The Senate

Foreign Affairs, Defence and Trade References Committee

Use of the Quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force

December 2018

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www.openarms.gov.au

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www.lifeline.org.au

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1300 78 99 78
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Recommendations

Recommendation 1

5.25 The committee recommends that the terms of reference of the Departments of Defence and Veterans' Affairs Human Research Ethics Committee be updated to explicitly include consideration that prospective research participants may be vulnerable to perceived coercion to participate.

Recommendation 2

5.28 The committee recommends that all members of the Australian Defence Force who are invited to participate in medical research have access to a confidential conversation with an independent participant advocate prior to consenting to participate.

Recommendation 3

5.45 The committee recommends that the Department of Veterans' Affairs expedite their investigation on antimalarial claims lodged since September 2016 and continue to offer individuals assistance to lodge their claims and facilitate access to an advocate if required.

Recommendation 4

5.49 The committee recommends that the Department of Veterans' Affairs continue to provide ongoing training, information and support for the officers working in the Complex Case Team.

Recommendation 5

5.62 The committee recommends that the Department of Veterans' Affairs, in addition to the existing program of consultation forums, ensure matters raised by attendees and families are followed up. The forums should continue to be promoted widely and in consultation with ex-service organisations and advocate groups.

Recommendation 6

5.63 The committee recommends that the Department of Veterans' Affairs make the material provided at the consultation sessions available online.

Recommendation 7

5.64 The committee recommends that the Department of Defence attend the Department of Veterans' Affairs' consultation forums to maintain their knowledge of the issues raised by the veteran community. This will assist Defence to ensure their dedicated website is updated appropriately.

Recommendation 8

5.65 The committee recommends that the Department of Veterans' Affairs undertake a targeted awareness raising campaign, in consultation with ex-service organisations and veterans' advocates, to increase veterans' awareness of the non-liability pathway.

Recommendation 9

5.72 The committee recommends that the Department of Veterans' Affairs and Department of Defence, in collaboration with the Royal Australian College of General Practitioners and other health professionals, review and update the clinical guidelines developed in 2016 to recognise the complex conditions with which some veterans may present.

Recommendation 10

5.73 The committee recommends that the Department of Veterans' Affairs consult with the Royal Australian College of General Practitioners to assess whether General Practitioner briefings, like the one that occurred in Townsville in 2016 would be beneficial in other areas, including around major bases.

Recommendation 11

5.77 The committee recommends that the Department of Veterans' Affairs review the University of Queensland research findings due in late 2018 with a view to further inform the development of any new initiatives and the ongoing review of existing programs.

Recommendation 12

5.82 The committee recommends that the Department of Veterans' Affairs prioritise the development of the Neurocognitive Health Program. To enable veterans to access this program as soon as possible, consideration should be given to the rollout of a pilot program to a targeted population.

Recommendation 13

5.83 The committee recommends that the pilot program undertaken as part of the Neurocognitive Health Program be formally evaluated and that the evaluation report be made publicly available.

Recommendation 14

5.86 The committee recommends that, following the evaluation of the Neurocognitive Health Program pilot, a collaborative working group be established, including those who contributed to the development of the program, veterans and advocates, medical professionals and the Department of Veterans' Affairs. This group would consider the outcomes of the pilot and, if supported by the evaluation, how best to roll out and promote the program to all veterans it could assist.

Executive Summary

This has been a complex and challenging inquiry for the committee. The committee wishes to thank the individuals who appeared before it to share their personal stories. During the course of the inquiry the committee read and heard many moving personal accounts of individuals suffering from debilitating symptoms. The committee is deeply concerned to hear their distress as well as the frustration and dismay experienced by these individuals when seeking help.

The committee recognises that for these individuals to appear before a parliamentary committee is not easy. It showed their determination to contribute in a positive way to ensure that they and their mates and families receive the support they need. The committee also thanks the family members who spoke with the committee about the challenges of getting their loved ones and themselves access to assistance and support.

The disagreement over the cause of symptoms

A common theme was presenting to a medical practitioner with various symptoms, being referred to multiple specialists and eventually being diagnosed with Posttraumatic stress disorder (PTSD). However, individuals and advocates claim it is their exposure, in most cases, over 18 years ago, to the antimalarial drugs mefloquine and/or tafenoquine, which has resulted in their current symptoms and some of them are being misdiagnosed with PTSD.

It is important to note that although individuals presenting evidence to the committee appeared to group them together, mefloquine and tafenoquine are different drugs that act differently in the body.

The first issue from the evidence is whether the symptoms being experienced now by individuals can be causally related to prior antimalarial drug use. The Australian Quinoline Veterans and Families Association claim there is a condition which they call 'mefloquine poisoning' or an acquired brain injury (ABI)[1]. The Quinism Foundation in the USA calls it 'chronic quinoline encephalopathy' or 'neuropsychiatric quinism'.

The committee needs to state that it is not comprised of medical professionals or health experts and so cannot make any findings or rulings in relation to the medical causes for health issues. However, it notes that the weight of prevailing medical evidence provided to the committee in response to these claims is that long term problems as a result of taking mefloquine are rare and there is no compelling evidence that tafenoquine causes long term effects. To be clear, there has always been recognition by Defence that mefloquine, like any drug, has side effects and this has been taken into consideration in the development of its health policy.

The committee takes confidence that Australia's independent medical bodies have looked at the claim of ABI from the use of mefloquine. The committee was informed that the claim that mefloquine and tafenoquine results in ABI is not backed by

1 An umbrella term covering any damage to the brain that occurs after birth.

definitive evidence. In August 2017, the Repatriation Medical Authority (RMA) found there was insufficient sound medical evidence to support this claim. This decision was reviewed by the Specialist Medication Review Council which in September 2018 supported the decision of the RMA.

The medical evidence provided to the committee shows that the incidence of long term or persistent neuropsychiatric adverse reactions to mefloquine is very rare. If the committee looks at the 40 million doses of mefloquine worldwide, the committee was provided with no evidence that the same symptoms are manifesting in the Australian population or across the world in the civilian population. To the committee this is a critical point. The committee heard there is no evidence of an emerging global public health issue. The medical evidence is presented in Chapter 2 (covering ToR a(ii), b and d).

The committee was reassured that, should any sound medical-scientific evidence pertinent to this inquiry arise in the future, it would be identified through existing channels and responded to by Defence and DVA.

The committee notes that tafenoquine, which was not an approved drug at the time of the Australian Defence Force (ADF) trials, was approved in 2018 by the US Food and Drug Administration (US FDA) and the Australian Therapeutic Goods Administration (TGA). Tafenoquine has undergone a rigorous safety evaluation by these regulatory bodies. TGA's Advisory Committee on Medicines and the US FDA's Antimicrobial Drug Advisory Committee (AMDAC) have all had input for both indications, prevention and radical cure, and the findings are consistent. The processes of the US FDA and TGA included an audit of the relevant Defence studies.

This issue appears to be manifested in military populations where it seems to the committee trying to assign a single cause to veterans' illnesses does not reflect the many potential contributors to their physical and mental health at the time and in the years since the medications were taken.

The symptoms are real

However, the committee does not doubt that the symptoms being experienced by individuals are real and regardless of the cause or causes, these veterans are unwell and should receive the assistance to which they are entitled. The committee notes that this is not a different view to that stressed by the Department of Defence (Defence) and the Department of Veterans' Affairs (DVA), i.e. that regardless of the cause of the symptoms, help is available. It will therefore be the committee's focus in Chapter 4 to review and improve processes to ensure that any current and past ADF members receive appropriate treatment and support they need.

