug has been found to be as acceptable as chloroquine and proguanil (C+P - previously used by the ADF for malaria chemoprophylaxis), with better compliance though more CNS adverse events[i]. These side effects included depression, strange thoughts and altered spatial appreciation which is clearly of importance under operational conditions. Nevertheless, the finding of more adverse events with MQ is not a consistent outcome[ii] when observed among recreational tourists, though withdrawals are consistently higher than with other chemoprophylaxis agents[iii]. Australians using MQ report higher compliance though more adverse events than those using doxycycline (DX) for malaria chemoprophylaxis[iv]. These were recreational travelers with short-term use and were questioned after return from travel.

Large retrospective trials on military populations indicate MQ as well tolerated and has better compliance than C+P[v], though these trials were among Italian soldiers over relatively shorter periods (average three months) than present ADF deployments.

During the recent Tafenoquine prophylaxis trial using MQ as a control group a small group was placed on MQ unblinded. This group spent in excess of three months during the wet season in East Timor without any cases of malaria developing.

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2. Justification for Investigation

There is clear evidence of adverse events and non-compliance related to MQ in smaller studies, however, no large studies conducted on Australian soldiers or under field conditions define the adverse event profile. Mefloquine appears from the preliminary evidence available from current trials to be an effective and well accepted chemoprophylaxis for the ADF under operational conditions. The acceptance levels and effectiveness of doxycycline leave scope for improvement under these conditions.

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3. Objectives

The objective of the study is to define the adverse events of mefloquine and compare these with those of doxycycline. A secondary objective is comparing effectiveness of these preparations.

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4. Study Design

The study design is an open clinical trial. Volunteers of the core elements of the Battalion group will be given a loading dose of mefloquine followed by three weekly doses pre-deployment in accordance with HPD215. A further sub-population (Company size) will be randomly selected for more detailed investigation. The remaining non-core elements of the Battalion group will be provided conventional chemoprophylaxis in accordance with HPD215, viz. doxycycline 100mg daily.

The Company sub-group selected will undergo pharmacokinetic studies at key intervals throughout the deployment. These key intervals include following loading dose, on return from a patrol period (high workload and intense field conditions), on return from a rest period, and prior to redeployment to Australia.

All core elements of the Battalion group will be supervised using a log return system of reviewing compliance with chemoprophylaxis as recorded by responsible individual, generally the Platoon Sergeant. Questionnaires will also be delivered requesting information regarding adverse events at key intervals including following loading dose, midway through the deployment and prior to return to Australia.

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5. Study Population

The study population will include the core elements of the forward Australian Battalion groups deploying to East Timor under Operation Tanager during the period April 2001 and May 2002. The core elements of the Battalion group include Rifle Company and attachments. Headquarter elements, Administration Company and Support Company groups with other Battalion group attachments will remain on chemoprophylaxis in accordance with HPD215 and will be monitored with existing surveillance systems.

a. ***Inclusion Criteria***: To be included in the study the trial volunteer must:

i. Be male or female between 18 and 55 years of age;
ii. Be Medical Class 1 or 2; and
iii. Be willing and able to give written informed consent and comply with the study protocol.

b. ***Exclusion Criteria***: Volunteers will be ineligible for inclusion into the study if any of the following applies:

i. They are pregnant or unwilling/unable to comply with recognised contraception methods for 30 days after administration of the study drugs;
ii. They have a known hypersensitivity to any component of the study drugs;
iii. They are unwilling/unable to give blood collections required in the study;
iv. They are taking any other investigational drug during, or within 30 days, of taking the study drugs for this study.

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6. Volunteer Identification

All consenting volunteers will be issued a unique alphanumerical code consisting of a letter indicating their trial and three numbers (eg A123) in order to identify their specimens and minimize the possibility of data entry errors.

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7. Sample Size

The core elements of an ADF Battalion groups in Operation Tanager approximate 1500 in number.

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8. Risks

All volunteers will be at risk of malaria infection by the nature of the operational deployment. Estimates from historical data indicate that up to 25% of ADF personnel returning from malarious areas of East Timor are at risk of developing malaria.

All volunteers are accepting, as part of the study, the possibility of clinical events either known or unknown associated with the study medication. The primary clinical events associated with MQ include gastrointestinal disturbances and neurological manifestations.

Phlebitis following venepuncture remains a risk. Venepuncture will be necessary for post-deployment screening whether the potential volunteer chooses to be involved in the study or not. Trial venepuncture will be coordinated with this intervention.

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9. Benefits

Malaria is a very serious and debilitating disease resulting in disruption of usual activities including a significant personnel loss on operations. For the individual the prevention of malaria prevents both acute and potentially chronic morbidity. For the Battalion group, protection from malaria is a force multiplying effect.

The benefit for the individual in taking MQ rather than the conventional chemoprophylaxis is convenience in that MQ is a weekly medication and DX is daily, in addition to potentially fewer adverse events associated with DX, particularly in the field environment, the development of gastrointestinal symptoms, photosensitivity and pedal intertrigo.

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10. Quality Procedures / Assurance

a. ***Outcome Measures:*** The outcome measures are response to delivered questionnaires on adverse events and compliance, identified log returns on compliance and a positive malaria blood smear confirming clinical malaria.

b. ***Safety Parameters:*** Safety parameters established for the trial are the monitoring of:

i. Routine clinical laboratory tests (haematology and biochemistry) on a representative sample following loading dose;
ii. Adverse events as per outcomes; and
iii. Pregnancy testing

c. ***Clinical Trial Material:*** All MQ will be provided through the ADF Supply system using conventional distribution methods.

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11. Laboratory Procedures

Whole venous blood will be collected by venepuncture. Each sample will be collected in 5ml Lithium Heparin tubes, with no more than 30mls of blood being collected for this study.

Methodology for all laboratory procedures will be included in the trial SOP. Procedures will include:

a. ***Measurement of Parasitaemia*** - Thick and thin blood films for malaria will be obtained from a venous sample to confirm malaria as required by clinical examination. Blood films will be stained with Giemsa and evaluated by standard techniques. A confirmed instance of positive parasitaemia will be considered a failure of chemoprophylaxis.

b. ***Haematology*** - The following haematology tests will be performed following loading dose on a representative selection of the group, with a manual differentiation performed on abnormal findings:

i. Haemoglobin;
ii. PCV (Haematocrit);
iii. Platelets;
iv. Total White Cell Count;
v. Lymphocyte Count.

c. ***Biochemistry*** - Biochemistry will be performed following loading dose on a representative selection of the group. Investigations will include Creatinine and ALT (SGOT) analysed on site using Reflotron. Additionally, the following parameters will be analysed by AMI on frozen serum:

i. Sodium;
ii. Potassium;
iii. Albumin;
iv. Urea;
v. Total Bilirubin;
vi. Alkaline Phosphatase.

d. ***Pharmacology Venous Blood Sampling Schedule***- Venous blood samples will be collected following loading dose and at intervals throughout the deployment as outlined above.

All blood samples will be immediately stored on ice and then centrifuged at 2,000 rpm for 15 minutes. Plasma will be separated and stored at -20°C until analysed. Plasma concentrations of MQ will be measured by HPLC at AMI.

e. ***Pregnancy Testing*** - All volunteers of child bearing potential will be tested for pregnancy at screening by urine testing techniques using standardised test kits. Although the dosing period is only 14 days maximum, women who believe they have become (or think they are) pregnant or who record a positive result on urine testing will be excluded from the study.

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12. Drug Dose

The study drug will be supplied as Mefloquine 250mg tablets taken as follows:

a. Loading dose: 250 mg second daily for three doses in a week,
b. Predeployment maintenance: 250mg weekly for three weeks, and
c. Maintenance dose in AO: 250mg weekly.

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13. Drug Storage, Inventory and Log Sheets

The conventional supply system for the Battalion group will be utilised. Study drugs will be stored according to the manufacturer's recommendations at ambient temperature (not greater than 25°C). The principal investigators will keep a record of all study drugs used. The drug will be distributed to individuals weekly by Platoon NCO in accordance with Formation Routine Orders and logged. The Investigator will collect log returns weekly.

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14. *Personnel Responsibilities*

The Principal Investigators or Co-investigators shall:

a. obtain informed consent from volunteers in the study
b. issue and collect all documentation, and
c. investigate all reported adverse events.

Only clinically endorsed personnel will perform blood sampling.

Contents

15. Adverse Events

Volunteers will have a history and physical examination done whenever there are reported adverse events. All adverse events will be notified and discussed with a Principle Investigator within one week for a decision regarding continuation on MQ.

In the case of clinical malaria, full clinical records from the treatment facility will be obtained for all confirmed cases.

All deaths, potentially lethal events and hospitalisation are serious adverse events (SAE). These are to be notified to a Principle Investigator within 24 hours for continuation of the individual in the trial.

Any adverse reaction will be treated as medically indicated regardless of enrolment in the trial.

The definitions and reporting requirements for adverse events (AE) and serious adverse events (SAE) are detailed at Annex B.

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16. Withdrawal of Volunteers

Volunteers may withdraw themselves or be withdrawn from the study at any time without prejudice or compromise to appropriate treatment or chemoprophylaxis or detriment to military career. Volunteers will be withdrawn from the study if they experience significant adverse events to the study medicine, or if concomitant illness is likely to compromise their physical well being or their participation in the study. Reasons for withdrawal will be recorded in the CRF. If withdrawal is due to an Adverse Event then an Adverse Event Form will be completed.

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17. Concurrent Medication

If a volunteer develops an infection requiring treatment with antibiotics, the attending study clinician will, if possible, prescribe an antibiotic without known antimalarial action. All other concurrent medication will be recorded on the CRF.

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18. Contraception

Female volunteers determined to be non-pregnant on entry to the study will be counselled on contraception, and encouraged to continue precautions until 4 weeks after the last dose of study drug.

Contents

19. Data Management and Analysis

Data will be entered from Case Record Forms (CRF's) onto a computerised database (MS Access). At the end of the study, all data will be crosschecked against original data capture sheets. The following arrangements for data management and analysis will be applied:

a. ***Data Storage and Retrieval*** - CRFs provided by AMI will be completed for each volunteer and will include the volunteer Consent Form and Adverse Event Form. Completed original CRFs, signed by the investigator, will be retained by AMI. CRF data will be edited where necessary with the agreement of the investigator to ensure completeness and consistency. The investigators will endeavour to ensure all data is complete, with phone followup initiated if indicated.

b. ***Effectiveness Analysis*** - The effectiveness end point will be the proportion of volunteers developing patent parasitaemia during the twelve (12) months after redeployment to Australia.

c. ***Safety Analysis*** - The study population will serve as the denominator for tolerability. Incidence of all adverse events will be determined, reported and tabulated. Adverse events will be recorded along with the event's intensity, seriousness, investigator-attributed causality, onset and cessation. Clinical laboratory values 1.5 times outside the normal range will be flagged.

d. ***Blood Drug Analysis*** - Plasma concentrations of MQ will be determined and related to prophylaxis failure rates.

e. ***Use of data:*** A copy of the clinical record forms, the personal medication diaries, drug control logs, adverse event forms and the original laboratory record sheets will be kept on file at AMI for a period of not less than 7 years. It is expected that these data will be reported in both scientific journals and at scientific meetings, and may be submitted to governmental medication regulatory authorities for review. Confidentiality of volunteers will be maintained. Volunteers will be informed in general terms of the results as soon as practical. All publications resulting from this study will be cleared through the Australian Defence Force.

Contents

20. Volunteer Consent

Volunteers will be recruited using non-coercive means. No inducement will be offered. The investigator is responsible for ensuring the volunteer understands the nature and purpose of the study. Volunteers who are invited to take part in a clinical trial are entitled to make a choice based on full and complete information presented in a manner that is understandable and ethnically appropriate. The Information and Consent Form (Annex A) is designed to assure the protection of the volunteer's rights.

The investigator will inform the volunteer of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it may entail. In addition, a copy of the Information and Consent Form will be provided which outlines this detail. The volunteer will be given every opportunity to clarify any points that he/she may not understand and to seek additional information. The volunteer will retain the right to withdraw from the study at any time without penalty. The investigator is responsible for ensuring that the volunteer has full knowledge and for obtaining the volunteer's freely given informed consent.

The informed consent will be recorded in writing with the investigator and the volunteer both signing and dating the Information and Consent Form.

The signed Information and Consent Form will be retained with the original CRF.

Contents

References:

1 IND #38503 (Etaquine), Surgeon General, U.S Army, Section 8.2.1.1.

2 IND #38503 (Etaquine), Surgeon General, U.S Army, Section 8.2.1.1.

3 Investigator's Brochure (1997 revised), WR 238,605, U.S Army, Office of the Surgeon General.

[redacted]

Version 1.6

CONSENT FORM PROTOCOL

Regimental Number: _____ Volunteers Initials: _____

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

As you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to observe a less commonly used drug, Mefloquine, under field conditions.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent malaria infection from overseas deployments in the future.

WHAT IS THE MEDICINE?

Mefloquine one tablet weekly in the AO and for two weeks after return to Australia. You will initially be given at least six tablets prior to deployment. The usual medicine is Doxycycline one tablet daily through deployment and for two weeks after. You are initially given two tablets prior to deployment.

WHAT IS THE STUDY?

The study is looking at how satisfactory Mefloquine is under field conditions. You will be provided with one tablet weekly through the standard supply system in the field. Supply and use of each tablet weekly will be recorded. You will be asked immediately prior to deployment, several times throughout the deployment and on return to Australia, whether you had any problems you thought were due to the antimalarial tablet. A small group will be (randomly) selected to additionally give blood on two occasions during deployment.

LENGTH OF THE STUDY

The study will begin 4 weeks prior to your redeployment and will be continued until 12 months after your deployment is completed. Your only involvement after redeployment will be if you develop malaria.

STUDY TESTS

All volunteers will be asked to complete a questionnaire immediately prior to deployment, during deployment and prior to returning to Australia. As the investigators are looking at baseline drug levels in blood, and measuring biochemistry and haematology levels to monitor safety, a small group will be requested to donate two samples of blood from your arm. The amount of blood collected for the study amounts to no more than about 20mls, or the equivalent of 4 teaspoons.

RISKS / DISCOMFORTS

There may be some bruising with blood taken from the veins in your arm.

When Mefloquine is used to treat people ill with malaria especially children less than 45kg, side effects have been reported and recorded. These include over 1% reporting sleepiness, insomnia, abnormal dreams, dizziness, loss of balance, headache, nausea and vomiting, diarrhoea or abdominal pain. Less than 1% had episodes of anxiety, confusion, depression, restlessness, forgetfulness, hallucinations and psychotic or paranoid reactions, nerve damage, convulsions, tiredness, fever, chills, loss of appetite, rash, itchiness, hair loss, visual disturbances, muscle weakness, cramps, muscle and joint pain, ringing in the ears, hearing disorders, low or high blood pressure, fainting, palpitations, extra heart beats, slow heart rate, or lowering of the clotting cells in the blood, or white cells (used for fighting infection) and fewer than 0.1% had brain damage, psychotic events, severe hypersensitivity reactions in the skin and heart block.

Overall, Mefloquine has fewer side effects than Doxycycline in trials among travellers (including Australians).

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have had any anxiety attacks or serious depression in the past you also may not be able to use Mefloquine. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

CONFIDENTIALITY

In all reports only a number will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

Mefloquine is authorised to use as an antimalarial by civilian authorities in Australia in addition to being directed for use as an alternative to Doxycycline by the Director General, Defence Health Services in HPD215. This trial has also been approved by the Australian Defence Medical Ethics Committee.

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the RMO or AMI (0407 150384).

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the RMO or study investigators. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP2-7-66
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3925

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal antimalarial course of Doxycycline daily and an eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____ **Date:**_____

INVESTIGATOR'S SIGNATURE _____ **Date:**_____

ANNEX B to
Protocol MQ001

ADVERSE EXPERIENCES GUIDELINES

Adverse Experiences

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out below.

Eliciting and Documenting Adverse Experiences

It is the responsibility of the investigator to document all adverse experiences which occur during the investigation. An adverse experience includes any noxious, pathological or unintended change in anatomical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical study whether associated with the study drug or placebo and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the case record under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences.

In the case of studies involving a marketed drug in an established indication, an adverse experience includes significant failure of the expected pharmacological or biological action.

All adverse experiences occurring after the start of the study must be reported. Subject entry into the study is defined as the time at which informed consent is obtained (This must be before any protocol-specific diagnostic procedures or interventions) All subsequent adverse experiences, whether no drug (ie. during reference 'run-in' or 'wash-out' period) or when active drug or placebo is being administered, must be reported REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.

At each visit /assessment, adverse experiences will.be evaluated by the investigator. Adverse experiences not previously documented in the study will be recorded in the adverse experience section of the subject's case record form. The nature of each experience date and time (where appropriate) of onset, duration, severity and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the case record form.

Adverse experiences already documented in the CRF ie. at a previous assessment and designated as `continuing' should be reviewed. If these have resolved, the documentation in the CRF should be completed. NB. If an adverse experience changes in frequency or severity during a study period, a new record of the experience will be started.

Ask the subject or the subjects parent or legal guardian a non-leading question such as:

> "Do you feel different in any way since starting the new treatment/the last assessment?"

Assessment of Severity

Maximum intensity should be assigned to one of the following categories:

Mild: For example, an adverse experience which is easily tolerated by the subject, causing minimal discomfort not interfering with everyday activities.

Moderate: For example, an adverse experience that is sufficiently discomforting to interfere with normal everyday activities.

Severe: For example, an adverse experience which prevents normal everyday activities

Assessment of Causality

Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: ***not related***, ***unlikely***, ***suspected*** (reasonable possibility), ***probable.***

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, eg. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The experience having often been reported in literature for similar drug as drug related eg. skin rashes, blood dyscrasia
- The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

Following-up of Adverse Experiences

Investigators should follow-up subjects with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the subject's subsequent course must be submitted to the clinical study monitor.

Serious Adverse Experiences

Definition of Serious Adverse Experiences

A serious adverse experience is any event which is fatal, life threatening, disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event.

Life threatening – definition:

An adverse experience is life threatening if the subject was at immediate risk of death from the event as it occurred; ie. It does not include a reaction that if it had occurred in a more serious form might have caused death For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Disability /incapacitating definition:

An adverse experience is incapacitating or disabling if the experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions

Reporting Serious Adverse Experiences

Any serious adverse experiences that occur during the clinical study whether or not related to the study drug, must be reported by the investigator to the study monitor (by telephone within 24hrs).

All serious adverse experiences must be reported by telephone within 24hrs to the study monitor or Principle Investigator.

Name: Major Scott Kitchener

Telephone: s47F [redacted]

The telephone report should be followed by full written summary detailing relevant aspects of the adverse experiences in question. Where applicable information from relevant hospital case records and autopsy reports should be obtained.

Instances of death cancer or congenital abnormality if brought to the attention of the investigator *AT ANY TIME* after the cessation of study medication and linked by the investigator to a previous clinical trial, should be reported to the study monitor.

Overdose

Any instance of overdose (suspected or confirmed) must be communicated the Principle Investigator within 24 hours and be fully documented as a serious adverse experience. Details of any signs of symptoms and their management should be recorded including details of any antidotes administered.

Pregnancy

Subjects who become pregnant during the dosing periods (clearing dosing and prophylactic dosing) should discontinue dosing immediately. However subjects who become pregnant during the followup phase of the study should continued to be monitored as originally scheduled.

Subjects should be instructed to notify the investigator if it is determined after the completion of the study that they became pregnant either during the treatment or prophylaxis-dosing phase of the study or during the followup period.

Whenever possible a pregnancy should be followed up to term, any premature terminations reported, and the status of the mother and child should be reported after delivery.