Regarding treatment, the committee notes that an independent review of the published literature by Professor Sandy McFarlane concluded that there is no specific way to diagnose chronic mefloquine effects as many symptoms are shared with other conditions such as PTSD and there is no specific treatment except to cease the drug and treat the symptoms.

As there is no specific treatment and there is help available for symptoms being experienced, in Chapter 4, the committee will look at the barriers to people accessing appropriate treatment. Some individuals were calling for there to be more treatment

available for neurocognitive issues and the committee was pleased to hear that a neurocognitive program is being developed by DVA which the committee commends and supports.

The committee notes with concern that for some individuals having their symptoms recognised as resulting from mefloquine or tafenoquine appears to be of overriding importance which may keep some of them from seeking and receiving available treatment.

The committee's inquiry into veterans' suicide highlighted to the committee how challenging it can be to deal with DVA, which is exacerbated when someone is unwell. The committee made a number of recommendations the government agreed to which the committee trusts are leading to improvements in service delivery over time. The committee has been monitoring actions being taken by DVA to improve services through the estimates process. However, the individual stories indicate to the committee that there is still work to be done and that some individuals and their families are not in a position to wait until improvements flow through the system from reforms. The committee has made more targeted recommendations which it believes will improve processes for those needing assistance.

Conduct of the studies

The second area of contention is the conduct of the antimalarial drug trials undertaken in the late 1990s and early 2000s. Individuals who blame mefloquine or tafenoquine for their current symptoms believe that the trials should not have taken place, were unethical and used them as 'guinea pigs'. These allegations have been investigated in an independent investigation outside the military chain of command by the Inspector-General of the ADF (IGADF). The investigation of some of the trials undertaken by the Army Malaria Institute (AMI) from 2000 to 2002 in Timor-Leste involving mefloquine and tafenoquine found that they 'were conducted ethically and lawfully' and 'in accordance with the National Guidelines issued by the NHMRC [National Health and Medical Research Council] and the TGA'.[2] The IGADF also found trial participants voluntarily consented to participate in the trials, and were adequately informed of the potential side effects known at the time.[3] The committee acknowledges that these findings have not been accepted by some veterans, but it is not the role of the committee to repeat or reopen the IGADF investigation. The Australian Defence Human Research Ethics Committee, TGA and US FDA have also examined the conduct of some of the trials and found no indication that good clinical practice was not followed.

However, the committee shares the IGADF and witnesses' concerns about how to ensure ADF members are able to provide informed consent in the military environment. The Departments of Defence and Veterans' Affairs Human Research Ethics Committee (DDVA HREC) already reviews research protocols in accordance

2 IGADF, *Inquiry report into issues concerning anti-malarial trials of the drug mefloquine between 2000 and 2002 involving Australian Defence members deploying to East Timor*, 2016, pp. ii–iii.

3 IGADF, *Inquiry report*, 2016, pp. iv, vi–vii.

with the NHMRC National Statement on Ethical Conduct in Human Research (National Statement). This identifies defence force personnel as a potentially vulnerable group due to the unequal relationships within the military hierarchy. However, there are opportunities to improve the consent process, as outlined in the recent correspondence asking DDVA HREC to consider additional measures to ensure participants 'are fully informed of all aspects of the studies and that there is no belief created that Command is endorsing or actively encouraging the study'.[4] The committee also suggests that the appointment of independent participant advocates should be considered.

The committee does not believe that all medical research with members of the ADF should be prohibited, provided it does not disrupt the work of the ADF and has been approved in accordance with the National Statement. This is because research is essential for advancing medical care and force protection measures, and the ADF has a duty of care to protect and maintain the health of its personnel. For example, in relation to the trials, the committee is aware that during the INTERFET deployment, 64 ADF members became infected with malaria and over 200 more developed malaria on return to Australia. These cases of malaria were of concern to Defence as potentially indicating resistance to the preferred antimalarial medication doxycycline, or non-compliance in taking the medication, and were the catalyst for approved clinical studies to be undertaken to assess whether policy changes were necessary to ensure adequate protection against malaria in the ADF.

The committee commends the work of the ADF Malaria and Infectious Disease Institute (formerly AMI), and recognises the importance of its research in protecting ADF members and the international community more broadly. The conduct of the trials and the issue of informed consent is discussed in Chapter 3 (covering ToR a, a(i), a(ii) and b).

Moving forward

The committee recognises that for some individuals, the outcomes of this inquiry will be insufficient unless the committee supports their view of the medical evidence and the trials and supports calls for a Royal Commission. As the committee does not have the role or expertise to make any medical findings and the conduct of the trials has been reviewed by the IGADF and some of the trials audited by the US FDA and TGA, the committee believes the focus of the recommendations for this inquiry should be on the common ground of making sure that individuals are able to access the assistance and support they need and are entitled to receive.

While the committee recognises that both Defence and DVA have taken actions to respond to the concerns raised by veterans, reports from veterans indicated that they were either unaware of many of the current initiatives, believed that they were inappropriate or did not go far enough. It was of concern to the committee that, despite the efforts made to date, the message that assistance is available is not being received by many veterans. Veterans are reporting that they are still facing a number

4 Defence, *Letter from AVM Tracy Smart AM to Mr Ian Tindall, Chair DDVA HREC*, 4 October 2018, [p. 1] (tabled 11 October 2018).

of practical barriers when trying to access assistance including: ADF cultural issues, the provision of information and trying to access and navigate the DVA claims process.

This suggests that improvements can be made to ensure that veterans have access to support and assistance. The committee heard a number of suggestions from veterans about the assistance and support they would like. While there have been concerns raised about some of the suggestions put forward by veterans, the committee emphasises that there is unanimous agreement that their symptoms are real and the veterans and their families who participated in this inquiry need help.

With this in mind, the committee's focus has been to explore how best to address the health concerns identified by veterans and their families and how to connect them with the help available. It is positive that DVA is actively taking steps to address concerns and it is important that this is continued. In particular, DVA has acknowledged that individuals need tailored, wrap around assistance and that this needs to include support from a range of specialists to address their complex needs.

The committee heard how the role of GPs is central to ensuring veterans have access to a range of health services and ongoing support. Actions have been taken to make GPs aware of the issues raised with the committee and suggestions were made to ensure this flow of information is continued and enhanced.

Noting the need for research to be independent so veterans can have confidence in the outcomes, the committee was pleased to hear that Defence and DVA have jointly commissioned the University of Queensland to undertake a research study looking at the self-reported health of ADF personnel using antimalarials on deployment. This research is due to be completed in late 2018. The committee anticipates that the findings of this research may be used by DVA in the context of developing services and support that address the challenges reported by this cohort of the veteran community.

The committee commends the recent consultation forums being undertaken by DVA and notes that preliminary feedback from the first forum is that some veterans who attended found it beneficial. These forums provide an opportunity to enhance trust in the system by facilitating greater collaboration and fostering connections.

Another important initiative being developed by DVA is a Neurocognitive Health Program to assist veterans who may have symptoms of a neurocognitive disorder. Further details about initiatives to improve veterans' access to assistance and to enhance collaboration between DVA and the veteran community are outlined in Chapter 4 (covering ToR c). ToR e is covered in Chapter 1.