Case Record Form – MQ001

Enrolment:

DEMOGRAPHIC DATA:

Volunteer No: _____ Volunteer Initials: _____
Corps: _____ Age: _____ (yrs)
Unit: _____ Sex: M F (please circle)
Weight: _____ (kgs) Height: _____ (cm)
Date admitted to the Study: _____ (dd/mm/yy)

ADMISSION CRITERIA:

The following questions must all be answered "No" for a volunteer to be eligible for study entry:

	Please Circle One	
Does the volunteer have any significant illness?	Y	N
Is the volunteer Medically Fit?	Y	N
Is the female volunteer using an established method of contraception	Y	N
Has the volunteer any known reactions to any of the study compounds?	Y	N
Is the volunteer ***unwilling*** to give blood smears and blood samples?	Y	N
Has written informed consent been obtained	Y	N

If female, the volunteer must have had a negative pregnancy test and have received counselling on contraception:

Result of pregnancy test: Pos / Neg Date: _____ (dd/mm/yy)

Contraceptive counselling: Yes / No Date: _____ (dd/mm/yy)

Explanation for any deviation from the appropriate responses:

(An explanation of any "N" response is to be given **and** the volunteer is to be excluded from the study.)

_____
_____
_____
_____
_____
_____

[redacted]
Version 1.6

Laboratory Test Results – MQ001

Vol ID:	Vol Init:

Haematology:

Date (dd/mm/yy)		
Schedule	Screening	Follow up
RBC (/pl)		
Haemoglobin(g/dl)		
Haematocrit(%)		
WCC(/nl)		
Neutrophils (%)		
Lymphocyes(%)		
Monocytes(%)		
Basophils(%)		
Eosinophils(%)		
Platelete Count(/nl)		

Biochemistry:

Date (dd/mm/yy)		
Schedule	Screening	Follow up
Total Bilirubin		
AST/SGOT		
ALT/SGPT		
GGT		
Glucose		
BUN		
Albumin		

If female - Pregnancy Test Results

Date (dd/mm/yy)	
Schedule	Screening

Record of Parasitaemia

Date (dd/mm/yy)			
Schedule	First Episode	Second Episode	Third Episode
Type / Count			

Exclusions from the study:

- **Haematological and biochemistry parameters greater than 1.5 times normal.**
- **Positive pregnancy test in women volunteers.**

Vol ID:	Vol Init:

Compliance (tick if logged return) **Loading dose date:**
Eradication dose date:

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
	14	15	16	17	18	19	20	21	22	23	24	25	26

Record reported adverse events as:
1. Mild (present but didn't impair completion of duties)
2. Moderate (Some impairment of duties), or
3. Severe (Prevent completion of duties)

Symptoms	Following loading	Field evaluation	On extraction
Sleep problems (specify)			
Balance problems (specify)			
Headache			
Nausea			
Vomiting			
Diarrhoea			
Abdominal pain			
Anxiety			
Confusion			
Memory loss			
Tiredness			
Muscle aches			
Joint aches			
Hallucinations			
Hearing problems			
Skin reaction (specify)			
Other			

MQ blood levels

Date				
MQ level				

[redacted] – Confidence

[redacted]

Name: _____ **Regimental Number** _____

Date of presentation: / /
Following Loading dose ☐ (tick one)
Field Evaluation ☐
RTA ☐

MQ001

Record reported adverse events as:

1. Mild (present but didn't impair completion of duties)
2. Moderate (some impairment of duties), or
3. Severe (prevent completion of duties

All reported symptoms must be rated: 1. 2. OR 3.

Return form with PM105 to RMO 4RAR

Symptoms	Rating	Comment
Nausea		
Vomiting		
Diarrhoea		
Abdominal pain		
Headache		
Tiredness		
Anxiety		
Confusion		
Memory Loss		
Hallucinations		
Sleep problems		
Muscle aches		
Joint aches		
Balance problems		
Skin Reaction		
Hearing Problems		
Comment on activity status		

Record all clinical history on PM105

PI contacted Yes / No

Bloods Taken Yes / No – Comment _____

[redacted] – Confidence

References

Contents

[i] Petersen E, Ronne T, Ronn A, Bygbjerg I, Larsen SO. Reported side effects to chloroquine, chloroquine plus proguanil, and mefloquine as chemoprophylaxis against malaria in Danish travelers. *J Travel Med* 2000 Mar-Apr;7(2):79-84.

[ii] Huzly D, Schonfeld C, Beuerle W, Bienzle U. Malaria Chemoprophylaxis in German Tourists: A Prospective Study on Compliance and Adverse Reactions. *J Travel Med* 1996 Sep 1;3(3):148-155.

[iii] Croft AM, Garner P. Mefloquine for preventing malaria in non-immune adult travellers. *Cochrane Database Syst Rev* 2000;(3):CD000138.

[iv] Phillips MA, Kass RB. User Acceptability Patterns for Mefloquine and Doxycycline Malaria Chemoprophylaxis. *J Travel Med* 1996 Mar 1;3(1):40-45.

[v] Peragallo MS, Sabatinelli G, Sarnicola G. Compliance and tolerability of mefloquine and chloroquine plus proguanil for long-term malaria chemoprophylaxis in groups at particular risk (the military). *Trans R Soc Trop Med Hyg* 1999 Jan-Feb;93(1):73-7.

DEFENCE PERSONNEL EXECUTIVE
DEFENCE HEALTH SERVICE BRANCH
CP2-7-66 Department of Defence CANBERRA ACT 2600

FOLIO
IC

2001/5344
ADMEC 249/01
DHSB 453 /2001

Major S. Kitchener
Officer In Charge Clinical Trials
Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Major Kitchener

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) – PROTOCOL 249/01: EVALUATION OF MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS

1. Thankyou for submitting for protocol modification dated 30th March 2001, version 1.5.. The proposed amendments were considered by The Australian Defence Medical Ethics Committee on Monday the 23rd April 2001.

2. ADMEC has considered your protocol and has approved the amendment. As such the protocol is now cleared to proceed with these modifications in place.

3. Please contact me if you would like to discuss this further.

Yours sincerely,

s22 [redacted]

R.A. LANDY
Major
Executive Secretary
Australian Defence Medical Ethics Committee

26 April, 2001

Department of Defence

MINUTE

FOLIO 9

548-7-45
AMI 49/01

Executive Secretary (Attention: Australian Defence Force Medical ethics Committee) (CP2-7-66)

AMENDMENTS TO MEFLOQUINE TRIAL ADMEC PROTOCOL 249/01

1. Attached is the final version (1.5) of the Mefloquine trial protocol with final amendments for consideration by ADMEC. Amendments include:

   a. Addition of CAPT A Jensen as an Investigator (page 1),

   b. Use of a sample (n=200) of 4RAR for post-loading dose biology and pharmacology assessment due to operational restrictions (page 3),

   c. Biological testing (Haematology and Biochemistry) in addition to pharmacological testing during deployment for a sample (n = one Rifle Company, approximately 100 pers.) of the group (page 3), and

   d. Addition of an Adverse Event Form (Enclosure 2).

2. I trust these have not significantly altered the intent of previous approval from ADMEC.

3. As an interim update, approximately 600 volunteers were recruited and have begun the loading dose of Mefloquine. Every volunteer will be reviewed for adverse events during DFSU training prior to deployment as directed by protocol. To date, no serious adverse events have been recorded.

S J KITCHENER
MAJ
OC CLINICAL FIELD

ARMY MALARIA INSTITUTE

30 Mar 01

CLINICAL TRIAL PROTOCOL

PROTOCOL NO. MQ001
Version 1.5 (ADMEC amended)

PROTOCOL TITLE:

Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers

Principal Investigator:

MAJ Scott Kitchener MBBS MPH
OC Clinical Field AMI

CAPT John Cunningham BSc (Hon) MBBS
RMO 4RAR

Co-Investigators:

LTCOL Mike Edstein PhD
Deputy Director AMI

LTCOL Peter Nasveld MBBS BSc Med (Hons)
RO Clinical Studies AMI

CAPT Anne Jensen
RO Clinical Studies AMI

LT Michael Reid
RO Clinical Studies AMI

Study Coordinator:

Professor Karl Rieckmann MD
Director AMI

Summary of Protocol:

TITLE	Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers
SPONSOR	Australian Army Malaria Institute
PLANNED STUDY START	April 2001
INDICATION	Malaria prophylaxis
INVESTIGATOR	Major Scott Kitchener – Australian Army Malaria Institute
OBJECTIVES	The objective of the study is primarily to define the safety and tolerability of mefloquine under operational conditions. Secondary objectives are to assess the effectiveness of mefloquine under operational conditions.
STUDY DESIGN	Active reporting of adverse events / side effects to medication using a questionnaire system, pharmacokinetics (on a core group of one Company), log returns for compliance review and active surveillance for malaria cases.
SAMPLE SIZE	800 volunteers.
SELECTION CRITERIA	Volunteers recruited from exposed groups of troops serving in East Timor (4RAR and 2RAR Battalion group core elements).
FORMULATIONS	1. Mefloquine 250mg, second daily for 3 doses, then weekly, 2. Primaquine 15mg bd for 14 days on RTA. 3. All volunteers on primaquine continue with mefloquine weekly as per current ADF policy
ROUTE OF ADMINISTRATION	Oral
OUTCOME VARIABLES: SAFETY AND TOLERABILITY **EFFECTIVENESS**	Clinical adverse events Changes of laboratory values (haematology, biochemistry, plasma drug levels Compliance Protection from malaria infections

Overview of Study - Protocol No: MQ001

	Screening	Loading Safety	Field Safety	Followup[1]
Study Visit	1	2	3	As required
Day	Prior to deployment D-25 (days)	D-7	Variable	As required
Written informed consent	*			
Inclusion/exclusion criteria	*			
Physical Examination				*
Medical history/ demography	*		*	*
Medication issued	*			Supply by RAP in field conditions
Malaria blood smears				*
Haematology/ Biochemistry		* (sample)	* (sample)	*
Pharmacology		* (sample)	* (sample)	*
Pregnancy test	*			* (if female)
Adverse event review		*	*	*
Concomitant medicine review	*	*	*	*

Notes:

1. Followup initiated by treating medical facility in cooperation with AMI Investigators once diagnosis of malaria has been made.

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17. Concurrent Medication

18. Contraception

19. Data Management and Analysis
    a. Data Storage and Retrieval
    b. Efficacy Analysis
    c. Safety Analysis
    d. Blood Drug Analysis
    e. Use of data

20. Volunteer Consent

REFERENCES

ANNEXES:

A. Consent Form

B. Adverse Experience Guidelines

ENCLOSURES:

1. Case Record Form

2. Adverse Experience Form

3. Severe Adverse Experience Form

1. Background

Mefloquine (MQ) is presently included as an alternative malaria chemoprophylaxis agent in the Health Policy Directive 215, however a cloud has existed over the adverse events arising. No definitive prospective study under field conditions has been conducted to determine these outcomes. The drug has been found to be as acceptable as chloroquine and proguanil (C+P - previously used by the ADF for malaria chemoprophylaxis), with better compliance though more CNS adverse events[i]. These side effects included depression, strange thoughts and altered spatial appreciation which clearly of importance under operational conditions. Nevertheless, the finding of more adverse events with MQ is not a consistent outcome[ii] when observed among recreational tourists, though withdrawals are consistently higher than with other chemoprophylaxis agents[iii]. Australians using MQ report higher compliance though more adverse events than those using doxycycline (DX) for malaria chemoprophylaxis[iv]. These were recreational travelers with short-term use and were questioned after return from travel.

Large retrospective trials on military populations indicate MQ as well tolerated and has better compliance than C+P[v], though these trials were among Italian soldiers over relatively shorter periods (average three months) than present ADF deployments.

During the recent Tafenoquine prophylaxis trial using MQ as a control group a small group was placed on MQ unblinded. This group spent in excess of three months during the wet season in East Timor without any cases of malaria developing.

Contents

2. Justification for Investigation

There is clear evidence of adverse events and non-compliance related to MQ in smaller studies, however, no large studies conducted on Australian soldiers or under field conditions define the adverse event profile. Mefloquine appears from the preliminary evidence available from current trials to be an effective and well accepted chemoprophylaxis for the ADF under operational conditions. The acceptance levels and effectiveness of doxycycline leave scope for improvement under these conditions.

Contents

3. Objectives

The objective of the study is to define the adverse events of mefloquine and compare these with those of doxycycline. A secondary objective is comparing effectiveness of these preparations.

Contents

4. Study Design

The study design is an open clinical trial. Volunteers of the core elements of the Battalion group will be given a loading dose of mefloquine followed by three weekly doses pre-deployment in accordance with HPD215. A further sub-population (Company size) will be randomly selected for more detailed investigation. The remaining non-core elements of the Battalion group will be provided conventional chemoprophylaxis in accordance with HPD215, viz. doxycycline 100mg daily.

The Company sub-group selected will undergo pharmacokinetic studies at key intervals throughout the deployment. These key intervals include following loading dose, on return from a patrol period (high workload and intense field conditions), on return from a rest period, and prior to redeployment to Australia.

All core elements of the Battalion group will be supervised using a log return system of reviewing compliance with chemoprophylaxis as recorded by responsible individual, generally the Platoon Sergeant. Questionnaires will also be delivered requesting information regarding adverse events at key intervals including following loading dose, midway through the deployment and prior to return to Australia.

Contents

5. Study Population

The study population will include the core elements of the forward Australian Battalion groups deploying to East Timor under Operation Tanager during the period April 2001 and May 2002. The core elements of the Battalion group include Rifle Company and attachments. Headquarter elements, Administration Company and Support Company groups with other Battalion group attachments will remain on chemoprophylaxis in accordance with HPD215 and will be monitored with existing surveillance systems.

a. ***Inclusion Criteria***: To be included in the study the trial volunteer must:

i. Be male or female between 18 and 55 years of age;
ii. Be Medical Class 1 or 2; and
iii. Be willing and able to give written informed consent and comply with the study protocol.

b. ***Exclusion Criteria***: Volunteers will be ineligible for inclusion into the study if any of the following applies:

i. They are pregnant or unwilling/unable to comply with recognised contraception methods for 30 days after administration of the study drugs;
ii. They have a known hypersensitivity to any component of the study drugs;
iii. They are unwilling/unable to give blood collections required in the study;
iv. They are taking any other investigational drug during, or within 30 days, of taking the study drugs for this study.

Contents

6. Volunteer Identification

All consenting volunteers will be issued a unique alphanumerical code consisting of a letter indicating their trial and three numbers (eg A123) in order to identify their specimens and minimize the possibility of data entry errors.

Contents

7. Sample Size

The core elements of an ADF Battalion group in Operation Tanager approximate 400 in number. A sub-group of 120 individuals will be selected by Company group from each Battalion group to undertake the pharmacokinetic studies.

Contents

8. Risks

All volunteers will be at risk of malaria infection by the nature of the operational deployment. Estimates from historical data indicate that up to 25% of ADF personnel returning from malarious areas of East Timor are at risk of developing malaria.

All volunteers are accepting, as part of the study, the possibility of clinical events either known or unknown associated with the study medication. The primary clinical events associated with MQ include gastrointestinal disturbances and neurological manifestations.

Phlebitis following venepuncture remains a risk. Venepuncture will be necessary for post-deployment screening whether the potential volunteer chooses to be involved in the study or not. Trial venepuncture will be coordinated with this intervention.

Contents

9. Benefits

Malaria is a very serious and debilitating disease resulting in disruption of usual activities including a significant personnel loss on operations. For the individual the prevention of malaria prevents both acute and potentially chronic morbidity. For the Battalion group, protection from malaria is a force multiplying effect.

The benefit for the individual in taking MQ rather than the conventional chemoprophylaxis is convenience in that MQ is a weekly medication and DX is daily, in addition to potentially fewer adverse events associated with DX, particularly in the field environment, the development of gastrointestinal symptoms, photosensitivity and pedal intertrigo.

Contents

10. Quality Procedures / Assurance

a. ***Outcome Measures:*** The outcome measures are response to delivered questionnaires on adverse events and compliance, identified log returns on compliance and a positive malaria blood smear confirming clinical malaria.

b. ***Safety Parameters:*** Safety parameters established for the trial are the monitoring of:

i. Routine clinical laboratory tests (haematology and biochemistry) on a representative sample following loading dose;
ii. Adverse events as per outcomes; and
iii. Pregnancy testing

c. ***Clinical Trial Material:*** All MQ will be provided through the ADF Supply system using conventional distribution methods.

Contents

11. Laboratory Procedures

Whole venous blood will be collected by venepuncture. Each sample will be collected in 5ml Lithium Heparin tubes, with no more than 30mls of blood being collected for this study.

Methodology for all laboratory procedures will be included in the trial SOP. Procedures will include:

a. ***Measurement of Parasitaemia*** - Thick and thin blood films for malaria will be obtained from a venous sample to confirm malaria as required by clinical examination. Blood films will be stained with Giemsa and evaluated by standard techniques. A confirmed instance of positive parasitaemia will be considered a failure of chemoprophylaxis.

b. ***Haematology*** - The following haematology tests will be performed following loading does on a representative selection of the group, with a manual differentiation performed on abnormal findings:

i. Haemoglobin;
ii. PCV (Haematocrit);
iii. Platelets;
iv. Total White Cell Count;
v. Lymphocyte Count.

c. ***Biochemistry*** - Biochemistry will be performed following loading does on a representative selection of the group. Investigations will include Creatinine and ALT (SGOT) analysed on site using Reflotron. Additionally, the following parameters will be analysed by AMI on frozen serum:

i. Sodium;
ii. Potassium;
iii. Albumin;
iv. Urea;
v. Total Bilirubin;
vi. Alkaline Phosphatase.

d. ***Pharmacology Venous Blood Sampling Schedule-*** Venous blood samples will be collected following loading dose and at intervals throughout the deployment as outlined above.

All blood samples will be immediately stored on ice and then centrifuged at 2,000 rpm for 15 minutes. Plasma will be separated and stored at -20°C until analysed. Plasma concentrations of MQ will be measured by HPLC at AMI.

e. ***Pregnancy Testing*** - All volunteers of child bearing potential will be tested for pregnancy at screening by urine testing techniques using standardised test kits. Although the dosing period is only 14 days maximum, women who believe they have become (or think they are) pregnant or who record a positive result on urine testing will be excluded from the study.

Contents

12. Drug Dose

The study drug will be supplied as Mefloquine 250mg tablets taken as follows:

a. Loading dose: 250 mg second daily for three doses in a week,
b. Predeployment maintenance: 250mg weekly for three weeks, and
c. Maintenance dose in AO: 250mg weekly.

Contents

13. Drug Storage, Inventory and Log Sheets

The conventional supply system for the Battalion group will be utilised. Study drugs will be stored according to the manufacturer's recommendations at ambient temperature (not greater than 25°C). The principal investigators will keep a record of all study drugs used. The drug will be distributed to individuals weekly by Platoon NCO in accordance with Formation Routine Orders and logged. The Investigator will collect log returns weekly.

Contents

14. Personnel Responsibilities

The Principal Investigators or Co-investigators shall:

a. obtain informed consent from volunteers in the study
b. issue and collect all documentation, and
c. investigate all reported adverse events.

Only clinically endorsed personnel will perform blood sampling.

Contents

15. Adverse Events

Volunteers will have a history and physical examination done whenever there are reported adverse events. All adverse events will be notified and discussed with a Principle Investigator within one week for a decision regarding continuation on MQ.

In the case of clinical malaria, full clinical records from the treatment facility will be obtained for all confirmed cases.

All deaths, potentially lethal events and hospitalisation are serious adverse events (SAE). These are to be notified to a Principle Investigator within 24 hours for continuation of the individual in the trial.

Any adverse reaction will be treated as medically indicated regardless of enrolment in the trial.

The definitions and reporting requirements for adverse events (AE) and serious adverse events (SAE) are detailed at Annex B.

Contents

16. Withdrawal of Volunteers

Volunteers may withdraw themselves or be withdrawn from the study at any time without prejudice or compromise to appropriate treatment or chemoprophylaxis or detriment to military career. Volunteers will be withdrawn from the study if they experience significant adverse events to the study medicine, or if concomitant illness is likely to compromise their physical well being or their participation in the study. Reasons for withdrawal will be recorded in the CRF. If withdrawal is due to an Adverse Event then an Adverse Event Form will be completed.

Contents

17. Concurrent Medication

If a volunteer develops an infection requiring treatment with antibiotics, the attending study clinician will, if possible, prescribe an antibiotic without known antimalarial action. All other concurrent medication will be recorded on the CRF.

Contents

18. Contraception

Female volunteers determined to be non-pregnant on entry to the study will be counselled on contraception, and encouraged to continue precautions until 4 weeks after the last dose of study drug.