Chapter 1
Introduction

Referral

1.1 On 19 June 2018, the Senate referred the following matter to the Senate Foreign Affairs, Defence and Trade References Committee for inquiry and report by 17 September 2018:

(a) the current and past policies and practices for:

(i) prescribing Quinoline anti-malarial drugs to ADF personnel, and

(ii) identifying and reporting adverse drug reactions from Quinoline anti-malarial drugs among ADF personnel;

(b) the nature and extent of any adverse health effects of those who have taken Mefloquine/Tafenoquine on serving and former ADF personnel;

(c) the support available for partners, carers and families of personnel who experience any adverse health effects of Quinoline anti-malarial drugs;

(d) a comparison of international evidence/literature available on the impact of Quinoline anti-malarials;

(e) how other governments have responded to claims regarding Quinoline anti-malarials; and

(f) any other related matters.[1]

1.2 On 20 August 2018, the Senate agreed a reporting extension until 29 November 2018.[2] On 29 November 2018 the Senate agreed to a further extension until 6 December 2018.[3] The committee decided to table on 4 December 2018.

Conduct of the inquiry

1.3 Details of the inquiry were placed on the committee's website at http://www.aph.gov.au/senate_fadt. The committee also contacted a number of relevant individuals and organisations to notify them of the inquiry and invite submissions by 31 July 2018. The committee continued to receive submissions after the closing date. Submissions received are listed at Appendix 1.

1.4 The committee held six public hearings: Brisbane on 30 August; Townsville on 31 August; Melbourne on 5 November and Canberra on 11 October, 15 October and 8 November 2018. A list of witnesses who gave evidence is available at Appendix 3. Following the hearing on 30 August in Brisbane, the committee conducted a site

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1 *Journals of the Senate*, No. 99 —19 June 2018, p. 3187.

2 *Journals of the Senate*, No. 110 —20 August 2018, p. 3534.

3 *Journals of the Senate*, No. 133 —29 November 2018, p. 4325.

visit to the Australian Defence Force Malaria and Infectious Disease Institute (ADFMIDI) at Enoggera Barracks.

Acknowledgement

1.5 The committee thanks the organisations and individuals who made submissions and those who participated in the public hearings for the inquiry.

1.6 The committee recognises the difficulties faced by individuals who are unwell in participating in the inquiry processes and thanks those who were able to make submissions and provide evidence. The committee appreciates that many individuals made submissions with their mates and families in mind and that they told their story also for those who, for whatever reason, are unable to at this time. The committee sincerely appreciates their efforts.

1.7 The committee wishes to particularly acknowledge the partners and families of veterans who also provided evidence to the committee.

Assistance provided

1.8 Realising the challenges for potential submittors, the committee provided assistance to those who wished to make submissions and thanks the Department of Veterans' Affairs (DVA) who also made assistance available. DVA also made staff available at hearings to facilitate access to support and services if required.

Structure of the report

- Chapter 1 includes key terminology, concepts and medications and summarises some other relevant inquiries (ToR e);
- Chapter 2 details the disagreement evident during the inquiry between individuals and advocates and the medical community over the cause of their symptoms (ToR a(ii), b and d);
- Chapter 3 covers Australian Defence Force (ADF) antimalarial polices and details about the trials, including the issue of informed consent (ToR a, a(i), a(ii) and b);
- Chapter 4 covers the actions taken by the Department of Defence (Defence) and DVA to date, assistance available, witnesses' experience of seeking assistance and what assistance needs to be provided moving forward; (ToR c) and
- Chapter 5 details the committee's conclusions and recommendations.

Key terminology, concepts and medications

Atovaquone and proguanil	Listed on the Australian Register of Therapeutic Goods for malaria treatment since 1998 and prevention since late 2001.[4] It

4 TGA Product and Consumer Medicine Information, Malarone; Defence, *Submission 1*, p. 11.

hydrochloride (brand name Malarone)	is a combination of two drugs: atovaquone and proguanil.[5] It has been the second line preventative antimalarial for the ADF since 2006, used when doxycycline is not suitable. It needs to be taken daily.[6]
Doxycycline	An antibiotic. There are a number of brands listed on the Australian Register of Therapeutic Goods. It is listed on the World Health Organization (WHO) Model List of Essential Medicines for treating bacterial infections as well as for malaria treatment and prevention.[7]
Malaria chemoprophylaxis or malaria prophylaxis	Taking one or more dugs to prevent malaria.
Mefloquine (brand name Lariam)	An antimalarial for prevention and treatment which was put on the Australian Register of Therapeutic Goods on 27 January 1993.[8] Roche Products Pty Ltd advised that mefloquine emerged from 'An extensive research program undertaken independently by the United States Army [the Walter Reed Army Institute of Research] in 1963, in which over 100,000 separate compounds were evaluated prior to mefloquine being selected'.[9] As at 19 February 2018, mefloquine was approved in 27 countries and more than 40 million patients have been treated since it was first made available.[10] It is listed on the WHO Model List of Essential Medicines for both malaria prevention and treatment.[11] It is also listed by the US Centers

5 Adjunct Professor John Skerritt, Deputy Secretary, Health Products Regulation, Department of Health, *Committee Hansard*, 11 October 2018, p. 42.

6 Defence, *Submission 1*, p. 11.

7 WHO Model List of Essential Medicines, 20th edition, March 2017.

8 Department of Health, *Submission 3*, pp. 1–2. Note: Roche Products Pty Ltd advised that mefloquine was approved in Australia on 3 September 1986. See additional information from Roche Products Pty Ltd, received 19 November 2018.

9 *Submission 12*, p. 2.

10 *Submission 12*, p. 2. Mr Svend Peterson, Managing Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 1.

11 WHO Model List of Essential Medicines, 20th edition, March 2017. The RMA notes that the WHO Model List of Essential Medicines is an expert assessment of the minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. RMA, *Submission 4*, p. 9; Mr Svend Peterson, Managing Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 1.

	for Disease Control and Prevention for malaria prevention and treatment.[12] It is still a recommended preventative antimalarial for travellers to Timor-Leste.[13]
Primaquine	An antimalarial used to prevent and treat relapses of malaria. It is given to people as they leave a malarious area as eradication, to kill any malaria parasites that may still be present in the body. It is taken twice daily for 14 days.[14]
Prophylaxis	Medication given to prevent disease.
Radical cure	Prevention of relapse.
Tafenoquine	Recently approved by the US FDA for prevention[15] and radical cure of malaria.[16] In September 2018 it was approved by the Australian Therapeutic Goods Administration (TGA) for prevention[17] and radical cure[18] of malaria. At the time of the trials it was not yet approved in Australia for use as an anti-malarial medication. It is chemically related to primaquine[19] and is structurally different to mefloquine.[20] Like primquine, tafenoquine shares a key safety concern which is the potential to cause hemolysis (destruction of red blood cells) in individuals with a hereditary disorder, deficiency of Glucose-6-Phosphate-Dehydrogenase (G6PD) enzyme. Hence individuals

12 CDC, Yellow Book, Chapter 3, Infectious Diseases Related to Travel, Malaria: https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria, accessed 15 October 2018.

13 Defence, *Submission 1*, p. 2.

14 Defence, *Submission 1*, p. 15.

15 On 26 July 2018 Sixty Degrees Pharmaceuticals announced that the Antimicrobial Drugs Advisory Committee of the US Food and Drug Administration voted to support tafenoquine for the prevention of malaria in adults which will be marketed under the brand name Arakoda. See Sixty Degrees Pharma, 'US FDA Advisory Committee votes in favour of Tafenoquine for the prevention of malaria', *Media release*, 26 July 2018.