Contents

19. Data Management and Analysis

Data will be entered from Case Record Forms (CRF's) onto a computerised database (MS Access). At the end of the study, all data will be crosschecked against original data capture sheets. The following arrangements for data management and analysis will be applied:

a. ***Data Storage and Retrieval*** - CRFs provided by AMI will be completed for each volunteer and will include the volunteer Consent Form and Adverse Event Form. Completed original CRFs, signed by the investigator, will be retained by AMI. CRF data will be edited where necessary with the agreement of the investigator to ensure completeness and consistency. The investigators will endeavour to ensure all data is complete, with phone followup initiated if indicated.

b. ***Effectiveness Analysis*** - The effectiveness end point will be the proportion of volunteers developing patent parasitaemia during the twelve (12) months after redeployment to Australia.

c. ***Safety Analysis*** - The study population will serve as the denominator for tolerability. Incidence of all adverse events will be determined, reported and tabulated. Adverse events will be recorded along with the event's intensity, seriousness, investigator-attributed causality, onset and cessation. Clinical laboratory values 1.5 times outside the normal range will be flagged.

d. ***Blood Drug Analysis*** - Plasma concentrations of MQ will be determined and related to prophylaxis failure rates.

e. ***Use of data:*** A copy of the clinical record forms, the personal medication diaries, drug control logs, adverse event forms and the original laboratory record sheets will be kept on file at AMI for a period of not less than 7 years. It is expected that these data will be reported in both scientific journals and at scientific meetings, and may be submitted to governmental medication regulatory authorities for review. Confidentiality of volunteers will be maintained. Volunteers will be informed in general terms of the results as soon as practical. All publications resulting from this study will be cleared through the Australian Defence Force.

Contents

20. Volunteer Consent

Volunteers will be recruited using non-coercive means. No inducement will be offered. The investigator is responsible for ensuring the volunteer understands the nature and purpose of the study. Volunteers who are invited to take part in a clinical trial are entitled to make a choice based on full and complete information presented in a manner that is understandable and ethnically appropriate. The Information and Consent Form (Annex A) is designed to assure the protection of the volunteer's rights.

The investigator will inform the volunteer of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it may entail. In addition, a copy of the Information and Consent Form will be provided which outlines this detail. The volunteer will be given every opportunity to clarify any points that he/she may not understand and to seek additional information. The volunteer will retain the right to withdraw from the study at any time without penalty. The investigator is responsible for ensuring that the volunteer has full knowledge and for obtaining the volunteer's freely given informed consent.

The informed consent will be recorded in writing with the investigator and the volunteer both signing and dating the Information and Consent Form.

The signed Information and Consent Form will be retained with the original CRF.

Contents

References:

1 IND #38503 (Etaquine), Surgeon General, U.S Army, Section 8.2.1.1.

2 IND #38503 (Etaquine), Surgeon General, U.S Army, Section 8.2.1.1.

3 Investigator's Brochure (1997 revised). WR 238,605, U.S Army, Office of the Surgeon General.

CONSENT FORM PROTOCOL

Regimental Number: ___ ___ ___ ___ ___ ___ Volunteers Initials: ___ ___

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

As you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to observe a less commonly used drug, Mefloquine, under field conditions.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent malaria infection from overseas deployments in the future.

WHAT IS THE MEDICINE?

Mefloquine one tablet weekly in the AO and for two weeks after return to Australia. You will initially be given at least six tablets prior to deployment. The usual medicine is Doxycycline one tablet daily through deployment and for two weeks after. You are initially given two tablets prior to deployment.

WHAT IS THE STUDY?

The study is looking at how satisfactory Mefloquine is under field conditions. You will be provided with one tablet weekly through the standard supply system in the field. Supply and use of each tablet weekly will be recorded. You will be asked immediately prior to deployment, several times throughout the deployment and on return to Australia, whether you had any problems you thought were due to the antimalarial tablet. A small group will be (randomly) selected to additionally give blood on two occasions during deployment.

LENGTH OF THE STUDY

The study will begin 4 weeks prior to your redeployment and will be continued until 12 months after your deployment is completed. Your only involvement after redeployment will be if you develop malaria.

STUDY TESTS

All volunteers will be asked to complete a questionnaire immediately prior to deployment, during deployment and prior to returning to Australia. As the investigators are looking at baseline drug levels in blood, and measuring biochemistry and haematology levels to monitor safety, a small group will be requested to donate two samples of blood from your arm. The amount of blood collected for the study amounts to no more than about 20mls, or the equivalent of 4 teaspoons.

RISKS / DISCOMFORTS

There may be some bruising with blood taken from the veins in your arm.

When Mefloquine is used to treat people ill with malaria especially children less than 45kg, side effects have been reported and recorded. These include over 1% reporting sleepiness, insomnia, abnormal dreams, dizziness, loss of balance, headache, nausea and vomiting, diarrhoea or abdominal pain. Less than 1% had episodes of anxiety, confusion, depression, restlessness, forgetfulness, hallucinations and psychotic or paranoid reactions, nerve damage, convulsions, tiredness, fever, chills, loss of appetite, rash, itchiness, hair loss, visual disturbances, muscle weakness, cramps, muscle and joint pain, ringing in the ears, hearing disorders, low or high blood pressure, fainting, palpitations, extra heart beats, slow heart rate, or lowering of the clotting cells in the blood, or white cells (used for fighting infection) and fewer than 0.1% had brain damage, psychotic events, severe hypersensitivity reactions in the skin and heart block.

Overall, Mefloquine has fewer side effects than Doxycycline in trials among travellers (including Australians).

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have had any anxiety attacks or serious depression in the past you also may not be able to use Mefloquine. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer

CONFIDENTIALITY

In all reports only a number will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

Mefloquine is authorised to use as an antimalarial by civilian authorities in Australia in addition to being directed for use as an alternative to Doxycycline by the Director General, Defence Health Services in HPD215. This trial has also been approved by the Australian Defence Medical Ethics Committee.

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the RMO or AMI (0407 150384).

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the RMO or study investigators. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP2-7-66
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3925

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal antimalarial course of Doxycycline daily and an eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____ **Date:**_____

INVESTIGATOR'S SIGNATURE _____ **Date:**_____

ANNEX B to
Protocol MQ001

ADVERSE EXPERIENCES GUIDELINES

Adverse Experiences

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out below.

Eliciting and Documenting Adverse Experiences

It is the responsibility of the investigator to document all adverse experiences which occur during the investigation. An adverse experience include any noxious, pathological or unintended change in anatomical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of thew clinical study whether associated with the study drug or placebo and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the case record under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences.

In the case of studies involving a marketed drug in an established indication, an adverse experience includes significant failure of the expected pharmacological or biological action.

All adverse experiences occurring after the start of the study must be reported. Subject entry into the study is defined as the time at which informed consent is obtained (This must be before any protocol-specific diagnostic procedures or interventions) All subsequent adverse experiences, whether no drug (ie. during reference 'run-in' or 'wash-out' period) or when active drug or placebo is being administered, must be reported REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.

At each visit /assessment, adverse experiences will.be evaluated by the investigator. Adverse experiences not previously documented in the study will be recorded in the adverse experience section of the subject's case record form. The nature of each experience date and time (where appropriate) of onset, duration, severity and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the case record form.

Adverse experiences already documented in the CRF ie. at a previous assessment and designated as 'continuing' should be reviewed. If these have resolved, the documentation in the CRF should be completed. NB. If an adverse experience changes in frequency or severity during a study period, a new record of the experience will be started.

Ask the subject or the subjects parent or legal guardian a non-leading question such as:

"Do you feel different in any way since starting the new treatment/the last assessment?"

Assessment of Severity

Maximum intensity should be assigned to one of the following categories:

Mild: For example, an adverse experience which is easily tolerated by the subject, causing minimal discomfort not interfering with everyday activities.

Moderate: For example, an adverse experience that is sufficiently discomforting to interfere with normal everyday activities.

Severe: For example, an adverse experience which prevents normal everyday activities

Assessment of Causality

Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: ***not related, unlikely, suspected*** (reasonable possibility), ***probable.***

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, eg. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The experience having often been reported in literature for similar drug as drug related eg. skin rashes, blood dyscrasia
- The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

Following-up of Adverse Experiences

Investigators should follow-up subjects with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the subject's subsequent course must be submitted to the clinical study monitor.

[redacted]

Serious Adverse Experiences

Definition of Serious Adverse Experiences

A serious adverse experience is any event which is fatal, life threatening, disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event.

Life threatening – definition:

An adverse experience is life threatening if the subject was at immediate risk of death from the event as it occurred; ie. It does not include a reaction that if it had occurred in a more serious form might have caused death For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Disability /incapacitating definition:

An adverse experience is incapacitating or disabling if the experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions

Reporting Serious Adverse Experiences

Any serious adverse experiences that occur during the clinical study whether or not related to the study drug, must be reported by the investigator to the study monitor (by telephone within 24hrs).

All serious adverse experiences must be reported by telephone within 24hrs to the study monitor or Principle Investigator.

Name: Major Scott Kitchener

Telephone: 0407 150384

The telephone report should be followed by full written summary detailing relevant aspects of the adverse experiences in question. Where applicable information from relevant hospital case records and autopsy reports should be obtained.

Instances of death cancer or congenital abnormality if brought to the attention of the investigator *AT ANY TIME* after the cessation of study medication and linked by the investigator to a previous clinical trial, should be reported to the study monitor.

[redacted]

Overdose

Any instance of overdose (suspected or confirmed) must be communicated the Principle Investigator within 24 hours and be fully documented as a serious adverse experience. Details of any signs of symptoms and their management should be recorded including details of any antidotes administered.

Pregnancy

Subjects who become pregnant during the dosing periods (clearing dosing and prophylactic dosing) should discontinue dosing immediately. However subjects who become pregnant during the followup phase of the study should continued to be monitored as originally scheduled.

Subjects should be instructed to notify the investigator if it is determined after the completion of the study that they became pregnant either during the treatment or prophylaxis-dosing phase of the study or during the followup period.

Whenever possible a pregnancy should be followed up to term, any premature terminations reported, and the status of the mother and child should be reported after delivery.

[redacted]
Version 1.5

Case Record Form – MQ001

Enrolment:

DEMOGRAPHIC DATA:

Volunteer No: _____ Volunteer Initials: _____
Corps: _____ Age: _____ (yrs)
Unit: _____ Sex: M F (please circle)
Weight: _____ (kgs) Height: _____ (cm)
Date admitted to the Study: _____ (dd/mm/yy)

ADMISSION CRITERIA:

The following questions must all be answered "No" for a volunteer to be eligible for study entry:

	Please Circle One	
Does the volunteer have any significant illness?	Y	N
Is the volunteer Medically Fit?	Y	N
Is the female volunteer using an established method of contraception	Y	N
Has the volunteer any known reactions to any of the study compounds?	Y	N
Is the volunteer ***unwilling*** to give blood smears and blood samples?	Y	N
Has written informed consent been obtained	Y	N

If female, the volunteer must have had a negative pregnancy test and have received counselling on contraception:

Result of pregnancy test: Pos / Neg Date: _____ (dd/mm/yy)

Contraceptive counselling: Yes / No Date: _____ (dd/mm/yy)

Explanation for any deviation from the appropriate responses:

(An explanation of any "N" response is to be given and the volunteer is to be excluded from the study.)

_____
_____
_____
_____
_____
_____

[redacted]

Laboratory Test Results – MQ001

Vol ID:	Vol Init:

Haematology:

Date (dd/mm/yy)		
Schedule	Screening	Follow up
RBC (/pl)		
Haemoglobin(g/dl)		
Haematocrit(%)		
WCC(/nl)		
Neutrophils (%)		
Lymphocyes(%)		
Monocytes(%)		
Basophils(%)		
Eosinophils(%)		
Platelete Count(/nl)		

Biochemistry:

Date (dd/mm/yy)		
Schedule	Screening	Follow up
Total Bilirubin		
AST/SGOT		
ALT/SGPT		
GGT		
Glucose		
BUN		
Albumin		

If female - Pregnancy Test Results

Date (dd/mm/yy)	
Schedule	Screening

Record of Parasitaemia

Date (dd/mm/yy)			
Schedule	First Episode	Second Episode	Third Episode
Type / Count			

Exclusions from the study:

- **Haematological and biochemistry parameters greater than 1.5 times normal.**
- **Positive pregnancy test in women volunteers.**

Vol ID:	Vol Init:

Compliance (tick if logged return) **Loading dose date:**
Eradication dose date:

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
	14	15	16	17	18	19	20	21	22	23	24	25	26

Record reported adverse events as:
1. Mild (present but didn't impair completion of duties)
2. Moderate (Some impairment of duties), or
3. Severe (Prevent completion of duties)

Symptoms	Following loading	Field evaluation	On extraction
Sleep problems (specify)			
Balance problems (specify)			
Headache			
Nausea			
Vomiting			
Diarrhoea			
Abdominal pain			
Anxiety			
Confusion			
Memory loss			
Tiredness			
Muscle aches			
Joint aches			
Hallucinations			
Hearing problems			
Skin reaction (specify)			
Other			

MQ blood levels

Date				
MQ level				

[redacted]

[redacted]

Name: _____ Regimental Number _____

Date of presentation: / /
Following Loading dose ... (tick one)
Field Evaluation ...
RTA ...

MQ001

Record reported adverse events as:

1. Mild (present but didn't impair completion of duties)
2. Moderate (some impairment of duties), or
3. Severe (prevent completion of duties

All reported symptoms must be rated: 1. 2. OR 3.

Return form with PM105 to RMO 4RAR

Symptoms	Rating	Comment
Nausea		
Vomiting		
Diarrhoea		
Abdominal pain		
Headache		
Tiredness		
Anxiety		
Confusion		
Memory Loss		
Hallucinations		
Sleep problems		
Muscle aches		
Joint aches		
Balance problems		
Skin Reaction		
Hearing Problems		
Comment on activity status		

Record all clinical history on PM105

PI contacted Yes / No

Bloods Taken Yes / No – Comment _____

[redacted]

References

Contents

[i] Petersen E, Ronne T, Ronn A, Bygbjerg I, Larsen SO. Reported side effects to chloroquine, chloroquine plus proguanil, and mefloquine as chemoprophylaxis against malaria in Danish travelers. *J Travel Med* 2000 Mar-Apr;7(2):79-84.

[ii] Huzly D, Schonfeld C, Beuerle W, Bienzle U. Malaria Chemoprophylaxis in German Tourists: A Prospective Study on Compliance and Adverse Reactions. *J Travel Med* 1996 Sep 1;3(3):148-155.

[iii] Croft AM, Garner P. Mefloquine for preventing malaria in non-immune adult travellers. *Cochrane Database Syst Rev* 2000;(3):CD000138.

[iv] Phillips MA, Kass RB. User Acceptability Patterns for Mefloquine and Doxycycline Malaria Chemoprophylaxis. *J Travel Med* 1996 Mar 1;3(1):40-45.

[v] Peragallo MS, Sabatinelli G, Sarnicola G. Compliance and tolerability of mefloquine and chloroquine plus proguanil for long-term malaria chemoprophylaxis in groups at particular risk (*the military*). *Trans R Soc Trop Med Hyg* 1999 Jan-Feb;93(1):73-7.

DEFENCE PERSONNEL EXECUTIVE
DEFENCE HEALTH SERVICE BRANCH
CP2-7-66 Department of Defence CANBERRA ACT 2600

8

2001/5344
ADMEC 249/01
DHSB 450/2001

Major S. Kitchener
Officer In Charge Clinical Trials
Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Major Kitchener

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) PROTOCOL 249/01: EVALUATION OF MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS

1. Thank you for providing the requested amendments to your protocol. ADMEC has now cleared your project, Protocol No MQ001, Version 1.4 to proceed. Please note that ethical clearance from ADMEC does not automatically confer access to ADF personnel; this will have to be sought from the relevant military commanders.

2. Your protocol has been allocated ADMEC Protocol Number 249/01, and this number should be quoted in all correspondence. Six-monthly progress reports are required, the first being due on the 30th September 2001. ADMEC's compliance with the NHMRC National Statement on Ethical Conduct in Research Involving Humans requires that your progress reports include, where applicable, comment on: the security of your records; compliance with the approved consent procedures and documentation, and compliance with any other special conditions that ADMEC may have required.

3. For completeness, would you please sign the enclosed researcher's agreement and return it to me at your convenience. I have also enclosed ADMEC's Guidelines for Volunteers, a copy of which is to be given to each study participant.

4. The Committee wishes you well with your research. Please contact me if I can be of any assistance.

Yours sincerely,

s22 [redacted]

RAPHAELA JARVIS
Assistant Executive Secretary
Australian Defence Medical Ethics Committee

21 March, 2001

[redacted]
Version 1.4

6

CLINICAL TRIAL PROTOCOL

PROTOCOL NO. MQ001
Version 1.4 (ADMEC amended)

PROTOCOL TITLE:

Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers

Principal Investigator:

MAJ Scott Kitchener MBBS MPH
OC Clinical Field AMI

CAPT John Cunningham BSc (Hon) MBBS
RMO 4RAR

Co-Investigators:

LTCOL Mike Edstein PhD
Deputy Director AMI

LTCOL Peter Nasveld MBBS BSc Med (Hons)
RO Clinical Studies AMI

LT Michael Reid
RO Clinical Studies AMI

Study Coordinator:

Professor Karl Rieckmann MD
Director AMI

Summary of Protocol:

TITLE	Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers
SPONSOR	Australian Army Malaria Institute
PLANNED STUDY START	April 2001
INDICATION	Malaria prophylaxis
INVESTIGATOR	Major Scott Kitchener – Australian Army Malaria Institute
OBJECTIVES	The objective of the study is primarily to define the safety and tolerability of mefloquine under operational conditions. Secondary objectives are to assess the effectiveness of mefloquine under operational conditions.
STUDY DESIGN	Active reporting of adverse events / side effects to medication using a questionnaire system, pharmacokinetics (on a core group of one Company), log returns for compliance review and active surveillance for malaria cases.
SAMPLE SIZE	800 volunteers.
SELECTION CRITERIA	Volunteers recruited from exposed groups of troops serving in East Timor (4RAR and 2RAR Battalion group core elements).
FORMULATIONS	1. Mefloquine 250mg, third daily for 3 doses, then weekly, 2. Primaquine 15mg bd for 14 days on RTA. 3. All volunteers on primaquine continue with mefloquine weekly as per current ADF policy
ROUTE OF ADMINISTRATION	Oral
OUTCOME VARIABLES: **SAFETY AND TOLERABILITY** **EFFECTIVENESS**	 Clinical adverse events Changes of laboratory values (haematology, biochemistry, plasma drug levels Compliance Protection from malaria infections

Overview of Study - Protocol No: MQ001

	Screening	Loading Safety	Field Safety	Followup[1]
Study Visit	1	2	3	As required
Day	Prior to deployment D-25 (days)	D-7	Variable	As required
Written informed consent	*			
Inclusion/exclusion criteria	*			
Physical Examination				*
Medical history/ demography	*		*	*
Medication issued	*			Supply by RAP in field conditions
Malaria blood smears				*
Haematology/ Biochemistry		*		*
Pharmacology		*	*	*
Pregnancy test	*			* (if female)
Adverse event review		*	*	*
Concomitant medicine review	*	*	*	*

Notes:

1. Followup initiated by treating medical facility in cooperation with AMI Investigators once diagnosis of malaria has been made.

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19. Data Management and Analysis
    a. Data Storage and Retrieval
    b. Efficacy Analysis
    c. Safety Analysis
    d. Blood Drug Analysis
    e. Use of data

20. Volunteer Consent

REFERENCES

ANNEXES:

A. Consent Form

B. Adverse Experience Guidelines

ENCLOSURES:

1. Case Record Form

2. Adverse Experience Form

3. Severe Adverse Experience Form

[redacted]
Version 1.4

1. Background

Mefloquine (MQ) is presently included as an alternative malaria chemoprophylaxis agent in the Health Policy Directive 215, however a cloud has existed over the adverse events arising. No definitive prospective study under field conditions has been conducted to determine these outcomes. The drug has been found to be as acceptable as chloroquine and proguanil (C+P - previously used by the ADF for malaria chemoprophylaxis), with better compliance though more CNS adverse events[i]. These side effects included depression, strange thoughts and altered spatial appreciation which clearly of importance under operational conditions. Nevertheless, the finding of more adverse events with MQ is not a consistent outcome[ii] when observed among recreational tourists, though withdrawals are consistently higher than with other chemoprophylaxis agents[iii]. Australians using MQ report higher compliance though more adverse events than those using doxycycline (DX) for malaria chemoprophylaxis[iv]. These were recreational travelers with short-term use and were questioned after return from travel.

Large retrospective trials on military populations indicate MQ as well tolerated and has better compliance than C+P[v], though these trials were among Italian soldiers over relatively shorter periods (average three months) than present ADF deployments.

During the recent Tafenoquine prophylaxis trial using MQ as a control group a small group was placed on MQ unblinded. This group spent in excess of three months during the wet season in East Timor without any cases of malaria developing.

Contents

2. Justification for Investigation

There is clear evidence of adverse events and non-compliance related to MQ in smaller studies, however, no large studies conducted on Australian soldiers or under field conditions define the adverse event profile. Mefloquine appears from the preliminary evidence available from current trials to be an effective and well accepted chemoprophylaxis for the ADF under operational conditions. The acceptance levels and effectiveness of doxycycline leave scope for improvement under these conditions.

Contents

3. Objectives

The objective of the study is to define the adverse events of mefloquine and compare these with those of doxycycline. A secondary objective is comparing effectiveness of these preparations.

Contents

4. Study Design

The study design is an open clinical trial. Volunteers of the core elements of the Battalion group will be given a loading dose of mefloquine followed by three weekly doses pre-deployment in accordance with HPD215. A further sub-population (Company size) will be randomly selected for more detailed investigation. The remaining non-core elements of the Battalion group will be provided conventional chemoprophylaxis in accordance with HPD215, viz. doxycycline 100mg daily.

The Company sub-group selected will undergo pharmacokinetic studies at key intervals throughout the deployment. These key intervals include following loading dose, on return from a patrol period (high workload and intense field conditions), on return from a rest period, and prior to redeployment to Australia.

All core elements of the Battalion group will be supervised using a log return system of reviewing compliance with chemoprophylaxis as recorded by responsible individual, generally the Platoon Sergeant. Questionnaires will also be delivered requesting information regarding adverse events at key intervals including following loading dose, midway through the deployment and prior to return to Australia.

Contents

5. Study Population

The study population will include the core elements of the forward Australian Battalion groups deploying to East Timor under Operation Tanager during the period April 2001 and May 2002. The core elements of the Battalion group include Rifle Company and attachments. Headquarter elements, Administration Company and Support Company groups with other Battalion group attachments will remain on chemoprophylaxis in accordance with HPD215 and will be monitored with existing surveillance systems.

a. ***Inclusion Criteria***: To be included in the study the trial volunteer must:

i. Be male or female between 18 and 55 years of age;
ii. Be Medical Class 1 or 2; and
iii. Be willing and able to give written informed consent and comply with the study protocol.

b. ***Exclusion Criteria***: Volunteers will be ineligible for inclusion into the study if any of the following applies:

i. They are pregnant or unwilling/unable to comply with recognised contraception methods for 30 days after administration of the study drugs;
ii. They have a known hypersensitivity to any component of the study drugs;
iii. They are unwilling/unable to give blood collections required in the study;
iv. They are taking any other investigational drug during, or within 30 days, of taking the study drugs for this study.

Contents

6. Volunteer Identification

All consenting volunteers will be issued a unique alphanumerical code consisting of a letter indicating their trial and three numbers (eg A123) in order to identify their specimens and minimize the possibility of data entry errors.

Contents

7. Sample Size

The core elements of an ADF Battalion group in Operation Tanager approximate 400 in number. A sub-group of 120 individuals will be selected by Company group from each Battalion group to undertake the pharmacokinetic studies.

Contents

8. Risks

All volunteers will be at risk of malaria infection by the nature of the operational deployment. Estimates from historical data indicate that up to 25% of ADF personnel returning from malarious areas of East Timor are at risk of developing malaria.

All volunteers are accepting, as part of the study, the possibility of clinical events either known or unknown associated with the study medication. The primary clinical events associated with MQ include gastrointestinal disturbances and neurological manifestations.

Phlebitis following venepuncture remains a risk. Venepuncture will be necessary for post-deployment screening whether the potential volunteer chooses to be involved in the study or not. Trial venepuncture will be coordinated with this intervention.

Contents

9. Benefits

Malaria is a very serious and debilitating disease resulting in disruption of usual activities including a significant personnel loss on operations. For the individual the prevention of malaria prevents both acute and potentially chronic morbidity. For the Battalion group, protection from malaria is a force multiplying effect.

The benefit for the individual in taking MQ rather than the conventional chemoprophylaxis is convenience in that MQ is a weekly medication and DX is daily, in addition to potentially fewer adverse events associated with DX, particularly in the field environment, the development of gastrointestinal symptoms, photosensitivity and pedal intertrigo.

Contents

10. Quality Procedures / Assurance

a. ***Outcome Measures:*** The outcome measures are response to delivered questionnaires on adverse events and compliance, identified log returns on compliance and a positive malaria blood smear confirming clinical malaria.

b. ***Safety Parameters:*** Safety parameters established for the trial are the monitoring of:

i. Routine clinical laboratory tests (haematology and biochemistry) on a representative sample following loading dose;
ii. Adverse events as per outcomes; and
iii. Pregnancy testing

c. ***Clinical Trial Material:*** All MQ will be provided through the ADF Supply system using conventional distribution methods.

Contents

11. Laboratory Procedures

Whole venous blood will be collected by venepuncture. Each sample will be collected in 5ml Lithium Heparin tubes, with no more than 30mls of blood being collected for this study.

Methodology for all laboratory procedures will be included in the trial SOP. Procedures will include:

a. ***Measurement of Parasitaemia*** - Thick and thin blood films for malaria will be obtained from a venous sample to confirm malaria as required by clinical examination. Blood films will be stained with Giemsa and evaluated by standard techniques. A confirmed instance of positive parasitaemia will be considered a failure of chemoprophylaxis.

b. ***Haematology*** - The following haematology tests will be performed following loading does on a representative selection of the group, with a manual differentiation performed on abnormal findings:

i. Haemoglobin;
ii. PCV (Haematocrit);
iii. Platelets;
iv. Total White Cell Count;
v. Lymphocyte Count.

c. ***Biochemistry*** - Biochemistry will be performed following loading does on a representative selection of the group. Investigations will include Creatinine and ALT (SGOT) analysed on site using Reflotron. Additionally, the following parameters will be analysed by AMI on frozen serum:

i. Sodium;
ii. Potassium;
iii. Albumin;
iv. Urea;
v. Total Bilirubin;
vi. Alkaline Phosphatase.

d. ***Pharmacology Venous Blood Sampling Schedule***- Venous blood samples will be collected following loading dose and at intervals throughout the deployment as outlined above.

All blood samples will be immediately stored on ice and then centrifuged at 2,000 rpm for 15 minutes. Plasma will be separated and stored at -20°C until analysed. Plasma concentrations of MQ will be measured by HPLC at AMI.

e. ***Pregnancy Testing*** - All volunteers of child bearing potential will be tested for pregnancy at screening by urine testing techniques using standardised test kits. Although the dosing period is only 14 days maximum, women who believe they have become (or think they are) pregnant or who record a positive result on urine testing will be excluded from the study.

Contents

12. Drug Dose

The study drug will be supplied as Mefloquine 250mg tablets taken as follows:

a. Loading dose: 250 mg second daily for three doses in a week,
b. Predeployment maintenance: 250mg weekly for three weeks, and
c. Maintenance dose in AO: 250mg weekly.

Contents

13. Drug Storage, Inventory and Log Sheets

The conventional supply system for the Battalion group will be utilised. Study drugs will be stored according to the manufacturer's recommendations at ambient temperature (not greater than 25°C). The principal investigators will keep a record of all study drugs used. The drug will be distributed to individuals weekly by Platoon NCO in accordance with Formation Routine Orders and logged. The Investigator will collect log returns weekly.

Contents

14. Personnel Responsibilities

The Principal Investigators or Co-investigators shall:

a. obtain informed consent from volunteers in the study
b. issue and collect all documentation, and
c. investigate all reported adverse events.

Only clinically endorsed personnel will perform blood sampling.

Contents

15. Adverse Events

Volunteers will have a history and physical examination done whenever there are reported adverse events. All adverse events will be notified and discussed with a Principle Investigator within one week for a decision regarding continuation on MQ.

In the case of clinical malaria, full clinical records from the treatment facility will be obtained for all confirmed cases.

All deaths, potentially lethal events and hospitalisation are serious adverse events (SAE). These are to be notified to a Principle Investigator within 24 hours for continuation of the individual in the trial.

Any adverse reaction will be treated as medically indicated regardless of enrolment in the trial.

The definitions and reporting requirements for adverse events (AE) and serious adverse events (SAE) are detailed at Annex B.

Contents

16. Withdrawal of Volunteers

Volunteers may withdraw themselves or be withdrawn from the study at any time without prejudice or compromise to appropriate treatment or chemoprophylaxis or detriment to military career. Volunteers will be withdrawn from the study if they experience significant adverse events to the study medicine, or if concomitant illness is likely to compromise their physical well being or their participation in the study. Reasons for withdrawal will be recorded in the CRF. If withdrawal is due to an Adverse Event then an Adverse Event Form will be completed.

Contents

17. Concurrent Medication

If a volunteer develops an infection requiring treatment with antibiotics, the attending study clinician will, if possible, prescribe an antibiotic without known antimalarial action. All other concurrent medication will be recorded on the CRF.

Contents

18. Contraception

Female volunteers determined to be non-pregnant on entry to the study will be counselled on contraception, and encouraged to continue precautions until 4 weeks after the last dose of study drug.

Contents

19. Data Management and Analysis

Data will be entered from Case Record Forms (CRF's) onto a computerised database (MS Access). At the end of the study, all data will be crosschecked against original data capture sheets. The following arrangements for data management and analysis will be applied:

a. ***Data Storage and Retrieval*** - CRFs provided by AMI will be completed for each volunteer and will include the volunteer Consent Form and Adverse Event Form. Completed original CRFs, signed by the investigator, will be retained by AMI. CRF data will be edited where necessary with the agreement of the investigator to ensure completeness and consistency. The investigators will endeavour to ensure all data is complete, with phone followup initiated if indicated.

b. ***Effectiveness Analysis*** - The effectiveness end point will be the proportion of volunteers developing patent parasitaemia during the twelve (12) months after redeployment to Australia.

c. ***Safety Analysis*** - The study population will serve as the denominator for tolerability. Incidence of all adverse events will be determined, reported and tabulated. Adverse events will be recorded along with the event's intensity, seriousness, investigator-attributed causality, onset and cessation. Clinical laboratory values 1.5 times outside the normal range will be flagged.

d. ***Blood Drug Analysis*** - Plasma concentrations of MQ will be determined and related to prophylaxis failure rates.

e. ***Use of data:*** A copy of the clinical record forms, the personal medication diaries, drug control logs, adverse event forms and the original laboratory record sheets will be kept on file at AMI for a period of not less than 7 years. It is expected that these data will be reported in both scientific journals and at scientific meetings, and may be submitted to governmental medication regulatory authorities for review. Confidentiality of volunteers will be maintained. Volunteers will be informed in general terms of the results as soon as practical. All publications resulting from this study will be cleared through the Australian Defence Force.

Contents

20. Volunteer Consent

Volunteers will be recruited using non-coercive means. No inducement will be offered. The investigator is responsible for ensuring the volunteer understands the nature and purpose of the study. Volunteers who are invited to take part in a clinical trial are entitled to make a choice based on full and complete information presented in a manner that is understandable and ethnically appropriate. The Information and Consent Form (Annex A) is designed to assure the protection of the volunteer's rights.

The investigator will inform the volunteer of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it may entail. In addition, a copy of the Information and Consent Form will be provided which outlines this detail. The volunteer will be given every opportunity to clarify any points that he/she may not understand and to seek additional information. The volunteer will retain the right to withdraw from the study at any time without penalty. The investigator is responsible for ensuring that the volunteer has full knowledge and for obtaining the volunteer's freely given informed consent.

The informed consent will be recorded in writing with the investigator and the volunteer both signing and dating the Information and Consent Form.

The signed Information and Consent Form will be retained with the original CRF.

Contents

References:

1 IND #38503 (Etaquine), Surgeon General, U.S Army, Section 8.2.1.1.

2 IND #38503 (Etaquine), Surgeon General, U.S Army, Section 8.2.1.1.

3 Investigator's Brochure (1997 revised), WR 238,605, U.S Army, Office of the Surgeon General.

[redacted]
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CONSENT FORM PROTOCOL

Regimental Number: _____ Volunteers Initials: _____
You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

As you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to observe a less commonly used drug, Mefloquine, under field conditions.
The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent malaria infection from overseas deployments in the future.

WHAT IS THE MEDICINE?

Mefloquine one tablet weekly in the AO and for two weeks after return to Australia. You will initially be given at least six tablets prior to deployment. The usual medicine is Doxycycline one tablet daily through deployment and for two weeks after. You are initially given two tablets prior to deployment.

WHAT IS THE STUDY?

The study is looking at how satisfactory Mefloquine is under field conditions. You will be provided with one tablet weekly through the standard supply system in the field. Supply and use of each tablet weekly will be recorded. You will be asked immediately prior to deployment, several times throughout the deployment and on return to Australia, whether you had any problems you thought were due to the antimalarial tablet. A small group will be (randomly) selected to additionally give blood on two occasions during deployment.

LENGTH OF THE STUDY

The study will begin 4 weeks prior to your redeployment and will be continued until 12 months after your deployment is completed. Your only involvement after redeployment will be if you develop malaria.

STUDY TESTS

All volunteers will be asked to complete a questionnaire immediately prior to deployment, during deployment and prior to returning to Australia. As the investigators are looking at baseline drug levels in blood, and measuring biochemistry and haematology levels to monitor safety, a small group will be requested to donate two samples of blood from your arm. The amount of blood collected for the study amounts to no more than about 20mls, or the equivalent of 4 teaspoons.

RISKS / DISCOMFORTS

There may be some bruising with blood taken from the veins in your arm.

When Mefloquine is used to treat people ill with malaria especially children less than 45kg, side effects have been reported and recorded. These include over 1% reporting sleepiness, insomnia, abnormal dreams, dizziness, loss of balance, headache, nausea and vomiting, diarrhoea or abdominal pain. Less than 1% had episodes of anxiety, confusion, depression, restlessness, forgetfulness, hallucinations and psychotic or paranoid reactions, nerve damage, convulsions, tiredness, fever, chills, loss of appetite, rash, itchiness, hair loss, visual disturbances, muscle weakness, cramps, muscle and joint pain, ringing in the ears, hearing disorders, low or high blood pressure, fainting, palpitations, extra heart beats, slow heart rate, or lowering of the clotting cells in the blood, or white cells (used for fighting infection) and fewer than 0.1% had brain damage, psychotic events, severe hypersensitivity reactions in the skin and heart block.

Overall, Mefloquine has fewer side effects than Doxycycline in trials among travellers (including Australians).

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have had any anxiety attacks or serious depression in the past you also may not be able to use Mefloquine. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

CONFIDENTIALITY

In all reports only a number will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

Mefloquine is authorised to use as an antimalarial by civilian authorities in Australia in addition to being directed for use as an alternative to Doxycycline by the Director General, Defence Health Services in HPD215. This trial has also been approved by the Australian Defence Medical Ethics Committee.

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the RMO or AMI (0407 150384).

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the RMO or study investigators. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP4-7-65
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3818

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal antimalarial course of Doxycycline daily and an eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____ **Date:**_____

INVESTIGATOR'S SIGNATURE _____ **Date:**_____

ANNEX B to
Protocol MQ001

ADVERSE EXPERIENCES GUIDELINES

Adverse Experiences

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out below.

Eliciting and Documenting Adverse Experiences

It is the responsibility of the investigator to document all adverse experiences which occur during the investigation. An adverse experience include any noxious, pathological or unintended change in anatomical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of thew clinical study whether associated with the study drug or placebo and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the case record under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences.

In the case of studies involving a marketed drug in an established indication, an adverse experience includes significant failure of the expected pharmacological or biological action.

All adverse experiences occurring after the start of the study must be reported. Subject entry into the study is defined as the time at which informed consent is obtained (This must be before any protocol-specific diagnostic procedures or interventions) All subsequent adverse experiences, whether no drug (ie. during reference 'run-in' or 'wash-out' period) or when active drug or placebo is being administered, must be reported REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.

At each visit /assessment, adverse experiences will.be evaluated by the investigator. Adverse experiences not previously documented in the study will be recorded in the adverse experience section of the subject's case record form. The nature of each experience date and time (where appropriate) of onset, duration, severity and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the case record form.

Adverse experiences already documented in the CRF ie. at a previous assessment and designated as `continuing' should be reviewed. If these have resolved, the documentation in the CRF should be completed. NB. If an adverse experience changes in frequency or severity during a study period, a new record of the experience will be started.

Ask the subject or the subjects parent or legal guardian a non-leading question such as:

"Do you feel different in any way since starting the new treatment/the last assessment?"

Assessment of Severity

Maximum intensity should be assigned to one of the following categories:

Mild: For example, an adverse experience which is easily tolerated by the subject, causing minimal discomfort not interfering with everyday activities.

Moderate: For example, an adverse experience that is sufficiently discomforting to interfere with normal everyday activities.

Severe: For example, an adverse experience which prevents normal everyday activities

Assessment of Causality

Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: ***not related***, ***unlikely***, ***suspected*** (reasonable possibility), ***probable.***

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, eg. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The experience having often been reported in literature for similar drug as drug related eg. skin rashes, blood dyscrasia
- The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

Following-up of Adverse Experiences

Investigators should follow-up subjects with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the subject's subsequent course must be submitted to the clinical study monitor.

Serious Adverse Experiences

Definition of Serious Adverse Experiences

A serious adverse experience is any event which is fatal, life threatening, disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event.

Life threatening – definition:

An adverse experience is life threatening if the subject was at immediate risk of death from the event as it occurred; ie. It does not include a reaction that if it had occurred in a more serious form might have caused death For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Disability /incapacitating definition:

An adverse experience is incapacitating or disabling if the experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions

Reporting Serious Adverse Experiences

Any serious adverse experiences that occur during the clinical study whether or not related to the study drug, must be reported by the investigator to the study monitor (by telephone within 24hrs).

All serious adverse experiences must be reported by telephone within 24hrs to the study monitor or Principle Investigator.

Name: Major Scott Kitchener

Telephone: s22 [redacted]

The telephone report should be followed by full written summary detailing relevant aspects of the adverse experiences in question. Where applicable information from relevant hospital case records and autopsy reports should be obtained.

Instances of death cancer or congenital abnormality if brought to the attention of the investigator *AT ANY TIME* after the cessation of study medication and linked by the investigator to a previous clinical trial, should be reported to the study monitor.

Overdose

Any instance of overdose (suspected or confirmed) must be communicated the Principle Investigator within 24 hours and be fully documented as a serious adverse experience. Details of any signs of symptoms and their management should be recorded including details of any antidotes administered.

Pregnancy

Subjects who become pregnant during the dosing periods (clearing dosing and prophylactic dosing) should discontinue dosing immediately. However subjects who become pregnant during the followup phase of the study should continued to be monitored as originally scheduled.

Subjects should be instructed to notify the investigator if it is determined after the completion of the study that they became pregnant either during the treatment or prophylaxis dosing phase of the study or during the followup period.

Whenever possible a pregnancy should be followed up to term, any premature terminations reported, and the status of the mother and child should be reported after delivery.

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Version 1.4

Case Record Form – MQ001

Enrolment:

DEMOGRAPHIC DATA:

Volunteer No: _____ Volunteer Initials: _____
Corps:_____ Age: _____ (yrs)
Unit: _____ Sex: M F (please circle)
Weight: _____ (kgs) Height: _____ (cm)
Date admitted to the Study: _____ (dd/mm/yy)

ADMISSION CRITERIA:

The following questions must all be answered "No" for a volunteer to be eligible for study entry:

	Please Circle One	
Does the volunteer have any significant illness?	Y	N
Is the volunteer Medically Fit?	Y	N
Is the female volunteer using an established method of contraception	Y	N
Has the volunteer any known reactions to any of the study compounds?	Y	N
Is the volunteer ***unwilling*** to give blood smears and blood samples?	Y	N
Has written informed consent been obtained	Y	N

If female, the volunteer must have had a negative pregnancy test and have received counselling on contraception:

Result of pregnancy test: Pos / Neg Date: _____ (dd/mm/yy)

Contraceptive counselling: Yes / No Date: _____ (dd/mm/yy)

Explanation for any deviation from the appropriate responses:
(An explanation of any "N" response is to be given **and** the volunteer is to be excluded from the study.)