16 GlaxoSmithKline (GSK) R&D in partnership with Medicines for Malaria Venture announced that on 20 July 2018 the FDA approved single dose tafenoquine (tradename Krintafel) for the radical cure (prevention of relapse) of P. vivax malaria in patients aged 16 years and older. See GSK, *Submission 8*, p. 2.

17 To be marketed as Kodatef, sponsor Biocelect Pty Ltd.

18 To be marketed as Kozenis, sponsor GlaxoSmithKline Australia Pty Ltd.

19 See Professor Geoffrey Quail, President, Australian College of Tropical Medicine, *Committee Hansard*, 30 August 2018, p. 44; Adjunct Professor Skerritt, *Committee Hansard*, 11 October 2018, p. 40.

20 GSK, *Submission 8*, p. 2.

	must be tested for G6PD deficiency before receiving either of these drugs.[21] More than 4,000 people, both military and civilian, have taken tafenoquine in clinical studies around the world.[22]

The difference between mefloquine and tafenoquine

1.9 The differences between mefloquine and tafenoquine were discussed with GlaxoSmithKline Australia Pty Ltd. Dr Alison Webster, Head, Global Health Clinical Research and Development, GSK advised:

> They're members broadly of a class of drugs that are called quinolines, but within that class there are very different chemicals, or medicines. Tafenoquine is an analogue of primaquine. Primaquine and tafenoquine are 8-aminoquinolines. They uniquely have an activity against the dormant liver stage of vivax malaria and so uniquely have the ability to prevent relapse of vivax malaria. They also share a particular safety issue, which is that they can cause anaemia in patients who lack a certain enzyme called G6PD. All patients who take either primaquine or tafenoquine must be tested for G6PD deficiency before they receive the drug. Mefloquine is a different kind of quinoline, but there are many others. Chloroquine is a member of that group, as well…All of these are unique chemicals with their own specific safety profile and their own specific activity against malaria.[23]

1.10 Mr Svend Peterson, Managing Director, Roche Products Pty Ltd explained to the committee it is important that there are a range of malaria prevention and treatment options available to reduce the risk of infection and death from malaria as not all patients can tolerate the medications and certain parasites have become resistant to some antimalarials.[24]

Malaria

1.11 Malaria is a life threatening disease caused by parasites which are transmitted to people by mosquitoes. There are five parasite species that cause malaria in humans with P. falciparum[25] and P. vivax causing most of the disease burden.[26]

1.12 According to the latest WHO World Malaria Report released in November 2018 there were an estimated 219 million cases of malaria in 2017, up from 216 million cases in 2016. In 2017 there were an estimated 435,000 malaria-related

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21 GSK, *Submission 8*, p. 2.

22 Defence, *Submission 1*, p. 2.

23 *Proof Committee Hansard*, 8 November 2018, pp. 11–12. See also Adjunct Professor Skerritt, *Committee Hansard*, 11 October 2018, p. 40.

24 *Proof Committee Hansard*, 8 November 2018, p. 1.

25 In the African region most cases are due to P. falciparum. See WHO World Malaria Report 2018, p. 15.

26 Australian Government, Indo-Pacific Centre for Health Security, *Submission 57*, p.1.

deaths, compared to 451,000 in 2016 and 607,000 in 2010.[27] The WHO has noted that resistance to antimalarial medicines is a recurring problem.[28] The UN Secretary-General's 2018 progress report on the UN Sustainable Development Goals states:

> The world is not on a trajectory towards ending malaria by 2030 — in fact, the trends are worrisome. In 2016, there were 216 million cases of malaria, compared with 210 million cases in 2013.[29]

1.13 Australian travellers to malaria endemic areas are at risk of contracting malaria and approximately 400 cases of imported malaria occur each year.[30]

1.14 The Medicines for Malaria Venture (MMV) reported that P.vivax malaria is responsible for a significant burden of illness.[31] The WHO estimated that 3.4 per cent of all malaria cases were caused by P. vivax, with 56 per cent of the vivax cases in the South-East Asia Region.[32]

1.15 In 2016 WHO estimated 8.5 million cases of P.vivax malaria of which around 5 million were in South-East Asia with 27,000 deaths.[33]

Malaria and the ADF

1.16 South East Asia is an area of operations for the military which puts ADF members at risk of malaria. In the ADF, 64 ADF members became infected with malaria during the INTERFET deployment and over 200 more developed malaria on return to Australia. These numbers were the catalyst for the approved clinical studies which were 'deemed necessary to help determine if Defence should review its policy of prescribing doxycycline as the preferred antimalarial…'.[34] Details about the trials are provided in Chapter 3.

1.17 In the ADF, between 1998 to 2007, 637 cases of malaria were recorded in ADF members; between 2012 and 2017 there were 30 cases recorded, at an average of five per year; and to date in 2018, four cases have been recorded.[35] Over these years the Australian Defence Force Malaria and Infectious Disease Institute (ADFMIDI) formerly known as the Australian Army Malaria Institute (AMI)[36], 'a world-renowned,

27 WHO, World Malaria Report 2018, p. xiii.

28 WHO, Malaria Fact Sheet, 11 June 2018.

29 UN Report of the Secretary-General, Progress towards the Sustainable Development Goals, 10 May 2018, p. 5.

30 Australasian Society for Infectious Diseases, *Submission 6*, p. 1.

31 *Submission 10*, [p. 2].

32 WHO, World Malaria Report 2018, p. 36.

33 WHO, World Malaria Report 2017, pp. 33, 34, 41.

34 Defence, *Submission 1*, p. 3. Defence, *Supplementary submission 1.1*, pp. 6–7.

35 Defence, *Submission 1*, p. 1.

36 Located at Gallipoli Barracks in Brisbane.

industry leader of malarial studies' has been responsible for developing solutions to the problem of malaria on operations.[37]

Other relevant Australian committee inquiries

1.18 On 17 March 2016, the Senate Foreign Affairs, Defence and Trade References Committee tabled a report on the mental health of ADF serving personnel. The report included two recommendations in relation to mefloquine.[38] Dated 15 September 2016, the government response sets out its response to the committee's recommendations.[39]

Other relevant inquiries

1.19 The use of mefloquine by defence forces overseas has been the subject of parliamentary and other inquiries or reviews in other jurisdictions.[40]

Canada

1.20 In June 2017, the House of Commons Standing Committee on Veterans Affairs undertook a study on 'mental health focused on improving the transitional support between Canadian Armed Forces and Veterans Affairs' which included the claims around the effect of mefloquine. There were two recommendations regarding mefloquine: that Veterans Affairs Canada reach out to members of the Canadian Armed Forced who served in Somalia, Rwanda or other deployment in that time period to ensure each is receiving the mental and physical health services, support, benefits and programs to which they are entitled; and that Veterans Affairs Canada cooperate with any institution concerned in any research program that would study the effects of mefloquine.[41]

1.21 In June 2017 Canada released a report from a military taskforce on mefloquine. Health Canada simultaneously made public its own findings about the safety of the drug. Both concluded there is no evidence that the drug causes long-lasting and permanent neurological and psychiatric problems. The military report recommended that mefloquine be considered as a drug of last resort. The findings of the reports have angered some Canadian veterans who claim they are experiencing symptoms as a result of 'mefloquine toxicity'.[42]

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37 Defence, *Submission 1*, p. 8.