_____
_____
_____
_____
_____
_____

[redacted]
Version 1.4

Laboratory Test Results – MQ001

Vol ID:	Vol Init:

Haematology:

Date (dd/mm/yy)		
Schedule	Screening	Follow up
RBC (/pl)		
Haemoglobin(g/dl)		
Haematocrit(%)		
WCC(/nl)		
Neutrophils (%)		
Lymphocyes(%)		
Monocytes(%)		
Basophils(%)		
Eosinophils(%)		
Platelete Count(/nl)		

Biochemistry:

Date (dd/mm/yy)		
Schedule	Screening	Follow up
Total Bilirubin		
AST/SGOT		
ALT/SGPT		
GGT		
Glucose		
BUN		
Albumin		

If female - Pregnancy Test Results

Date (dd/mm/yy)	
Schedule	Screening

Record of Parasitaemia

Date (dd/mm/yy)			
Schedule	First Episode	Second Episode	Third Episode
Type / Count			

Exclusions from the study:

- **Haematological and biochemistry parameters greater than 1.5 times normal.**
- **Positive pregnancy test in women volunteers.**

Vol ID:	Vol Init:

Compliance (tick if logged return) **Loading dose date:**
Eradication dose date:

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
	14	15	16	17	18	19	20	21	22	23	24	25	26

Record reported adverse events as:
1. Mild (present but didn't impair completion of duties)
2. Moderate (Some impairment of duties), or
3. Severe (Prevent completion of duties)

Symptoms	Following loading	Field evaluation	On extraction
Sleep problems (specify)			
Balance problems (specify)			
Headache			
Nausea			
Vomiting			
Diarrhoea			
Abdominal pain			
Anxiety			
Confusion			
Memory loss			
Tiredness			
Muscle aches			
Joint aches			
Hallucinations			
Hearing problems			
Skin reaction (specify)			
Other			

MQ blood levels

Date				
MQ level				

References

[i] Petersen E, Ronne T, Ronn A, Bygbjerg I, Larsen SO. Reported side effects to chloroquine, chloroquine plus proguanil, and mefloquine as chemoprophylaxis against malaria in Danish travelers. *J Travel Med* 2000 Mar-Apr;7(2):79-84.

[ii] Huzly D, Schonfeld C, Beuerle W, Bienzle U. Malaria Chemoprophylaxis in German Tourists: A Prospective Study on Compliance and Adverse Reactions. *J Travel Med* 1996 Sep 1;3(3):148-155.

[iii] Croft AM, Garner P. Mefloquine for preventing malaria in non-immune adult travellers. *Cochrane Database Syst Rev* 2000;(3):CD000138.

[iv] Phillips MA, Kass RB. User Acceptability Patterns for Mefloquine and Doxycycline Malaria Chemoprophylaxis. *J Travel Med* 1996 Mar 1;3(1):40-45.

[v] Peragallo MS, Sabatinelli G, Sarnicola G. Compliance and tolerability of mefloquine and chloroquine plus proguanil for long-term malaria chemoprophylaxis in groups at particular risk (the military). *Trans R Soc Trop Med Hyg* 1999 Jan-Feb;93(1):73-7.

FOLIO 5

DEFENCE PERSONNEL EXECUTIVE

DEFENCE HEALTH SERVICE BRANCH

CP2-7-66 Department of Defence CANBERRA ACT 2600

2001/5344
ADMEC 249/01
DHSB 320/2001

Major S. Kitchener
Officer In Charge Clinical Trials
Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Major Kitchener,

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) PROTOCOL 249/01: EVALUATION OF MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS

1. ADMEC has considered your protocol and approves in principle. However, some amendments are required before formal ethical clearance is given.

2. In particular ADMEC agreed to accept the protocol on the following conditions:
   a. The information and consent sheet are to be amended to clearly outline in quantitative terms the side effects of the medication, including CNS and cardiovascular side effects, and are to include rare events as well as common.
   b. The study should be retitled "Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers"" to more accurately reflect the intent of the study, and
   c. Six doses of the medication are to be given in Australia prior to deployment.

3. Please note that this protocol will be considered to be "pending" until the required amendments are received and sighted by the Executive Secretary. If all requirements have been met, your project will be formally approved and a Researcher's Agreement forwarded for your signature.

4. Please contact me if I can be of any assistance.

Yours sincerely,

s22 [redacted]

M. BLENKIN
Lieutenant Commander
Executive Secretary
Australian Defence Medical Ethics Committee

28 February, 2001

Department of Defence

MINUTE

(12)

548-7-13
AMI 30/01

Executive Secretary (Attention: Australian Defence Force Medical ethics Committee) (CP2–7–66)

SUBMISSION OF MEFLOQUINE TRIAL FOR CONSIDERATION

1. Attached is the AMI protocol MQ001, the evaluation of mefloquine for the prophylaxis of malaria in non-immune Australian soldiers, for consideration by ADMEC.

2. Forwarded for approval.

s22 [redacted]

S J KITCHENER
MAJ
OC CLINICAL FIELD

ARMY MALARIA INSTITUTE

09 Feb 01

249/01

[redacted]

CLINICAL TRIAL PROTOCOL

PROTOCOL NO. MQ001

PROTOCOL TITLE:

EVALUATION OF MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS

Principal Investigator:

MAJ Scott Kitchener MBBS MPH
OC Clinical Field AMI

Co-Investigators:

LTCOL Mike Edstein PhD
Deputy Director AMI

LTCOL Peter Nasveld MBBS BSc Med (Hons)
RO Clinical Studies AMI

LT Michael Reid
RO Clinical Studies AMI

Study Coordinator:

Professor Karl Rieckmann MD
Director AMI

Summary of Protocol MQ001:

TITLE	Evaluation of Mefloquine for Prophylaxis of Malaria in Non Immune Australian Soldiers
SPONSOR	Australian Army Malaria Institute
PLANNED STUDY START	April 2001
INDICATION	Malaria prophylaxis
INVESTIGATOR	Major Scott Kitchener – Australian Army Malaria Institute
OBJECTIVES	The objective of the study is primarily to define the safety and tolerability of mefloquine under operational conditions. Secondary objectives are to assess the effectiveness of mefloquine under operational conditions.
STUDY DESIGN	Active reporting of adverse events / side effects to medication using a questionnaire system, pharmacokinetics (on a core group of one Company), log returns for compliance review and active surveillance for malaria cases.
SAMPLE SIZE	800 volunteers.
SELECTION CRITERIA	Volunteers recruited from exposed groups of troops serving in East Timor (4RAR and 2RAR Battalion group core elements).
FORMULATIONS	1. Mefloquine 250mg, third daily for 3 doses, then weekly, 2. Primaquine 15mg bd for 14 days on RTA. 3. All volunteers on primaquine continue with mefloquine weekly as per current ADF policy
ROUTE OF ADMINISTRATION	Oral
OUTCOME VARIABLES: **SAFETY AND TOLERABILITY** **EFFECTIVENESS**	 Clinical adverse events Changes of laboratory values (haematology, biochemistry, plasma drug levels Compliance Protection from malaria infections

Overview of Study - Protocol No: MQ001

	Screening	Loading Safety	Field Safety	Followup[1]
Study Visit	1	2	3	As required
Day	Prior to deployment D-14 (days)	D-7	Variable	As required
Written informed consent	*			
Inclusion/exclusion criteria	*			
Physical Examination				*
Medical history/ demography	*		*	*
Medication issued	*			Supply by RAP in field conditions
Malaria blood smears				*
Haematology/ Biochemistry		*		*
Pharmacology		*	*	*
Pregnancy test	*			* (if female)
Adverse event review		*	*	*
Concomitant medicine review	*	*	*	*

Notes:

1. Followup initiated by treating medical facility in cooperation with AMI Investigators once diagnosis of malaria has been made.

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17. Concurrent Medication

18. Contraception

19. Data Management and Analysis
    a. Data Storage and Retrieval
    b. Efficacy Analysis
    c. Safety Analysis
    d. Blood Drug Analysis
    e. Use of data

20. Volunteer Consent

REFERENCES

ANNEXES:

A. Consent Form

B. Adverse Experience Guidelines

ENCLOSURES:

1. Case Record Form

2. Adverse Experience Form

3. Severe Adverse Experience Form

1. Background

Mefloquine (MQ) is presently included as an alternative malaria chemoprophylaxis agent in the Health Policy Directive 215, however a cloud has existed over the adverse events arising. No definitive prospective study under field conditions has been conducted to determine these outcomes. The drug has been found to be as acceptable as chloroquine and proguanil (C+P - previously used by the ADF for malaria chemoprophylaxis), with better compliance though more CNS adverse events[i]. These side effects included depression, strange thoughts and altered spatial appreciation which clearly of importance under operational conditions. Nevertheless, the finding of more adverse events with MQ is not a consistent outcome[ii] when observed among recreational tourists, though withdrawals are consistently higher than with other chemoprophylaxis agents[iii]. Australians using MQ report higher compliance though more adverse events than those using doxycycline (DX) for malaria chemoprophylaxis[iv]. These were recreational travelers with short-term use and were questioned after return from travel.

Large retrospective trials on military populations indicate MQ as well tolerated and has better compliance than C+P[v], though these trials were among Italian soldiers over relatively shorter periods (average three months) than present ADF deployments.

During the recent Tafenoquine prophylaxis trial using MQ as a control group a small group was placed on MQ unblinded. This group spent in excess of three months during the wet season in East Timor without any cases of malaria developing.

Contents

2. Justification for Investigation

There is clear evidence of adverse events and non-compliance related to MQ in smaller studies, however, no large studies conducted on Australian soldiers or under field conditions define the adverse event profile. Mefloquine appears from the preliminary evidence available from current trials to be an effective and well accepted chemoprophylaxis for the ADF under operational conditions. The acceptance levels and effectiveness of doxycycline leave scope for improvement under these conditions.

Contents

3. Objectives

The objective of the study is to define the adverse events of mefloquine and compare these with those of doxycycline. A secondary objective is comparing effectiveness of these preparations.

Contents

4. Study Design

The study design is an open clinical trial. Volunteers of the core elements of the Battalion group will be given a loading dose of mefloquine pre-deployment followed by weekly administration in accordance with HPD215. A further sub-population (Company size) will be randomly selected for more detailed investigation. The remaining non-core elements of the Battalion group will be provided

conventional chemoprophylaxis in accordance with HPD215, viz. doxycycline 100mg daily.

The Company sub-group selected will undergo pharmacokinetic studies at key intervals throughout the deployment. These key intervals include following loading dose, on return from a patrol period (high workload and intense field conditions), on return from a rest period, and prior to redeployment to Australia.

All core elements of the Battalion group will be supervised using a log return system of reviewing compliance with chemoprophylaxis as recorded by responsible individual, generally the Platoon Sergeant. Questionnaires will also be delivered requesting information regarding adverse events at key intervals including following loading dose, midway through the deployment and prior to return to Australia.

Contents

5. Study Population

The study population will include the core elements of the forward Australian Battalion groups deploying to East Timor under Operation Tanager during the period April 2001 and May 2002. The core elements of the Battalion group include Rifle Company and attachments. Headquarter elements, Administration Company and Support Company groups with other Battalion group attachments will remain on chemoprophylaxis in accordance with HPD215 and will be monitored with existing surveillance systems.

a. ***Inclusion Criteria***: To be included in the study the trial volunteer must:

i. Be male or female between 18 and 55 years of age;
ii. Be Medical Class 1 or 2; and
iii. Be willing and able to give written informed consent and comply with the study protocol.

b. ***Exclusion Criteria***: Volunteers will be ineligible for inclusion into the study if any of the following applies:

i. They are pregnant or unwilling/unable to comply with recognised contraception methods for 30 days after administration of the study drugs;
ii. They have a known hypersensitivity to any component of the study drugs;
iii. They are unwilling/unable to give blood collections required in the study;
iv. They are taking any other investigational drug during, or within 30 days, of taking the study drugs for this study.

Contents

6. Volunteer Identification

All consenting volunteers will be issued a unique alphanumerical code consisting of a letter indicating their trial and three numbers (eg A123) in order to identify their specimens and minimize the possibility of data entry errors.

Contents

7. Sample Size

The core elements of an ADF Battalion group in Operation Tanager approximate 400 in number. A sub-group of 120 individuals will be selected by Company group from each Battalion group to undertake the pharmacokinetic studies.

Contents

8. Risks

All volunteers will be at risk of malaria infection by the nature of the operational deployment. Estimates from historical data indicate that up to 25% of ADF personnel returning from malarious areas of East Timor are at risk of developing malaria.

All volunteers are accepting, as part of the study, the possibility of clinical events either known or unknown associated with the study medication. The primary clinical events associated with MQ include gastrointestinal disturbances and neurological manifestations.

Phlebitis following venepuncture remains a risk. Venepuncture will be necessary for post-deployment screening whether the potential volunteer chooses to be involved in the study or not. Trial venepuncture will be coordinated with this intervention.

Contents

9. Benefits

Malaria is a very serious and debilitating disease resulting in disruption of usual activities including a significant personnel loss on operations. For the individual the prevention of malaria prevents both acute and potentially chronic morbidity. For the Battalion group, protection from malaria is a force multiplying effect.

The benefit for the individual in taking MQ rather than the conventional chemoprophylaxis is convenience in that MQ is a weekly medication and DX is daily, in addition to potentially fewer adverse events associated with DX, particularly in the field environment, the development of gastrointestinal symptoms, photosensitivity and pedal intertrigo.

Contents

10. Quality Procedures / Assurance

a. ***Outcome Measures:*** The outcome measures are response to delivered questionnaires on adverse events and compliance, identified log returns on compliance and a positive malaria blood smear confirming clinical malaria.

b. ***Safety Parameters:*** Safety parameters established for the trial are the monitoring of:

i. Routine clinical laboratory tests (haematology and biochemistry) on a representative sample following loading dose;
ii. Adverse events as per outcomes; and
iii. Pregnancy testing

c. ***Clinical Trial Material:*** All MQ will be provided through the ADF Supply system using conventional distribution methods.

Contents

11. Laboratory Procedures

Whole venous blood will be collected by venepuncture. Each sample will be collected in 5ml Lithium Heparin tubes, with no more than 30mls of blood being collected for this study.

Methodology for all laboratory procedures will be included in the trial SOP. Procedures will include:

a. ***Measurement of Parasitaemia*** - Thick and thin blood films for malaria will be obtained from a venous sample to confirm malaria as required by clinical examination. Blood films will be stained with Giemsa and evaluated by standard techniques. A confirmed instance of positive parasitaemia will be considered a failure of chemoprophylaxis.

b. ***Haematology*** - The following haematology tests will be performed following loading does on a representative selection of the group, with a manual differentiation performed on abnormal findings:

i. Haemoglobin;
ii. PCV (Haematocrit);
iii. Platelets;
iv. Total White Cell Count;
v. Lymphocyte Count.

c. ***Biochemistry*** - Biochemistry will be performed following loading does on a representative selection of the group. Investigations will include Creatinine and ALT (SGOT) analysed on site using Reflotron. Additionally, the following parameters will be analysed by AMI on frozen serum:

i. Sodium;
ii. Potassium;
iii. Albumin;
iv. Urea;

v. Total Bilirubin;
vi. Alkaline Phosphatase.

d. ***Pharmacology Venous Blood Sampling Schedule-*** Venous blood samples will be collected following loading dose and at intervals throughout the deployment as outlined above.

All blood samples will be immediately stored on ice and then centrifuged at 2,000 rpm for 15 minutes. Plasma will be separated and stored at -20°C until analysed. Plasma concentrations of MQ will be measured by HPLC at AMI.

e. ***Pregnancy Testing*** - All volunteers of child bearing potential will be tested for pregnancy at screening by urine testing techniques using standardised test kits. Although the dosing period is only 14 days maximum, women who believe they have become (or think they are) pregnant or who record a positive result on urine testing will be excluded from the study.

Contents

12. Drug Dose

The study drug will be supplied as Mefloquine 250mg tablets taken as follows:

a. Loading dose: 250 mg second daily for three doses in the week prior to deployment; and
b. Maintenance dose: 250mg weekly.

Contents

13. Drug Storage, Inventory and Log Sheets

The conventional supply system for the Battalion group will be utilised. Study drugs will be stored according to the manufacturer's recommendations at ambient temperature (not greater than 25°C). The principal investigators will keep a record of all study drugs used. The drug will be distributed to individuals weekly by Platoon NCO in accordance with Formation Routine Orders and logged. The Investigator will collect log returns weekly.

Contents

14. Personnel Responsibilities

The Principal Investigators or Co-investigators shall:

a. obtain informed consent from volunteers in the study
b. issue and collect all documentation, and
c. investigate all reported adverse events.

Only clinically endorsed personnel will perform blood sampling.

Contents

15. Adverse Events

Volunteers will have a history and physical examination done whenever there are reported adverse events. All adverse events will be notified and discussed with a Principle Investigator within one week for a decision regarding continuation on MQ.

In the case of clinical malaria, full clinical records from the treatment facility will be obtained for all confirmed cases.

All deaths, potentially lethal events and hospitalisation are serious adverse events (SAE). These are to be notified to a Principle Investigator within 24 hours for continuation of the individual in the trial.

Any adverse reaction will be treated as medically indicated regardless of enrolment in the trial.

The definitions and reporting requirements for adverse events (AE) and serious adverse events (SAE) are detailed at Annex B.

Contents

16. Withdrawal of Volunteers

Volunteers may withdraw themselves or be withdrawn from the study at any time without prejudice or compromise to appropriate treatment or chemoprophylaxis or detriment to military career. Volunteers will be withdrawn from the study if they experience significant adverse events to the study medicine, or if concomitant illness is likely to compromise their physical well being or their participation in the study. Reasons for withdrawal will be recorded in the CRF. If withdrawal is due to an Adverse Event then an Adverse Event Form will be completed.

Contents

17. Concurrent Medication

If a volunteer develops an infection requiring treatment with antibiotics, the attending study clinician will, if possible, prescribe an antibiotic without known antimalarial action. All other concurrent medication will be recorded on the CRF.

Contents

18. Contraception

Female volunteers determined to be non-pregnant on entry to the study will be counselled on contraception, and encouraged to continue precautions until 4 weeks after the last dose of study drug.

Contents

19. Data Management and Analysis

Data will be entered from Case Record Forms (CRF's) onto a computerised database (MS Access). At the end of the study, all data will be crosschecked against original data capture sheets. The following arrangements for data management and analysis will be applied:

a. ***Data Storage and Retrieval*** - CRFs provided by AMI will be completed for each volunteer and will include the volunteer Consent Form and Adverse Event Form. Completed original CRFs, signed by the investigator, will be retained by AMI. CRF data will be edited where necessary with the agreement of the investigator to ensure completeness and consistency. The investigators will endeavour to ensure all data is complete, with phone followup initiated if indicated.

b. ***Effectiveness Analysis*** - The effectiveness end point will be the proportion of volunteers developing patent parasitaemia during the twelve (12) months after redeployment to Australia.

c. ***Safety Analysis*** - The study population will serve as the denominator for tolerability. Incidence of all adverse events will be determined, reported and tabulated. Adverse events will be recorded along with the event's intensity, seriousness, investigator-attributed causality, onset and cessation. Clinical laboratory values 1.5 times outside the normal range will be flagged.

d. ***Blood Drug Analysis*** - Plasma concentrations of MQ will be determined and related to prophylaxis failure rates.

e. ***Use of data:*** A copy of the clinical record forms, the personal medication diaries, drug control logs, adverse event forms and the original laboratory record sheets will be kept on file at AMI for a period of not less than 7 years. It is expected that these data will be reported in both scientific journals and at scientific meetings, and may be submitted to governmental medication regulatory authorities for review. Confidentiality of volunteers will be maintained. Volunteers will be informed in general terms of the results as soon as practical. All publications resulting from this study will be cleared through the Australian Defence Force.