38 Senate Foreign Affairs, Defence and Trade References Committee, *Mental health of ADF serving personnel*, 17 March 2016. See recommendations 5 and 6.

39 Available: https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Foreign_Affairs_Defence_and_Trade/ADF_Mental_Health/Government_Response

40 See Defence, *Submission 1*, pp. 49–53 for more detail.

41 Defence, *Submission 1*, pp. 50–51.

42 Gloria Galloway, 'Canadian Forces curb use of mefloquine, but study findings anger vets', *The Globe and Mail*, 2 June 2017.

1.22 In 2017 the Canadian Surgeon General noted in the Canadian Standing Committee on Veterans Affairs Review, *Mental Health of Canadian Veterans: A Family Purpose* that:

> More than 17,000 Canadian Armed Forces personnel and tens of millions of people wordwide have received Mefloquine since it was first licensed to prevent and treat malarial infection. We are aware of the potential short-term side effects of Mefloquine; however, even given this extensive use of Mefloquine, severe neuropsychiatric adverse effects have very rarely been associated with its use.[43]

UK

1.23 In May 2016 the House of Commons Defence Committee published its report: *An acceptable risk? The use of Lariam for military personnel*. The committee concluded that the Ministry of Defence should designate Lariam (Mefloquine) as a drug of last resort and that prescribing it should be restricted: only to those who are unable to tolerate the available alternatives; only after a face to face individual risk assessment has been conducted; and only after the patient has been made aware of the alternatives and have been given the choice between Lariam and another suitable antimalarial drug.[44]

1.24 Following this inquiry on 12 September 2016, the Ministry of Defence introduced a new policy on prescribing antimalarial drugs.[45] The revised policy directs that all antimalarial drugs are only supplied after a face to face travel health risk assessment performed by an appropriately trained and regulated health care professional. A hotline was also set up for anyone who had concerns. However, the new policy did not designate Lariam as a drug of last resort.[46]

1.25 In relation to the UK inquiry the then Vice Chief of the Defence Force, VADM Ray Griggs noted in 2016 that:

> The point I would make about the key difference between the UK and Australia is that, as I said at the outset, we have a tiered approach to the prescription of antimalarials, that mefloquine is our third in line and that it is being used quite rarely. In the UK, there is no tiering and mefloquine has been used much more extensively. The UK inquiry centred on whether people were given the appropriate amount of information and the

43 Defence, *Submission 1*, p. 13.

44 House of Commons, Defence Committee, *An acceptable risk? The use of Lariam for military personnel*, Fourth Report of Session 2015-16, 24 May 2016, p. 29.

45 Ministry of Defence, Mefloquine Prescribing in the UK Armed Forces, 12 September 2016 to 31 March 2018, published 17 May 2018.

46 Lydia Williams, 'Ministry of Defence will only hand out Lariam after face-to-face risk assessment', *The Telegraph*, 13 September 2016.

> counselling part prior to being prescribed the drug. So it was a slightly different emphasis.[47]

1.26 On 25 July 2018 the House of Commons Defence Committee presented a report on *Mental Health and the Armed forces, Part One: The Scale of mental health issues.* The report notes there is a lack of research into the mental health effects of physical exposure to factors such as neurotoxcity or mild traumatic brain injury:

> An example is the antimalarial drug Lariam, or Mefloquine, where our predecessor Committee found that a minority of those who used it suffered serious mental health issues. Such side effects were known to occur, yet the Ministry of Defence did not take the appropriate steps to minimise the risks to those whom it prescribed the drug. A number of witnesses have suggested that other drugs being prescribed by the Armed Forces may be having similar effects but that the current lack of research and data over neurotoxicity and its potential mental health effects may be resulting in cases being missed or being misdiagnosed, for example as PTSD.[48]

Other governments and organisations

US

1.27 Although there have been no specific inquiries, current US policy is that mefloquine 'should be reserved for individuals with intolerance or contraindications to both first-line medications [doxycycline and atovaquone-proguanil]'.[49] Defence advised:

> The Office of Secretary of Defence published a 2009 policy advising that doxycycline was the antimalarial of first choice, followed by atovaquone/proguanil, and that mefloquine use was restricted to only those personnel with contraindications to the other antimalarials, which is consistent with ADF policy. It further warned that it should be used cautiously in persons with a history of Traumatic Brain Injury or Post Traumatic Stress Disorder (PTSD) and other psychiatric diagnoses, such as depression, schizophrenia, and anxiety disorders.[50]

1.28 It was reported in the media that mefloquine was investigated as a contributing factor in a series of murder-suicides at Fort Bragg, North Carolina in 2002 but the military panel concluded it was an unlikely factor.[51]

1.29 More recently, the media has reported calls by individuals and organisations for Congressional hearings into the use of mefloquine in the US military.[52]

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47 VADM Ray Griggs, VCDF, Senate Foreign Affairs, Defence and Trade Legislation Committee, *Estimates Hansard,* 10 February 2016, p. 173.

48 House of Commons Defence Committee, *Mental Health and the Armed Forces, Part One: The Scale of mental health issues,* 25 July 2018, p. 8.

49 *Submission 1*, p. 51.

50 *Submission 1*, p. 51.

51 Greg Miller, 'A gruesome war crime renews concerns about a malaria drug's psychiatric side effects', *Wired,* 15 August 2013.

Germany

1.30 In December 2016 the German defence ministry took mefloquine off the list of medications prescribed for soldiers.[53] Defence advised that similar to Ireland, in late 2017 Roche withdrew Lariam from the German market which became the catalyst for the German Ministry of Defence to order the cessation of use of mefloquine. Prior to that mefloquine had become a third-line antimalarial in 2013 when a new manufacturer's 'black box'[54] warning was added.[55]

Ireland

1.31 Defence advised that mefloquine remains the first line antimalarial of the Irish Defence Force. Local advocates have campaigned for it to be a drug of last resort. Lariam was, however, withdrawn from sale in Ireland in July 2016 which the company said followed a review of the products and was not related to legal actions as it was still on the market in 16 other European countries. A number of current and serving members of the Irish Defence Force have submitted claims against the Defence Force and as at 27 June 2017 55 claims[56] had been received. One claim was settled on 30 November 2017 without admission of liability and the other cases are still pending.[57]

NATO

1.32 Defence advised that in response to concerns raised in countries about the use of mefloquine, the Force Health Protection Working Group of the Committee of the Chiefs of Military Medical Services in NATO was asked to review the matter. The working group has recommended that:

> …the use of mefloquine is still justified when prescribed in line with national prescribing guidelines and the standard product information. The recommendation will enter the ratification process by COMEDS within the next few weeks to months.[58]

1.33 Further detail is available in the submission from Defence.[59]

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52 See https://www.wusa9.com/article/news/investigations/investigation-vets-say-anti-malaria-drugs-they-were-ordered-to-take-caused-devastating-side-effects/65-560790227, accessed 25 July 2018.

53 Sheila Pratt, 'Germany bans drug linked to brain damage, ramps up pressure on Canada', *iPolitics*, 9 December 2016.

54 An FDA boxed warning, also known as a 'black box' warning appears on a prescription drug's label. It is the strictest warning used by the FDA and is designed to call attention to serious or life-threatening risks. See Defence, *Submission 1*, p. 53.