Contents

20. Volunteer Consent

Volunteers will be recruited using non-coercive means. No inducement will be offered. The investigator is responsible for ensuring the volunteer understands the nature and purpose of the study. Volunteers who are invited to take part in a clinical trial are entitled to make a choice based on full and complete information presented in a manner that is understandable and ethnically appropriate. The Information and Consent Form (Annex A) is designed to assure the protection of the volunteer's rights.

The investigator will inform the volunteer of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it may entail. In addition, a copy of the Information and Consent Form will be provided which outlines this detail. The volunteer will be given every opportunity to clarify any points that he/she may not understand and to seek additional information. The volunteer will retain the right to withdraw from the study at any time without penalty. The investigator is responsible for ensuring that the volunteer has full knowledge and for obtaining the volunteer's freely given informed consent.

The informed consent will be recorded in writing with the investigator and the volunteer both signing and dating the Information and Consent Form.

The signed Information and Consent Form will be retained with the original CRF.

Contents

References:

1 IND #38503 (Etaquine), Surgeon General, U.S Army, Section 8.2.1.1.

2 IND #38503 (Etaquine), Surgeon General, U.S Army, Section 8.2.1.1.

3 Investigator's Brochure (1997 revised), WR 238,605, U.S Army, Office of the Surgeon General.

[redacted]

ANNEX A to
Protocol MQ001

CONSENT FORM / INFORMATION SHEET

Volunteer Number: _____ Volunteers Initials: _____

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

As you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. Additionally, on completion of your deployment you will be given different drugs to eliminate the stage of vivax malaria that can lie dormant in your liver (hypnozoites). The purpose of this study is to look at how efficient two of these eradication drugs are in eliminating the hypnozoites (liver) stage. One of these drugs, Primaquine, is the current in service eradication course, while the other, Tafenaquine, is a new drug reported to be more effective and taken over a shorter period of time.

The benefit of taking part in the study is that you will be monitored for the development of malaria following your deployment and treated promptly. In addition, the study results may provide a better understanding on how to prevent vivax malaria infection following overseas deployments in the future.

WHAT IS THE MEDICINE?

Two drug schedules will be used in the study. They are:

a. Primaquine - one 7.5 mg tablet taken 3 times daily for 14 days, with Doxycyccline 100mg once daily for 14 days; and
b. Tafenaquine - one 500 mg tablet taken once a day for 3 days.

WHAT IS THE STUDY?

The study involves half of the redeploying group receiving the standard eradication drug, Primaquine, while the other half of the group takes the newer drug, Tafenaquine. The allocation to either drug is determined at random. Should you develop a fever within 12 months of returning home, you are asked to attend your local health facility and show them your study ID card. This ID card will contain details on how you should be investigated, how to contact the investigators, and how you should be treated if malaria is diagnosed.

[redacted]

LENGTH OF THE STUDY

The study will begin 4 days prior to your redeployment and will be continued until 12 months after your deployment is completed. However, your only involvement after redeployment will be to send back to AMI your *Personal Medication Diary*, unless of course you develop fever.

STUDY TESTS

As the investigators are looking at baseline drug levels in your blood, and measuring your biochemistry and haematology levels to monitor safety, you will be requested to donate two samples of blood from your arm. The amount of blood collected for the study amounts to no more than about 20mls, or the equivalent of 4 teaspoons.

Additionally, you will be asked to keep a record of your medication and complete the diary section recording any adverse experiences you may notice while on the medication. This diary is then to be returned to AMI two weeks after you return to Australia on redeployment.

RISKS / DISCOMFORTS

There may be some bruising with blood taken from the veins in your arm.

Both study drugs have a risk of producing a bleeding disorder if given to people who lack a particular enzyme called G6PD. You have been tested for this enzyme prior to deployment, and will not receive either drug if you have this deficiency. In seven clinical trials involving human subjects, Tafenaquine was noted to produce some nausea and diarrhoea in some subjects (usually self limiting and improved by taking the medication with food) and mild headache. Primaquine produces similar side effects. Both drugs are considered to be safe. Neither drug is recommended for use in pregnant females.

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have experienced this type of reaction, or if you think (females only) that you may be pregnant, please discuss this with the study Medical Officer.

Initials:_____

[redacted]

[redacted]

CONFIDENTIALITY

In all reports a number only will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

COMPENSATION

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. In the event that you believe that injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility, and the study investigators should be advised by calling the pager number on your study ID card.

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the study investigators, or your medical facility. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP4-6-45
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3807

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.

The study doctor has the right to withdraw you from the study if he/she feels it is appropriate to do so.

Initials:_____

[redacted]

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me and understand all the points. All questions raised by me have been answered to my satisfaction. I have been given a copy of this consent form/information sheet. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____
Date: _____

INVESTIGATOR'S SIGNATURE _____

Printed Name: _____
Date: _____

ANNEX B to
Protocol MQ001

ADVERSE EXPERIENCES GUIDELINES

Adverse Experiences

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out below.

Eliciting and Documenting Adverse Experiences

It is the responsibility of the investigator to document all adverse experiences which occur during the investigation. An adverse experience include any noxious, pathological or unintended change in anatomical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of thew clinical study whether associated with the study drug or placebo and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the case record under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences.

In the case of studies involving a marketed drug in an established indication, an adverse experience includes significant failure of the expected pharmacological or biological action.

All adverse experiences occurring after the start of the study must be reported. Subject entry into the study is defined as the time at which informed consent is obtained (This must be before any protocol-specific diagnostic procedures or interventions) All subsequent adverse experiences, whether no drug (ie. during reference 'run-in' or 'wash-out' period) or when active drug or placebo is being administered, must be reported REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.

At each visit /assessment, adverse experiences will.be evaluated by the investigator. Adverse experiences not previously documented in the study will be recorded in the adverse experience section of the subject's case record form. The nature of each experience date and time (where appropriate) of onset, duration, severity and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the case record form.

Adverse experiences already documented in the CRF ie. at a previous assessment and designated as `continuing' should be reviewed. If these have resolved, the documentation in the CRF should be completed. NB. If an adverse experience changes in frequency or severity during a study period, a new record of the experience will be started.

Ask the subject or the subjects parent or legal guardian a non-leading question such as:

> "Do you feel different in any way since starting the new treatment/the last assessment?"

Assessment of Severity

Maximum intensity should be assigned to one of the following categories:

Mild: For example, an adverse experience which is easily tolerated by the subject, causing minimal discomfort not interfering with everyday activities.

Moderate: For example, an adverse experience that is sufficiently discomforting to interfere with normal everyday activities.

Severe: For example, an adverse experience which prevents normal everyday activities

Assessment of Causality

Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: ***not related***, ***unlikely***, ***suspected*** (reasonable possibility), ***probable.***

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, eg. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The experience having often been reported in literature for similar drug as drug related eg. skin rashes, blood dyscrasia
- The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

Following-up of Adverse Experiences

Investigators should follow-up subjects with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the subject's subsequent course must be submitted to the clinical study monitor.

Serious Adverse Experiences

Definition of Serious Adverse Experiences

A serious adverse experience is any event which is fatal, life threatening, disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event.

Life threatening – definition:

An adverse experience is life threatening if the subject was at immediate risk of death from the event as it occurred; ie. It does not include a reaction that if it had occurred in a more serious form might have caused death For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Disability /incapacitating definition:

An adverse experience is incapacitating or disabling if the experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions

Reporting Serious Adverse Experiences

Any serious adverse experiences that occur during the clinical study whether or not related to the study drug, must be reported by the investigator to the study monitor (by telephone within 24hrs).

All serious adverse experiences must be reported by telephone within 24hrs to the study monitor or Principle Investigator.

Name: Major Scott Kitchener

Telephone: s22 [redacted]

The telephone report should be followed by full written summary detailing relevant aspects of the adverse experiences in question. Where applicable information from relevant hospital case records and autopsy reports should be obtained.

Instances of death cancer or congenital abnormality if brought to the attention of the investigator *AT ANY TIME* after the cessation of study medication and linked by the investigator to a previous clinical trial, should be reported to the study monitor.

[redacted]

Overdose

Any instance of overdose (suspected or confirmed) must be communicated the Principle Investigator within 24 hours and be fully documented as a serious adverse experience. Details of any signs of symptoms and their management should be recorded including details of any antidotes administered.

Pregnancy

Subjects who become pregnant during the dosing periods (clearing dosing and prophylactic dosing) should discontinue dosing immediately. However subjects who become pregnant during the followup phase of the study should continued to be monitored as originally scheduled.

Subjects should be instructed to notify the investigator if it is determined after the completion of the study that they became pregnant either during the treatment or prophylaxis-dosing phase of the study or during the followup period.

Whenever possible a pregnancy should be followed up to term, any premature terminations reported, and the status of the mother and child should be reported after delivery.

[redacted]

Case Record Form – MQ001

Enrolment:

DEMOGRAPHIC DATA:

Volunteer No: _____ Volunteer Initials: _____
Corps: _____ Age: _____ (yrs)
Unit: _____ Sex: M F (please circle)
Weight: _____ (kgs) Height: _____ (cm)
Date admitted to the Study: _____ (dd/mm/yy)

ADMISSION CRITERIA:

The following questions must all be answered "No" for a volunteer to be eligible for study entry:

	Please Circle One	
Does the volunteer have any significant illness?	Y	N
Is the volunteer Medically Fit?	Y	N
Is the female volunteer using an established method of contraception	Y	N
Has the volunteer any known reactions to any of the study compounds?	Y	N
Is the volunteer ***unwilling*** to give blood smears and blood samples?	Y	N
Has written informed consent been obtained	Y	N

If female, the volunteer must have had a negative pregnancy test and have received counselling on contraception:

Result of pregnancy test: Pos / Neg Date: _____ (dd/mm/yy)

Contraceptive counselling: Yes / No Date: _____ (dd/mm/yy)

Explanation for any deviation from the appropriate responses:

(An explanation of any "N" response is to be given **and** the volunteer is to be excluded from the study.)

_____
_____
_____
_____
_____
_____

[redacted]

[redacted]

Laboratory Test Results – MQ001

Vol ID:	Vol Init:

Haematology:

Date (dd/mm/yy)		
Schedule	Screening	Follow up
RBC (/pl)		
Haemoglobin(g/dl)		
Haematocrit(%)		
WCC(/nl)		
Neutrophils (%)		
Lymphocyes(%)		
Monocytes(%)		
Basophils(%)		
Eosinophils(%)		
Platelete Count(/nl)		

Biochemistry:

Date (dd/mm/yy)		
Schedule	Screening	Follow up
Total Bilirubin		
AST/SGOT		
ALT/SGPT		
GGT		
Glucose		
BUN		
Albumin		

If female - Pregnancy Test Results

Date (dd/mm/yy)	
Schedule	Screening

Record of Parasitaemia

Date (dd/mm/yy)			
Schedule	First Episode	Second Episode	Third Episode
Type / Count			

Exclusions from the study:

- **Haematological and biochemistry parameters greater than 1.5 times normal.**
- **Positive pregnancy test in women volunteers.**

[redacted]

Compliance (tick if logged return) **Loading dose date:** **Eradication dose date:**

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26

Questionnaire on adverse events

"Are there any health effects you attribute to your malaria prevention medication?"

Questionnaire Date	Describe the health effects and when they occurred? *(If "yes" to "Any health effects?")*
Following loading	
Any health effects?	
Yes/No	
Field value	
Any health effects?	
Yes/No	
During extraction	
Any health effects?	
Yes/No	

MQ blood levels

Date				
MQ level				

References

[i] Petersen E, Ronne T, Ronn A, Bygbjerg I, Larsen SO. Reported side effects to chloroquine, chloroquine plus proguanil, and mefloquine as chemoprophylaxis against malaria in Danish travelers. *J Travel Med* 2000 Mar-Apr;7(2):79-84.

[ii] Huzly D, Schonfeld C, Beuerle W, Bienzle U. Malaria Chemoprophylaxis in German Tourists: A Prospective Study on Compliance and Adverse Reactions. *J Travel Med* 1996 Sep 1;3(3):148-155.

[iii] Croft AM, Garner P. Mefloquine for preventing malaria in non-immune adult travellers. *Cochrane Database Syst Rev* 2000;(3):CD000138.

[iv] Phillips MA, Kass RB. User Acceptability Patterns for Mefloquine and Doxycycline Malaria Chemoprophylaxis. *J Travel Med* 1996 Mar 1;3(1):40-45.

[v] Peragallo MS, Sabatinelli G, Sarnicola G. Compliance and tolerability of mefloquine and chloroquine plus proguanil for long-term malaria chemoprophylaxis in groups at particular risk (the military). *Trans R Soc Trop Med Hyg* 1999 Jan-Feb;93(1):73-7.

Department of Defence

MINUTE

548-7-13

Executive Secretary (Attention: Australian Defence Force Medical ethics Committee) (CP2–7–66)

FURTHER SUPPORT TO PROTOCOL MQ001

1. Further to our telecon (19 Feb 01) regarding safety of Mefloquine for widespread use under trial conditions in an area of operations, I understand the concerns of a large trial in an operational area with possible neuropsychiatric adverse events arising from the chemoprophylaxis.

2. I forward the following points in support of the trial:

a) Mefloquine is currently the first alternative to Doxycycline for malaria chemoprophylaxis (HPD215), and is registered by the Australian TGA for use as such,

b) The Tafenoquine prophylaxis trial has been approved by ADMEC using Mefloquine for the control group,

c) Evidence from the Tafenoquine prophylaxis trial suggests minimal SAE and good protection from both agents,

d) This trial incorporates a pre-deployment phase with review of adverse events prior to deployment following a loading dose – AE should present during this period, and

e) The definitive review of Mefloquine is that for the Cochrane Library, Oxford, which concludes that the dramatic neuropsychiatric events related to Mefloquine are largely based on anecdotal evidence, that tolerability is the major problem, however, good evidence of the incidence and nature is not available (p10, Reviewer's conclusions attached). Garner and Croft go on to recommend studies to assess the tolerability of Mefloquine under field conditions (p12, attached).

3. I trust these points suitably address the concerns regarding this proposed trial.

s22 [redacted]

S J KITCHENER
MAJ
OC CLINICAL FIELD

ARMY MALARIA INSTITUTE

20 Feb 01

Surgeon General's Department – AD Med Pol

Croft AMJ, Garner P

Mefloquine for preventing malaria in non-immune adult travellers (*Cochrane Review*)

The Cochrane Library, Issue 4, 2000
Oxford: Update Software

Entry for the Alexander Memorial Prize 2000-2001

The controversy surrounding mefloquine demonstrates that at an international level there is a need to ensure that appropriate research is done, and that this research is used to develop valid, evidence-based guidelines on malaria prevention through an appropriately multiprofessional advisory panel. To achieve a balanced appraisal of which recommendations can be supported, and with what degree of certainty, the guideline development process should have the following characteristics:

1. The panel should optimally consist of between six to 10 members (Scott 1990, Woolf 1996). It should include representatives of key disciplines and interest groups (Bond 1995). Panel members need not necessarily have special expertise in the field of malaria prophylaxis, since excessive specialisation within a guidelines panel has been shown to introduce persuasive advocates and other subjectivities, and to act as a source of bias (Anonymous 1992, RCGP 1995, Woolf 1998). The production of any clinical guidelines must involve participants who are representative of the envisaged domain of practice (Leape 1992). Therefore at least one panel member should be a primary care physician (Lobach 1995).

2. Consumers should be represented on the panel (RCGP 1995).

3. The panel should use rigorous and pre-defined criteria for synthesising the best available research evidence (Woolf 1992).

4. The panel should evaluate the evidence base of all antimalaria strategies, i.e. bite avoidance measures, drugs, vaccines and environmental vector control. For each strategy, the strength of the scientific evidence should be quantified explicitly. Where uncertainty exists, this should be stated honestly (Haines 1992, CRD 1996).

5. Drugs should be systematically assessed according to their toxicity, efficacy, tolerability and convenience (Bero 1996, Greenhalgh 1997).

6. The guidelines issued by the panel should be risk-based, in that they should explicitly reflect the association between the degree of benefit resulting from different antimalarial strategies and the level of risk associated with each strategy (Davey Smith 1994).

7. At an early stage of their development, the guidelines should be submitted for scrutiny and comment by topic experts and interested agencies, both local and international (RCGP 1995). There should be a formal dissemination strategy for encouraging these agencies to assume ownership of the final product (AHCPR 1992, Haines 1992).

8. The language of the guidelines should be lucid, and the form and content should be accessible to all users. This can be achieved by using a structured format, and through judicious use of brief checklists and key summaries (Haines 1992).

9. The guidelines must be continually updated to take account of new scientific evidence, and particularly the results of randomised controlled trials and systematic reviews (Haines 1992, Eccles 1996).

The evidence-based guidelines produced by this multiprofessional international panel should be translated into national recommendations, both internally valid and externally reproducible. These national guidelines should include information on the costs of different chemoprophylactic regimens, and the costs of other preventive strategies (Bero 1996, CRD 1996). The national guidelines should be made available to practitioners in electronic format, both for ease of updating and to act as prompts to good practice (Omstein 1991, Litzelman 1993, Bargery 1994, Lobach 1995).

Consumers in each country should have ready access to the guidelines, and to a summary of the supporting evidence, so as to be empowered to make informed choices about their own health (RCGP 1995, Jacobson 1997, Liberati 1997).

Implications for research

It is often not possible to make a final risk-benefit assessment of a new drug until several years after marketing and broad clinical experience (Christ 1991). Where patients are healthy to start with, however (as is the case with most travellers), the pre-licensing evaluation of a

ANNEXE 2

Minutes from ADHREC meetings related to Protocol 240/01 Evaluation safety and adverse effects of mefloquine in the prophylaxis of malaria in non-immune Australia soldiers.

DEFENCE PERSONNEL EXECUTIVE

SG97-6600

See distribution

MINUTES OF THE FORTY FIRST MEETI NG OF THE AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE,
HELD AT CAMPBELL PARK OFFICES (CP2-5-04) CANBERRA ACT 2600 ON MONDAY 26 FEBRUARY AT 1630 HOURS

22

[redacted]

22

b. **Protocol 249/01 – Evaluation of Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Subjects**

(1) This protocol caused considerable debate when it becam e apparent that Mefloquine had potentially serious side effects of which ADMEC had been previously unaware. In particular, CNS side effects of depression and psychosis caused considerable concern to Com mittee, especially were they to occur in deployed troops. emphasised that this prospective study was scientifically necessary in order to accurately

categorise the side effect profile of the drug, which is currently the second line treatm ent of choice for m alaria. He also explained that by far the majority of side effects m anifest w ithin the first four doses of the drug, which will be adm inistered within Aust ralia. 47F

A revised consent and inform ation sheet

Decision

ADMEC agreed to accept the protocol on the following conditions:

a. The inf ormation and consent sheet are to be am ended to clearly outline in quantitative term s the side effects of the m edication, including CNS and cardiovascular side effects, and are to include rare events as well as common.
b. The study should be retitled “Evaluation of Safety and Adverse Effects of Mefloquine in the Prophylaxis of Malaria In Non-Immune Australian Soldiers"” to more accurately reflect the intent of the study.
c. Six doses of the medication are to be given in Australia prior to deployment.

22

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[redacted]

h. **Protocol 216/00 - A Randomised, Double-Blind, Comparative Study To Evaluate The Safety, Tolerability And Effectiveness Of Tafenoquine And Mefloquine For The Prophylaxis Of Malaria In Non-Immune Australian Soldiers Deployed To East Timor**

Decision
ADMEC agreed to accept the m odification to th e protocol. In addition, ADMEC decided to develop its own Serious Adverse Events form for use in the event that one was not otherwise provided by the researcher.
For action:
Exec Sec

22

13. ADMEC then considered and noted the following Progress reports:

22

22

f. **Protocol 216/00 - A Randomised, Doubl e-Blind, Comparative Study To Evaluate The Safety, Tolerability A nd Effectiveness Of Tafenoquine And Mefloquine For The Prophylaxis Of Malaria In Non-Immune Australian Soldiers Deployed To East Timor;**

22

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**MINUTES OF THE FORTY SECOND MEETING OF THE AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE,
HELD AT CAMPBELL PARK OFFICES (CP2-5-04) CANBERRA ACT 2600 ON MONDAY 23 APRIL AT 1630 HOURS**

22

[redacted]

22 [redacted]

b. **Protocol 249/01 – Evaluation of Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Soldiers.**

Decision
ADMEC approved the modifications as detailed.
For action:
Exec Sec

22 [redacted]

DEFENCE PERSONNEL EXECUTIVE

SG97-6600

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**MINUTES OF THE FORTY THIRD MEETI NG OF THE AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE,
HELD AT CAMPBELL PARK OFFICES (CP2-5-04) CANBERRA ACT 2600 ON MONDAY 18 JUNE AT 1630 HOURS**

22

[redacted]

22

(1) Serious Adverse Events (SAE) from the use of Tafenoquine in Protocol 216/00 – A Random ised Double Blind Com parative Study to Evaluate the Safety, Tolerability, and Effectiveness of Tafenoquine and Mefloquine for the Prophylaxis of Malaria in Non-Im mune Australian Soldiers Deployed to East Timor

6. 47F addressed ADHREC at length with regard to the SAEs observed in the above study. He referred in particular to the ke ratopathy resulting in whorls in front of the cornea which have been observed following ophtha lmological examination of study subjects. These effects have been found in approxim ately 75% of the 97 subjects randomly selected for detailed examination. 47F was unable to confirm whether this proportion related to the 75% of subjects receiving Tafenoquine, as the researchers are blinded to which subjects are receiving Tafenoquine, and which Mefloquine.

7. 47F in particular questioned 47F as to whether he had any knowledge of the keratopathy having long term manifestations, or whether the keratopathy had ever recurred at a later date, for example years later, following cessation of administration

of related drugs. 47F assured ADHREC that in his extensive research into these questions he had not discovered that either situation had ever arisen.

8. The Chair then asked 47F be excused. Lengthy discussion took place regarding the SAEs above, and the implications for any further use of the drug in the future. The Chair explained to ADHREC that this type of side effect is well known in other drugs of similar type, known as cationic amphiphilic compounds, notably amiodarone, which is used in the treatment of cardiac dysrhythmia. Keratopathy in this case is not regarded as an indication for cessation of treatment, but rather a sign that the patient is taking their medication. Changes are well known to be reversible on cessation of the medication.

9. 47F suggested to ADHREC that an opinion from an independent ophthalmologist be sought to advise Committee of the likely significance of the above findings. In addition, discussion took place as to how long a time period to full or partial resolution of the effects was reasonable. Discussion also took place to the effect that any commencement of further trials involving Tafenoquine could occur until these matters were resolved.

Recommendation:
The meeting resolved to request an independent ophthalmological assessment of the likely effects of keratopathy from the specialist Reserve ophthalmology consultant to the Defence Health Service. ADHREC maintained its position that no further administration of Tafenoquine is to take place in any AMI trials until formal ophthalmological review has shown that keratopathy has completely resolved, or that specialist advice is that it will resolve in the near future. An appropriate time frame for this resolution is to be indicated. This opinion is to be furnished in writing to ADHREC. Formal clearance in writing to AMI to proceed with any use of Tafenoquine will only be given when ADHREC has had the above matters addressed to its satisfaction.

For action:
Chair
Exec Sec

47F

(2) Protocol 249/01 – Evaluation of Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Soldiers

11. 47F addressed ADHREC on the above protocol.

Recommendation:
The meeting resolved to approve 47F request to extend the research sample size. The name of the protocol is to be changed to read: 'Evaluation of Tolerability of Mefloquine in the Prophylaxis of Malaria in Non-Immune Australian Soldiers'

For action:
Exec Sec

22

DEFENCE PERSONNEL EXECUTIVE

SG97-6600

See distribution

22

[redacted]

22 [redacted]

e. Protocol Audit Reports

(1) Protocol 216/00 – A Random ized, Double-Blind, Com parative Study to Evaluate the Safety, Tolerability and Effectivene ss of Tafenoquine and Mefloquine for the Prophylaxis of Malaria in Non-Im mune Australian Soldiers Deployed to East Timor.

19. 47F visited the Army Malaria Institute in Brisbane to conduct an audit on the above protocol. 47F [redacted] 47F 47F informed the com mittee that the ADHREC audit team was very well received by the unit, a nd that the level of record keeping was of a high standard.

20. During the course of the audit, it was f ound that there was one consent form missing. The unit has undertaken to inform ADHREC when this form is located.

DEFENCE PERSONNEL

DEFENCE PERSONNEL EXECUTIVE

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**MINUTES OF THE FORTY SIXTH MEETI NG OF THE AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE,
HELD AT CAMPBELL PARK OFFICES (CP2-5-04) CANBERRA ACT 2600 ON MONDAY 25 FEBRUARY 2002 AT 1630 HOURS**

22

e. Protocol 216/00 – A Randomiz ed, Double- Blind, Comparative Study to Evaluate the Safety, Tolerability and Effectiveness of Tafenoquine and Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Soldiers Deployed to East Timor.

(1) Safety Update.

13. 47F whilst the inform ation provided in this safety report was reassuring, it would be prefer able to have all inform ation conveyed openly and honestly to every m ember involved in curre nt and previous Tafenoquine trials. This will markedly reduce the risk of a perceived cover up.

Decision
The Principal Investigator is to provide a copy to ADHREC for review of the draft letter from Glaxo SmithKline that is proposed to be distributed to subjects.

For Action:
Exec Sec

(2) Progress Report.

Decision
The Progress Report was noted by ADHREC.

(3) Corrective Action Request – AMI Response.

14. The m issing consent form has not yet b een located. AMI will notify ADHREC when they find it.

Decision
Exec Sec and Assistant Exec Sec to m onitor this situation and report back to ADHREC when the missing form is found.

For Action:
Exec Sec
Assistant Exec Sec

22

DEFENCE PERSONNEL

DEFENCE PERSONNEL EXECUTIVE

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**MINUTES OF THE FORTY EIGHTH MEETING OF THE AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE,
HELD AT CAMPBELL PARK OFFICES (CP2-5-04) CANBERRA ACT 2600 ON MONDAY 17 JUNE 2002 AT 1630 HOURS**

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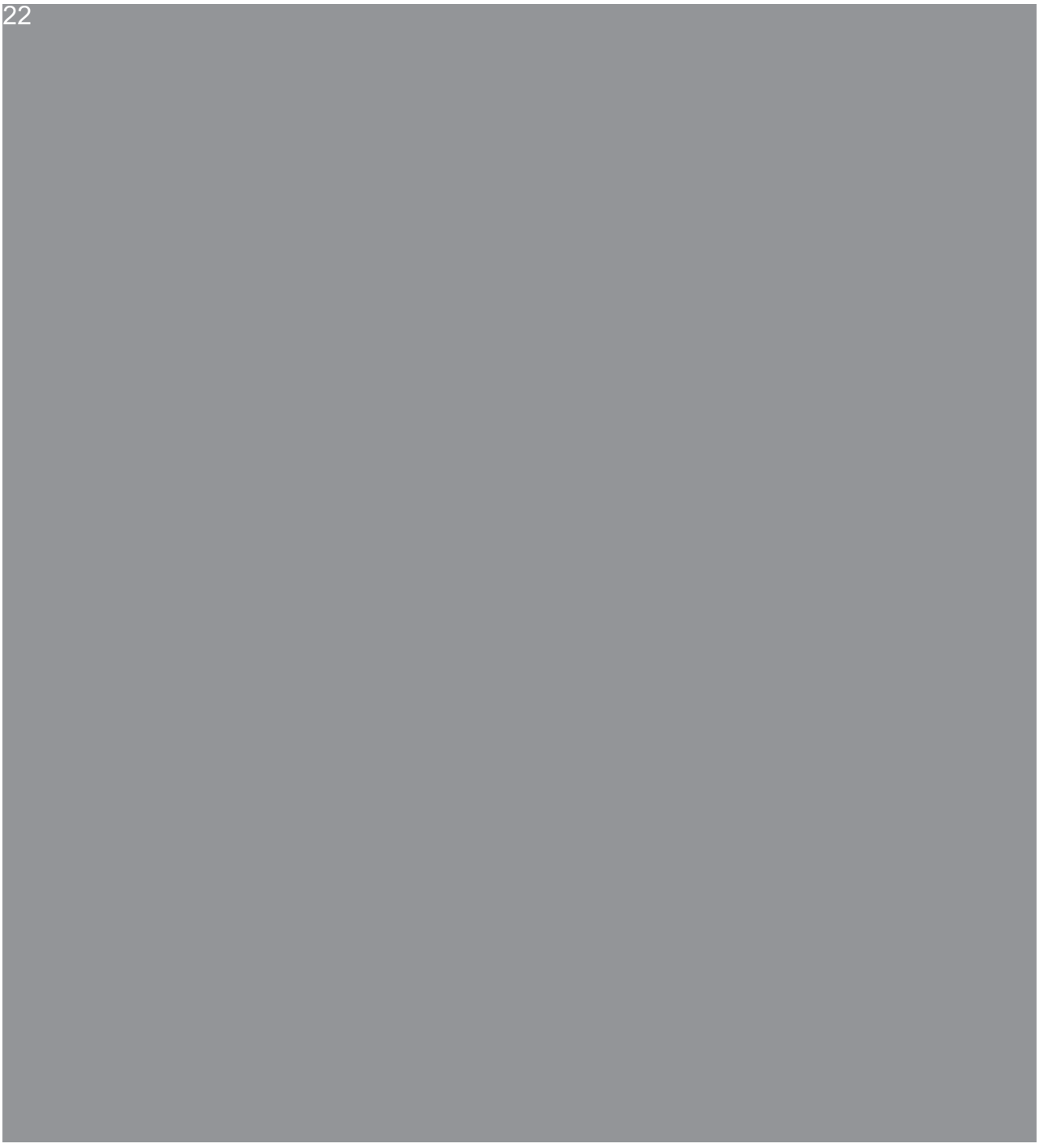

c. 47F **Protocols 216/00 – A Randomised, Double-Blind, Comparative Study to Evaluate the Safety, Tolerability and Effect iveness of Tafenoquine and Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Soldiers Deployed to East Timor** 47F

3. The Chair invited 47F 47F to address ADHREC. 47F inform ed ADHREC that the research relating to Protocol 216/00 is now com plete. The eye changes that were previously reported in some patients have now resolved, and there have been no further reports of visual disturbances experienced by any patient.

4. During the course of the analysis of the da ta collected, it was noted that there were a number of patients whose serum creatinine levels did not return to baseline, although they stayed within the norm al range. Am endment 7 was written to address this issue. 47F 47F asked ADHREC to consider whether it would be appropriate for the continued investigation of these patients to be conducted as clinical follow up instead of as a formal am endment to the Protocol. He stated that this would prevent f urther delay in the assessment of these patients. He also request ed that ADHREC consider appointing a renal physician to assist in the assessm ent of any patients whose serum creatinine is found to be still above baseline at the follow up assessm ent. He said that this had been a recom mendation from Glaxo SmithKline's renal consultative group.

5. 47F stated that, with ADHREC's approval, it was the intention of the researchers to close the study, but to continue to clinically monitor the patients who had been involved in the trial.

6. 47F were then asked to wait outside while the proposals were discussed.

Decision:
It was felt among the members that the researchers were displaying due diligence in following up on results that, even though they were still in the normal range, were not back to pre-trial levels. It was decided that;

(1) it would be appropriate for the affected patient s to be clinically m onitored, rather than amend the protocol,

(2) amendment 7 to Protocol 216/00 would be withdrawn, and

(3) a renal physician would be appointed to assist with clinical follow up if required.

For action:
Exec Sec
Assistant Exec Sec

DEFENCE PERSONNEL

DEFENCE PERSONNEL EXECUTIVE

SG97-6600

See distribution

**MINUTES OF THE FORTY NINTH MEETI NG OF THE AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE,
HELD AT CAMPBELL PARK OFFICES (CP2-5-04) CANBERRA ACT 2600 ON MONDAY 12 AUGUST 2002 AT 1630 HOURS**

22

[redacted]

(3) Protocol 249/01 – Evaluation of Mefloquine for the Prophylaxis of Malaria in Non-immune Australian Soldiers.

35. The apparent high incidence of adverse events was of concern to the Committee. The Exec Sec asked that the e-mail from 47F be taken away and reviewed by the Committee. She further explained that the AMI position on reporting of adverse events had been discussed with ADHREC previously. Following this discussion, the decision was made that AMI would only report on adverse events that were possibly drug related.

Decision:
ADHREC requires further information on the adverse events recorded in this study. This is to be circulated out of session for discussion at the next meeting.

The reporting of adverse events by researchers is to be tabled as a discussion point for the next meeting.

For action:
Exec Sec
Assistant Exec Sec

22

ANNEX A TO
1177/2002
DATED 6 DEC 2002

DEFENCE PERSONNEL EXECUTIVE
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MINUTES OF THE FIFTIETH MEETI NG OF THE AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE,
HELD AT CAMPBELL PARK OFFICES (CP2-5-04) CANBERRA ACT 2600 ON MONDAY 25 NOVEMBER 2002 AT 1600 HOURS

22

[redacted]

d. Protocol 249/01 – Evaluation of Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Soldiers.

15. There was still a deal of unease among the members with regard to this Protocol. The Chair explained that the psychological evaluation has become an operational requirement. However, there were other problems that the Committee felt needed to be addressed. These included listing 47F as the Principal Investigator in the Protocol submission, a concern that the protocol presented was different to the research being proposed, and a requirement for a new questionnaire to be produced by the researchers.

Decision:
This Protocol is to be flagged as one to be audited by the Secretariat in the New Year.

For action:
Exec Sec
Assistant Exec Sec

22

Australian Government

Department of Defence
Defence Personnel Executive

DEFENCE PERSONNEL EXECUTIVE

SG97-6600

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**MINUTES OF THE FIFTY SIXTH MEETI NG OF THE AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE,
HELD AT CAMPBELL PARK OFFICES (CP2-7-069) CANBERRA ACT 2600 ON MONDAY 05 JULY 2004 AT 1630 HOURS**

22

[redacted]

22 [redacted]

ITEM 2. BUSINESS ARISING FROM THE PREVIOUS MEETING

a. Protocol 249/01- Evaluation of Mefloquine for the Prophylaxis of Malaria in non-immune Australian soldiers.

6. At the last meeting ADHREC members requested that all researchers advise ADHREC of all SAE reports. AMI has drafted Standing Operating Procedures (SOPs) for dealing with serious adverse events (SAEs) related to current and future trials. The SGADF approved the draft SOPs out of session.

7. The Draft SOPs were tabled by the Chair for approval by the Committee.

Decision:
The Committee approved the SOPs but highlighted the need for all SAEs to be reported to ADREC.

For action:
Exec Sec
Assistant Exec Sec

22 [redacted]

Australian Government
Department of Defence
Defence Personnel Executive

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2002/1936/3
DHSB 214/05

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**MINUTES OF THE FIFTY-SEVENTH MEETING OF THE AUSTRALIAN DEFENCE HUMAN RESEARCH AND ETHICS COMMITTEE
CAMPBELL PARK OFFICES (CP2-7-069) CANBERRA ACT 2600
MONDAY 28 FEBRUARY 2005 AT 1600 HOURS**

22

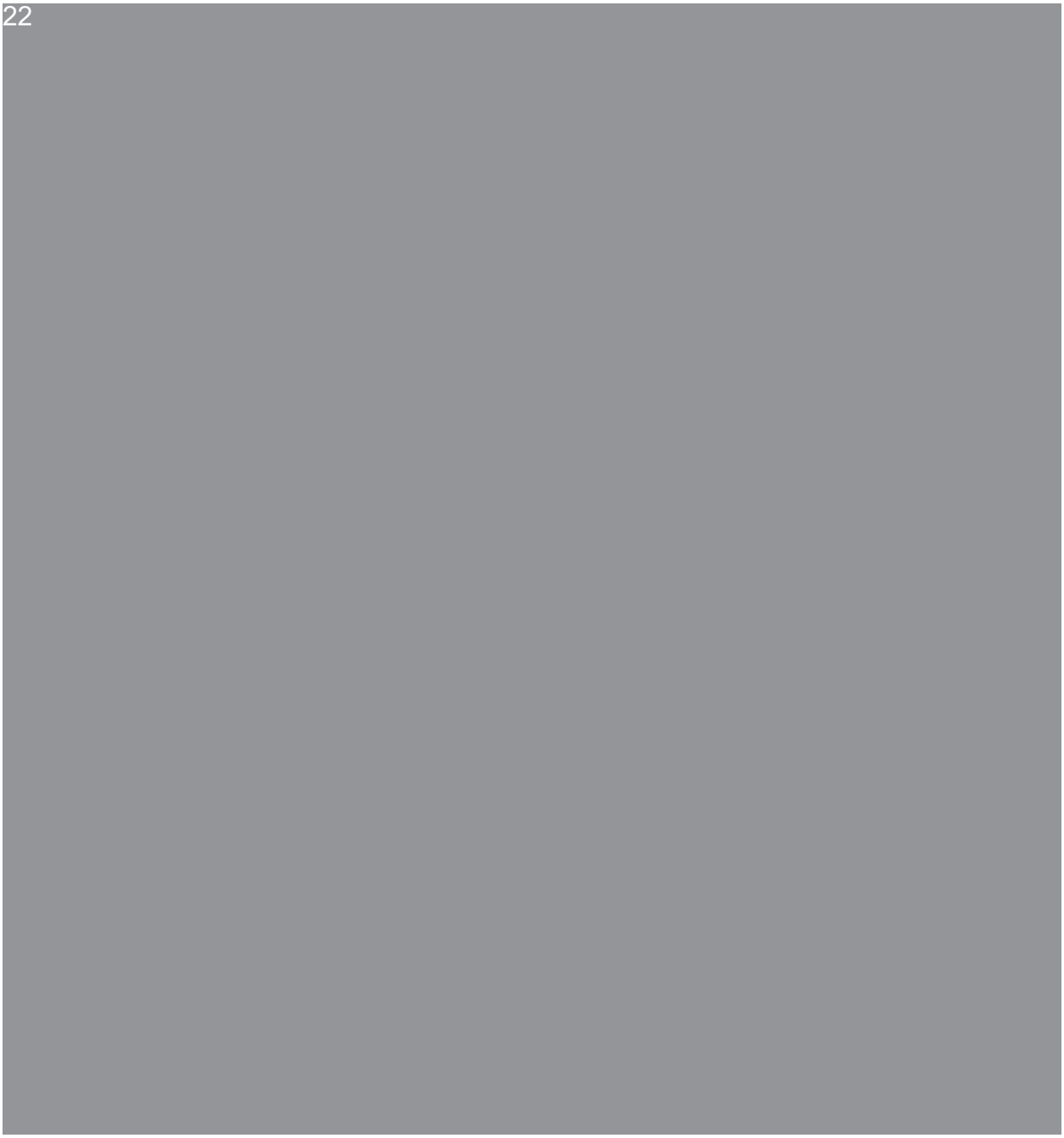
b. Protocol 249/01: Evalu ation of Mefloquine for the prop hylaxis of Malaria in non-immune Australian soldiers.

11. The committee noted that the modification details had not been clarified or presented from last m eeting. The Executive Secretary explained that the m odifications had been discussed with the Comm anding Officer of AMI. He would clarify th at the m odifications referred to were not to the p rotocol per se, but to the operat ional orders of the soldiers representing the protocol participants.

Decision:
The comm ittee requested the clarification of th e above m odifications, ie that they refer to operational modifications, not protocol modifications.