55 Defence, *Submission 1*, pp. 52–53.

56 Media in January 2018 reports 58 claims. Caroline O'Doherty, 'More soldiers to sue over malaria drug', *Irish Examiner*, 1 January 2018.

57 Defence, *Submission 1*, p. 52.

58 Defence, *Submission 1*, p. 53.

59 *Submission 1*, pp. 49–53.

Chapter 2

The causes of symptoms

Introduction

2.1 The committee received over 100 submissions from veterans suffering from chronic and complex symptoms which they attribute to taking mefloquine and/or tafenoquine over 18 years ago. The Quinism Foundation in the USA has proposed that there is a pattern of symptoms and has suggested the terms 'chronic quinoline encephalopathy' or 'neuropsychiatric quinism'.[1] Others such as the Australian Quinoline Veterans and Families Association (AQVFA) have used the terms 'mefloquine or quinoline poisoning'[2], 'mefloquine toxidrome'[3] or 'acquired brain injury'.[4] The Repatriation Medical Authority (RMA) notes other terminology used including 'chronic mefloquine toxicity syndrome', 'mefloquine intoxication syndrome', and 'chronic mefloquine-induced encephalopathy'.[5]

2.2 The weight of medical evidence presented to the committee in response to these claims is, in summary, that long term problems as a result of taking mefloquine are rare and there is no compelling evidence that tafenoquine causes long term effects. While committee members are not medical experts and can make no medical findings, this chapter provides a summary of the evidence on this issue provided to the committee.

2.3 This chapter contains a brief description of what is being claimed in relation to the medications; the broad response from the medical community; the safety profiles and side effects for mefloquine and tafenoquine; the use of mefloquine in the civilian population; the domestic and international evidence; the Therapeutic Good Administration (TGA) adverse event register; related medical inquiries by the RMA and Specialist Medical Review Council (SMRC); and attempts to explain what is occurring in some sections of the veteran community.

Disagreement over the cause of symptoms

2.4 Disagreement over the cause of symptoms was clearly evident during the inquiry. Associate Professor Harin Karunajeewa succinctly captured the issue:

> The point of controversy lies not in whether or not individuals are suffering from these symptoms, but in whether or not they are causally related to prior antimalarial drug use.[6]

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1 Dr Remington Nevin, *Committee Hansard*, 11 October 2018, p. 2.

2 AQVFA, *Submission 16*, pp. 8, 41.

3 AQVFA, *Submission 16*, p. 8.

4 AQVFA, *Submission 16*, p. 44. Mr Stuart McCarthy, *Submission 94*, p. 5.

5 RMA, *Submission 4*, Attachment 4, p. 53.

6 *Submission 15*, p. 5.

What is being asserted?

2.5 The AQVFA submitted that 'mefloquine poisoning', 'an accumulation of symptoms associated with adverse reactions to mefloquine' is responsible for the current symptoms being experienced by veterans. AQVFA advised that commonly reported symptoms include:

> …headache, tinnitus, dizziness, fatigue, anxiety, depression, sleep disturbances including vivid or lurid dreams, changes in thought and mood, confused thought processes and loss or diminution of working and / or long term memory, heightened feelings of aggression and paranoia. Acute physiological symptoms such as diarrhea, nausea, cutaneous rashes and cardiac arrhythmias…Severe acute adverse reactions include frank psychosis, hallucinations, and seizures. These symptoms represent a toxidrome which is clearly identifiable subsequent to mefloquine exposure...[7]

2.6 The AQVFA claim that 'an increasing body of evidence has established that serious symptoms of central nervous system dysfunction occur far more commonly tha[n] had been previously recognized[,] that had been originally intimated in the safety information associated with the drug and that these could be more prevalent and in military populations than has been previously anticipated'.[8]

2.7 Mr Stuart McCarthy, President of and spokesperson for the AQVFA argued that 'mefloquine is now known to be neurotoxic in some individuals, able to cause lasting or permanent brain damage, with chronic symptoms typically misdiagnosed as PTSD or other psychiatric disorders'.[9] He spoke of 'quinoline poisoning' and categorises symptoms as follows:

- psychiatric disorders including depression, anxiety, bipolar disorder and schizophrenia.
- cognitive impairments including memory and concentration difficulties.
- hearing problems including tinnitus, hearing loss and hyperacuity.
- vestibular disorders including dizziness, vertigo and spatial disorientation.
- neurological disorders including neuropathies, seizures, Parkinson's disease and motor neurone disease (MND).[10]

2.8 The AQVFA refers to work of Dr Remington Nevin[11] who is Executive Director of the Quinism Foundation, a US non-profit charitable organisation

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7 *Submission 16*, pp. 8-9.

8 *Submission 16*, p. 9.

9 *Submission 94*, p. 1. See also *Submission 16*, p. 42. *Submission 16.1*, p. 6; The Quinism Foundation, *Submission 17*, p. 5; Defence Force Welfare Association, *Submission 95*, p. 2.

10 *Submission 94*, p. 5.

11 According to his website, remingtonnevin.com, Dr Nevin 'was the first to publish clinical descriptions of the permanent toxic syndrome of brain and brainstem dysfunction caused by the use of mefloquine'.

established on 1 January 2018 which 'promotes and supports education and research on the family of medical disorders caused by poisoning by quinoline drugs'.[12] Dr Nevin is the only staff member and there is a board of directors consisting of five former US military officers or senior non-commissioned officers. The Foundation relies entirely on private donations.[13] The Quinism Foundation:

> …has proposed the term chronic quinoline encephalopathy, otherwise known as neuropsychiatric quinism, to define the clinical disorder caused by quinoline CNS neurotoxicity. The clinical features of neuropsychiatric quinism reflect the localization of observed neurotoxic injury across the broader quinoline class, with chronic dysfunction in affected areas of the brain and brainstem providing the most parsimonious explanation for the pattern of observed signs and symptoms from the disorder.[14]

2.9 Dr Nevin claims that for a 'sizeable minority of users we see this propensity to neuropsychiatric adverse effects and this risk of permanent disability associated with their use'. He stated that mefloquine and tafenoquine are 'idiosyncratic neurotoxicants at the doses used for prophylaxis' explaining that 'the drug is acting as a toxicant in some users and not in others—idiosyncratic. We don't know the reasons for that'.[15] He argued that it is inherently unsafe to use these drugs in a military environment as it is 'likely that the user will confuse or misattribute side effects from the drug to the stresses of travel, to the effects of crossing time zones and to the effects of stress on deployment'. His theory is that civilian users of mefloquine will stop taking the medication if they experience unpleasant symptoms whereas veterans 'in many cases they were simply ordered to take the drug' and 'never had the opportunity to stop [if they experienced unpleasant side effects]'.[16] Dr Nevin believes that 'veterans are disproportionately represented because in many cases they have been involuntarily intoxicated by these drugs'.[17]

The response of the medical community

2.10 The view of the medical professionals is that this syndrome put forward by Dr Nevin, AQVFA and others is not supported by the available medical evidence. Associate Professor Karunajeewa summarised this alternative theory being put forward:

> In recent years some authors have proposed an alternative theory that mefloquine (and tafenoquine) cause significant neurological toxicity that

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12 *Submission 17*, p. 2. See also Dr Remington Nevin, *Committee Hansard*, 11 October 2018, p. 2.

13 Dr Remington Nevin, *Committee Hansard*, 11 October 2018, p. 2.

14 *Submission 17*, p. 3. See Dr Remington Nevin, *Committee Hansard*, 11 October 2018, pp. 2-3 for further discussion of the theory being put forward.

15 *Committee Hansard*, 11 October 2018, p. 5. See also Associate Professor Jane Quinn, *Proof Committee Hansard*, 5 November 2018, p. 40.

16 *Committee Hansard*, 11 October 2018, pp. 4-5. See also Associate Professor Jane Quinn, *Proof Committee Hansard*, 5 November 2018, p. 41.

17 *Committee Hansard*, 11 October 2018, p. 5.

> results in neurological or psychiatric symptoms that can persist for many years after the drugs are ceased or even be permanent. This has variously been described using terms such as 'chronic mefloquine toxicity', 'mefloquine induced chronic CNS syndrome', 'acquired brain injury', and 'mefloquine (or quinoline) toxidrome'. This theory relies heavily on numerous assumptions, especially in extrapolating findings from older, more toxic quinoline drugs to mefloquine/ tafenoquine and from animal and laboratory studies to humans.[18]

2.11 Associate Professor Karunajeewa advised the committee that this should be regarded as a speculative hypothesis unless it can be supported by evidence from human subjects treated with mefloquine.[19] He added that the terminology being used such as 'chronic mefloquine toxicity' and 'mefloquine (or quinoline) toxidrome' are not 'widely used throughout the mainstream medical community, having until now been restricted to a fairly small core of authors with a particular interest and viewpoint on this matter'.[20]

2.12 The view of Associate Professor Karunajeewa was supported by Professor Geoffrey Quail, President, Australian College of Tropical Medicine:

> The theory that mefloquine causes long-term neuropsychiatric problems relates to work done with older drugs which were more toxic, and also from animal studies. It's very difficult to extrapolate from animal studies to humans. It [is] speculative unless supported by evidence from human treatment with mefloquine. Based on well-conducted studies of over 360,000 US military, which compared mefloquine with alternative drugs for malaria prophylaxis, the long-term mefloquine toxicity is quite minor. If it occurs at all, it's really topping up pre-existing neurological or neuropsychological problems. It is extremely rare for it to occur long term in someone who didn't have other problems. Thus in any subject with common psychological complaints—anxiety, depression, post-traumatic stress disorder—it is overwhelmingly likely to have existed due to factors other than mefloquine exposure.[21]

2.13 Professor Dennis Shanks in his personal submission also stated:

> As with all arguments of causation, there are elements of truth contained within the assertions regarding the toxicity of antimalarial drugs. However, the facts do not support the version of events put forward by some veterans which has symptoms developing years after drug administration and this causing current neuropsychiatric symptoms.[22]

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18 *Submission 15*, p. 4.

19 *Submission 15*, p. 4.

20 *Submission 15*, p. 6.

21 *Committee Hansard*, 30 August 2018, p. 42.

22 *Submission 13*, p. 1.

2.14 In looking at this issue, the RMA noted that '[t]here is no case definition for chronic mefloquine toxicity syndrome and no unique or distinctive group of symptoms has yet been specified…'.[23] The RMA concluded:

> The claim that there are persistent symptoms that are due to mefloquine is based on a small number of case reports and adverse event reports of a variety of commonly experienced symptoms in a widely prescribed medication. These same animal and human case reports are cited repeatedly as the basis for the contention of a syndrome resulting from permanent brain injury.[24]

2.15 Professor Nick Saunders AO, Chairperson, RMA responded to questions from the committee regarding the evidence presented by Dr Nevin:

> Doctor Nevin's evidence is based on case reports—case series. Epidemiologists have a hierarchy of evidence, and studies that generate evidence, for medical conditions. We consider, and epidemiological analysis considers, case reports to be the lowest level of evidence—very weak evidence. The sort of evidence that one would use to then properly design an epidemiological study to analyse or test the hypothesis that might come from that. Doctor Nevin is basing his premises and his assertions on the basis of a small number of case reports. It is very weak evidence, whereas there is much stronger evidence from larger studies, cohort studies, studies that have got controls in place, showing that, in fact, these drugs do not have demonstrable long-term neurocognitive ill-effects on the brain.[25]

2.16 Professor James McCarthy, Professor of Tropical Medicine and Infectious Diseases, Royal Brisbane Hospital and QIMR Berghofer Medical Research Institute spoke on the theory being put forward regarding mefloquine:

> Mefloquine is a drug that was discovered in the 1970s. Right at its very discovery, it was realised that it caused particular mental, psychologic and neurologic side effects in a small proportion of people who took it. That's been very clearly recognised by doctors and people involved in prevention and treatment of malaria, and I personally have observed that in patients I've treated with malaria. As well, there is a small proportion of people who take this drug for prophylaxis—that is, once a week—who unequivocally develop neurologic side effects and therefore should cease taking it, and certainly some groups of people are at higher risk of getting these side effects. What is not, in my mind, certain is the relationship between taking mefloquine for a short period of time and having long-term and permanent neuropsychiatric problems that are clearly caused by a short-term exposure to mefloquine. The literature and the scientific community do not believe that there's a strong link between people who've taken it and having long-term consequences. Certainly people have long-term consequences, but

23 RMA, *Submission 4*, Attachment 4, p. 58.

24 RMA, *Submission 4*, p. 8.

25 *Committee Hansard*, 15 October 2018, pp. 2-3.

> whether that's due to the mefloquine or something else is always very hard to figure out.[26]

2.17 When asked to respond to the evidence provided by Dr Nevin, Professor McCarthy responded:

> I suppose, being a doctor and a scientist, I try to return to what the evidence is and what's been published in the medical literature and what has been subjected to peer review. As I said before, the problem is you've got a situation where you've got a relatively common outcome in human populations, more common in soldiers that were deployed, and you've got a relatively low frequency of outcomes, and statistically it is very hard to be certain that there is an association that meets the criteria of being statistically significant. Although I may not be an epidemiologist, all of my work requires that I understand statistics and risk-benefit analysis. My view is in concurrence with the medical literature that there is no statistically significant association of tafenoquine with any of these purported problems—and, with mefloquine, for the long-term ones that I've described, not the short-term ones, it's very difficult to discern a statistically significant association between those things. That's not to say there might be an effect, but, if there is, it's very hard to find from the population data that we have available to us.[27]

2.18 Professor Dennis Shanks, Director, ADF Malaria and Infectious Disease Institute, also responded to the evidence by Dr Nevin:

> …I think that just about everything Remington Nevin said [to the committee] this morning was wrong. To make this short, when he stood up before the USFDA and tried to explain to people who understood drugs why his view of things—and it was the same view—was correct, he quoted two studies. One was a large study looking at 8-Aminoquinolines in monkeys which was done in the 1940s, and the one was a summer-student stem project done at Walter Reed which was never published. It's a poster. It's one-page long. I would be embarrassed trying to hang anything on those two studies. One was done long before mefloquine or tafenoquine were even synthesised, much less tested, and the other was a completely uncontrolled—interesting, but uncontrolled—study. The controlled studies with toxicity have come back with completely different answers. Tafenoquine and mefloquine are not the same drug. They don't have the same risk profile. What Remington Nevin says is wrong.[28]

2.19 At a Canberra hearing Associate Professor Karunajeewa summarised his view:

> In my submission I've done my best to summarise and synthesise the available evidence as I see it regarding neurotoxicity of mefloquine and tafenoquine. To restate my conclusions: for mefloquine I say that if

26 *Committee Hansard*, 11 October 2018, p. 22.