Action:
Exec sec

22



Australian Government
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Defence Personnel Executive

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2002/1936/3
DHSB 654/05

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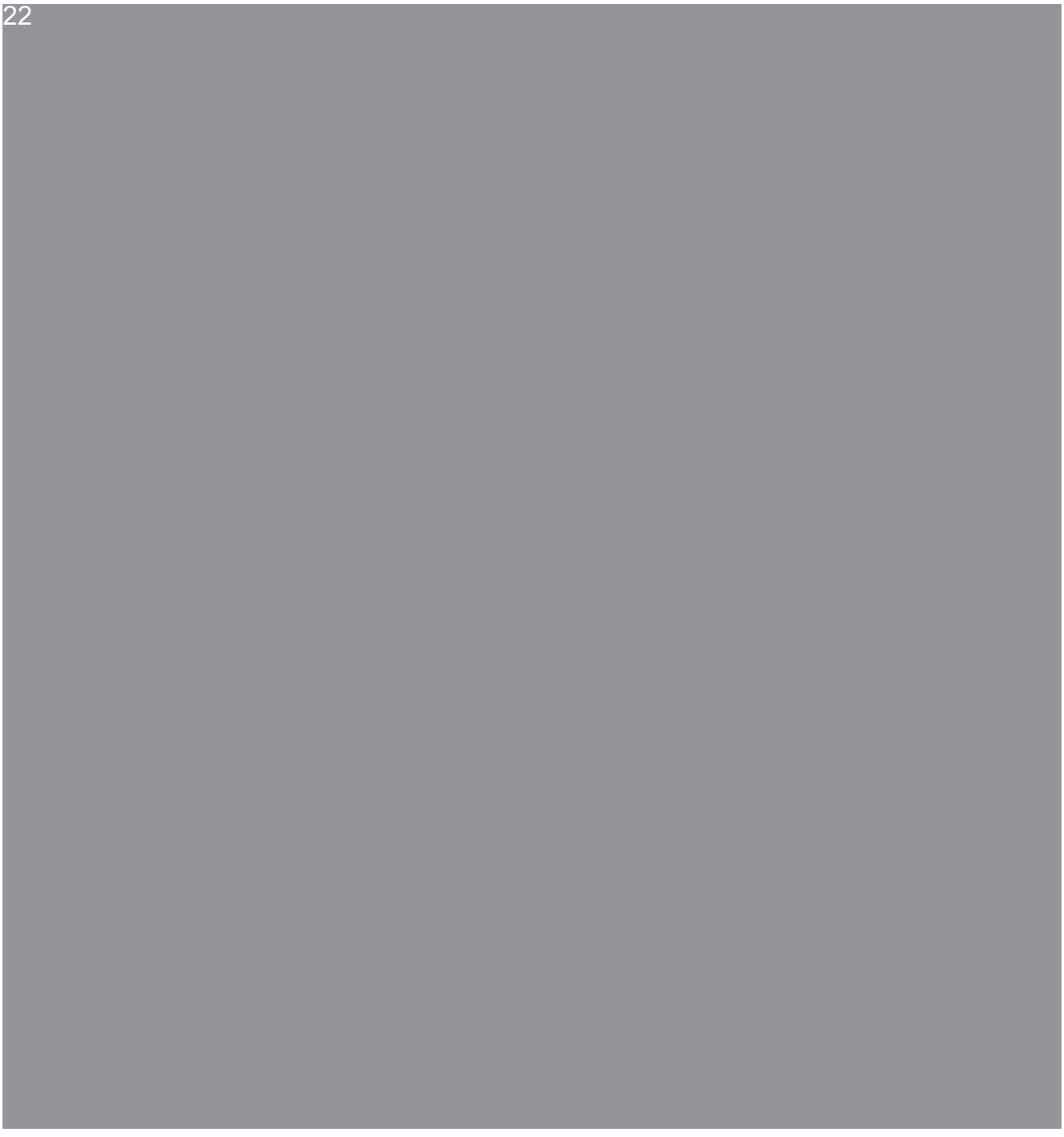
MINUTES OF AUSTRALI AN DEF ENCE H UMAN RESEARCH ETHICS COMMITTEE (ADHREC) FIFTY-NINTH MEETING HELD AT CAMPBELL PARK OFFICES (CP2-7-069) CANBERRA ACT 2600 ON MONDAY 4 JULY 2005 - 1630 HOURS

22



22 [redacted]

ITEM SEVEN – FINAL REPORTS

a. Protocol 249/01: Evaluation of mefloquine for the prophylaxis of malaria in non-immune australian soldiers

a) Article: "Mefloquine and Doxycycline Malaria Prophylaxis in Australian Soldiers in East Timor", Medical Journal of Australia, Vol 182 Number 4, 21 February 2005.

31. ADHREC noted that this was a very good paper.

32. The committee asked the Secretariat to look at the stated risks for doxcycline from this study and all studies using doxycycline that ADHREC holds.

33. The study contained one participant with undisclosed schizophrenia, one participant had epilepsy and one had depression. These numbers are within standard population rates.

Decision: Secretariat to write a letter of thanks fo r the report and congratulations on a project well completed. Secretariat to list risks of doxcycline from this and other Australian Malaria Institute (AMI) studies.

Action by: Exec Sec
Assist Exec Sec

b) Study report: "Evaluation of safety and adverse events of m efloquine in the prophylaxis of malaria in non-immune Australian soldiers", AMI Journal, January 2005.

34. Discussion occurred to the effect that this study is of benefit to the ADF. A query was raised as to whether the participants with p re-existing epilepsy were in the Res erve or Fu ll time service. It was presumed that they were in the Full time servic e, since participants were all from a regular Army Infantry Battalion.

22

[redacted]

22 [redacted]

ITEM ELEVEN- NEW BUSINESS

a. Complaint/query

55. ADHREC received a complaint/query from a member of the ADF, regarding *Protocol 249/01: Evaluation of Mefloquine for the prophylaxis of Malaria in non-immune Australian soldiers*. The member considered headaches suffered from about the time of taking mefloquine as a Serious Adverse Reaction and was not satisfied that the members' medical records were reflected in the final published report. Exec Sec has spoken at length with the complainant and 47F [redacted] on this issue. Responses from 47F [redacted] have been forwarded to the member concerned.

56. Exec Sec explained to the committee that the question of severity of symptoms was the issue. 47F [redacted] clarified with the member what Serious Adverse Reaction denoted, i.e. hospitalisation etc and that the headaches did not fall under this category.

57. The member having been given 47F [redacted] explanation made correspondence with the Secretariat just prior to the meeting and was satisfied with the explanations and efforts made by 47F [redacted] and the Executive Secretary and required no further action.

58. 47F [redacted]

Decision: ADHREC noted the complaint/query.

Action By:
Exec Sec
Assist Exec Sec

22

f. Protocol 216/00: Ran domised, d ouble blin d, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor- Antibody studies
Researchers requested that sam ples be re-tes ted using new technology and equipm ent. The samples are being tes ted f or Malar ia, as per th e origin al c onsent/information process. The committee noted and ratified the decision.

Decision: ADHREC concurred that the sam ples can be tested using the new technology. It requested researchers submit a formal request for extension of the protocol.

Action by:
Exec Sec
Assist Exec Sec

22

Australian Government
Department of Defence
Defence Personnel Executive

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CP2-7-068
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CANBERRA ACT 2600

2002/1936/3
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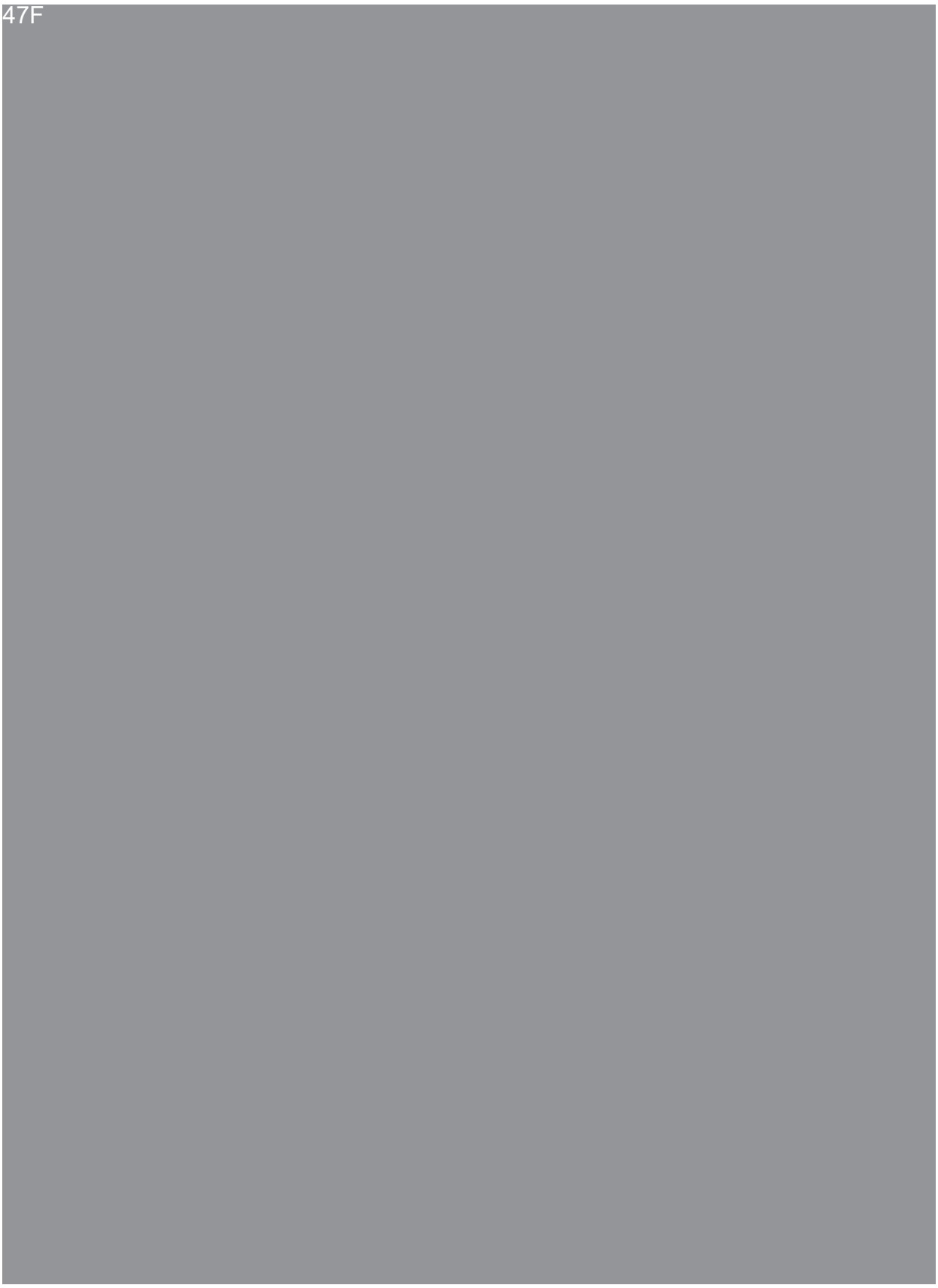
MINUTES OF AUSTRALI AN DEF ENCE H UMAN RESEARCH ETHICS COMMITTEE (ADHREC) SIXTIETH MEETING HELD AT CAMPBELL PARK OFFICES (CP2-7-069) CANBERRA ACT 2600 ON MONDAY 29 AUGUST 2005 - 1630 HOURS

47F

47F



d. Protocol 216/00: A randomiz ed, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor – Antibody studies.

70. ADHREC noted that the extension letter and approval out-of-session

Decision: No further action required.

Australian Government
Department of Defence
Defence Support Group

Defence Health Services
CP2-7-068
Campbell Park
CANBERRA ACT **2600**

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC)
SIXTY-SIXTH MEETING
CAMPBELL PARK OFFICES (CP2-7-069) CANBERRA ACT 2600
MONDAY 3 JULY 2006 - 1630 HOURS

22

22 [redacted]

7. Exec Sec was questioned at length as to why the progress report for **Protocol 216/00 A Randomized, Double-Blind, Comparative Study To Evaluate The Safety, Tolerability And Effectiveness Of Tafenoquine And Mefloquine For The Prophylaxis Of Malaria In Non-Immune Australian Soldiers Deployed To East Timor** is still overdue. She stated on a number of occasions that, by her recollection, Army Malaria Institute (AMI) were still waiting for further reports from the overseas sponsors of the study. Despite stating that she would confirm this with AMI, the issue was raised again later in the meeting, but Exec Sec was unable to add anything to her previous response***. Note by Exec Sec: For brevity, the issue is dealt with in full here. The protocol was initially closed on 12 June 2002, but re-opened following a request to do so by AMI on13 July 2005. ADHREC granted an extension on 1 August 2005 until 31 December 2007, to enable further analysis of samples which have been sent to America. As was recalled by Exec Sec, the final report from GlaxoSmithKline is still being awaited. Exec Sec spoke to Commanding Officer Army Malaria Institute on 4 July 2006.*** 47F [redacted] ***will provide a progress report to Exec Sec as a matter of urgency. A package summarising key events to do with Protocol 216/00 is enclosed with these Minutes***

22 [redacted]

Australian Government
Department of Defence
Defence Support Group

DEFENCE HEALTH SERVICES
CP2-7-121
Campbell Park
CANBERRA ACT 2600

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC)
SIXTY-SIXTH MEETING
CAMPBELL PARK OFFICES (CP2-7-069) CANBERRA ACT 2600
MONDAY 28 AUGUST 2006 - 1630 HOURS

22

[redacted]

ITEM EIGHT – FINAL REPORTS

37. Protocol 216/00: A randomised, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor.

23. Discussion occurred as to the apparent efficacy of both agents, with a different side-effect profile being the main differences.

Decision: Letter of thanks to be sent to the researcher.

Action:
Exec Sec
Asst Exec Sec

Australian Government
Department of Defence
Defence Support Group

Defence Health Services
CP2-7-124
Campbell Park
CANBERRA ACT 2600

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC)
SEVENTY-FIFTH MEETING
CAMPBELL PARK OFFICES (CP2-7-069) CANBERRA ACT 2600
MONDAY 15 OCTOBER 2007 - 1630 HOURS

22

22

[redacted]

ITEM EIGHT – FINAL REPORTS

21. Protocol 216/00: A randomized, double – blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor. Support Paper.

30. Letter of thanks to the Researchers.

Decision: Letter of thanks to the Researchers.

Action:
Exec Sec
Asst Exec Sec

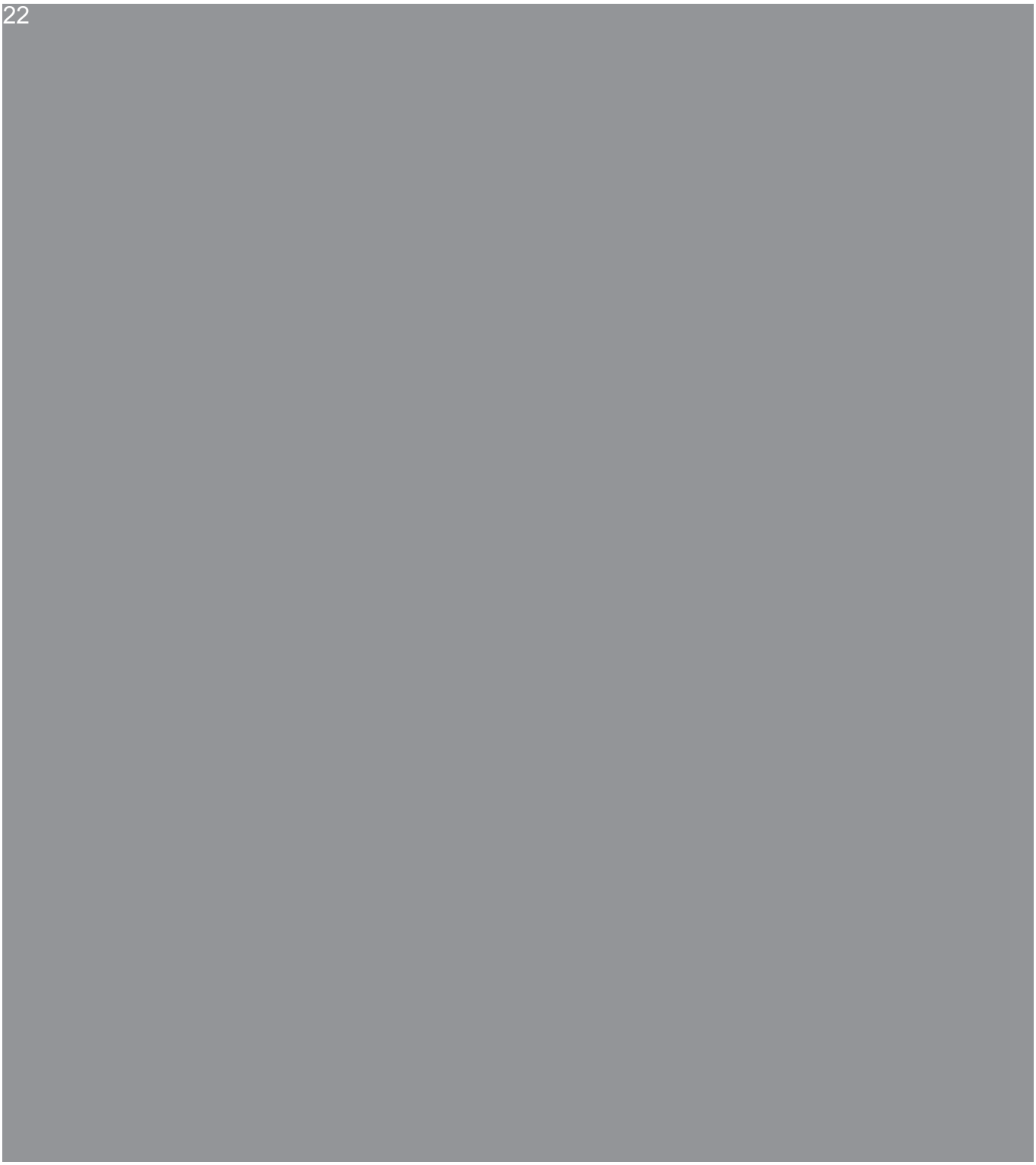
22. Protocol 249/01: Evaluation of mefloquine for the prophylaxis of malaria in non-immune Australian soldiers.

31. Letter of thanks to the Researchers.

Decision: Letter of thanks to the Researchers.

Action:
Exec Sec
Asst Exec Sec

22



JOINT HEALTH COMMAND

ADHREC, CP2-7-100, Campbell Park Offices, Campbell ACT 2600

ATTACHMENT A TO
ADHREC/OUT/2010/AF2061797

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC)
NINETY THIRD MEETING
CAMPBELL PARK OFFICES (CP2-7-069) CANBERRA ACT 2600
MONDAY 12 APRIL 2010 - 1630 HOURS

22

[redacted]

ITEM EIGHT – FINAL REPORTS

34. 216-00 A randomized, double – blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-imune Australian soldiers deployed to East Timor.

42. Scientific article published in "Antimicrobial Agents and Chemotherapy" Feb 2010.

Decision: Noted with thanks.
Action:
Executive

Defence Health

- Home
- All Hours Support Line 1800 628 036
- 1800 IMSICK
- Health Portal
- Health Resources
- Strategic Health Coordination
- Garrison Health Operations
- Mental Health, Psychology & Rehabilitation

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Mefloquine/Doxycycline Trials

During INTERFET, a large number of Australian Army soldiers who were taking doxycycline for prophylaxis against malaria developed the disease (see History). Doxycycline must be taken on a daily basis and evidence from studies in other militaries had identified compliance with taking the medication as a major issue. For this reason Defence needed to look at other options, including the then second line medication, mefloquine, to improve the protection of ADF personnel against malaria.

Mefloquine was registered in Australia by the Therapeutic Goods Administration (TGA) for malaria prophylaxis (prevention) in 1993, seven years before the field trials were conducted in Timor-Leste. As a weekly dose it had previously been shown to have better compliance than daily medications during studies in Australian tourists. Although adverse events were similar for those using mefloquine for malaria prevention compared with those using doxycycline, the drug appeared to have neuropsychiatric side effects that researchers were concerned could impact on operational effectiveness. Studies of other military populations showed mefloquine to be as well tolerated and have better compliance than daily anti-malarial medications when used over shorter periods than the typical ADF deployment. Nevertheless, it was important to understand the effects of these medications in the ADF population to inform the most appropriate anti-malarial regimen for force protection rather than just change the policy. As such, the AMI sought approval to conduct trials (field tests) of mefloquine in ADF troops deploying to Timor-Leste from 2001-2002.

The ADF trials of malaria medications were done according to strict ethical and scientific standards. The test protocols were carefully reviewed prior to the trial by the then Australian Defence Medical Ethics Committee (ADMEC), a committee of impartial experts charged with being certain that such testing is both ethically permissible and scientifically correct. Detailed written records were kept at all phases of the trial with this information later analysed and the results presented in scientific publications to document the trial's findings.