27 *Committee Hansard*, 11 October 2018, p. 26.

28 *Committee Hansard*, 11 October 2018, p. 58.

> permanent or long-term mefloquine toxicity does exist—and I think it's still a big 'if'—then it seems very unlikely that it causes a significant number of additional neurological and psychiatric problems over and above that which ordinarily occurs due to background rates of mental illness in the community. With respect to tafenoquine, my conclusions are, I think, even stronger still, and I say that there is no evidence at all that it causes increased rates of significant neurological or neuropsychiatric problems, whether acute or chronic, when used in conventional doses in humans.[29]

Possible side-effects

2.20 It is important to note that some evidence provided by individuals does not clearly distinguish between mefloquine and tafenoquine. Although they are both quinolines, tafenoquine is 'not structurally related to mefloquine' and is a primaquine[30] analogue.[31]

2.21 Given the numerous individual accounts of various symptoms the committee looked at the possible side effects of mefloquine and tafenoquine as stated in the advice to clinicians and patients as well as the possible duration of any side effects.

Mefloquine

2.22 Overseas, mefloquine was first granted marketing approval in Switzerland in 1984 and as at February 2018 was approved in approximately 27 countries worldwide. Around 40 million patients around the world have been treated with mefloquine since it was first made available. Mefloquine is listed as a malaria treatment option by the World Health Organization (WHO) and US Centres for Disease Control and Prevention (CDC). It is listed as a WHO essential medicine and is recommended in other authoritative guidelines for the prevention of malaria.[32]

2.23 In Australia, mefloquine is registered under the brand name Lariam, receiving regulatory approval and entered on to the Australian Register of Therapeutic Goods (ARTG) on 27 January 1993. It is indicated for malaria treatment and malaria chemoprophylaxis (prevention).[33] The submission and additional information from Roche indicates that mefloquine was approved in Australia on 3 September 1986.[34] Roche notes that this difference in dates:

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29 *Committee Hansard*, 11 October 2018, p. 29.

30 Primaquine is an antimalarial medication used to prevent and treat relapses of malaria. It is given to people as they leave a malarious area to kill any parasites that may be in the body. Defence, *Submission 1*, p. 15. See also Adjunct Professor John Skerritt, Department of Health, *Committee Hansard*, 11 October 2018, p. 40.

31 It is chemically closely related to primaquine. See 60P, *Submission 9*, p. 2; GSK, *Supplementary submission 8.1*, p. 1. See also Defence *Submission 1*, p. 15.

32 Roche, *Submission 12*, p. 2; Mr Svend Peterson, Managing Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 1.

33 Department of Health, *Submission 3*, p. 2.

34 Roche, *Submission 12*, p. 2.

> …reflects the introduction of the *Therapeutic Goods Act 1989* and the requirement for products to be listed on the Australian Register of Therapeutic Goods (ARTG). After the commencement of the legislation, products already approved and on the market were grandfathered into the ARTG. On the 27 January 1993, mefloquine was grandfathered into the ARTG. Mefloquine had indications for treatment and prophylaxis since is original registration in 1986.[35]

2.24 The Department of Health pointed out that as with all medicines there is a balance of benefits and risks for the population that will use them and regulatory approval by the TGA 'is based on an assessment that at a population level the benefits of the medicine exceed the risks'.[36]

2.25 Roche acknowledged that approval of a medication by the regulator does not indicate that the medication is suitable for everyone. Companies therefore work with regulators to develop and update Product Information (PI) and Consumer Medicine Information (CMI) which assist clinicians, pharmacists and patients to select the most appropriate medicine.[37] In the case of mefloquine, Roche advised that:

> …important safety information from patient and clinician reports have been included in PIs and CMIs since the medicine was made available in Australia. This has included information about neuropsychiatric side effects and precautions around use by people with existing mental health conditions. The purpose of this is to allow healthcare professionals to make a considered judgement on whether mefloquine or another antimalarial is most appropriate for a given person.[38]

Safety profile

2.26 The committee was told that long term problems as a result of taking mefloquine are rare.

2.27 The Department of Health noted that the use of mefloquine is contraindicated (i. e. not recommended for use) as follows: Patients with a past history of active depression, a recent history of depression, generalised anxiety disorder, psychosis or schizophrenia or other major psychiatric disorders or convulsions should not be prescribed Lariam prophylactically (to prevent malaria).[39]

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35 Roche, Additional information, received 19 November 2018.

36 *Submission 3*, p. 2.

37 *Submission 12*, p. 3.

38 *Submission 12*, p. 3. Roche noted over the time that mefloquine has been registered with the TGA the product information has been updated 15 times to provide more information to prescribers and consumers about the risks and benefits. Five of these related to information around neuropsychiatric adverse events. Ms Natalie Touzell, Director, Regulatory Affairs Australia-New Zealand, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 7.

39 Department of Health, *Submission 3*, p. 2. See also Professor James McCarthy, *Committee Hansard*, 11 October 2018, p. 24.

2.28 The adverse effects section of the Lariam Product Information (PI) notes:

> The rate of adverse events associated with Lariam is published to be similar to that with other antimalarial prophylactic medications. In chemoprophylaxis[40] the safety profile of Lariam adverse events is characterised by a predominance of neuropsychiatric adverse reactions.
>
> Due to the long half-life[41] of Lariam, adverse reactions to Lariam may occur or persist up to several weeks after the last dose. In a small number of patients it has been reports that dizziness or vertigo and loss of balance may continue for months after discontinuation of the medicine. There have been rare reports of suicidal ideations. No relationship to drug administration has been established.[42]

2.29 Regarding treatment:

> At the doses given for acute malaria, adverse reactions for Lariam may not be distinguishable from symptoms of the disease itself.
>
> Among subjects who received lariam for treatment, the most frequently observed adverse experiences included: dizziness, myalgia, nausea, fever, headache, vomiting, chills, diarrhoea, skin rash, abdominal pain, fatigue, loss of appetite and tinnitus. Those side effects occurring less frequently included bradycardia, hair loss, emotional problems, pruritis, asthenia, transient emotional disturbances and telogen effluvium (loss of resting hair). Seizures have also been reported.[43]

2.30 In summary Roche advised:

> Based on Roche's evaluation of all available information, including data from post-marketing experience, published literature and other safety-risk management sources, the benefit-risk profile of mefloquine use in the prevention and treatment of malaria remains positive. This is aligned with the views of regulators such as the TGA and bodies such as the WHO and CDC. As a result, it remains available as an option for clinicians and patients to consider when selecting a medicine to prevent or treat the serious condition of malaria.[44]

2.31 At the 8 November 2018 hearing in Canberra, Roche confirmed that the 'benefit-risk profile of mefloquine is well understood and remains positive'.[45]

2.32 The RMA noted:

> Given that mefloquine has been used by more than 35 million travellers for chemoprophylaxis worldwide since 1985 in Europe and since 1990 in the

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40 The use of drugs to prevent disease.

41 Persistence in the bloodstream.

42 Department of Health, *Submission 3*, p. 3.

43 Department of Health, *Submission 3*, p. 3.

44 *Submission 12*, p. 4.

45 Mr Peterson, *Proof Committee Hansard*, 8 November 2018, p. 1.

> USA, it would be expected that even rare effects would be able to be detected with reasonable frequency if a causal relationship existed. Instead, there are only five case reports of people with some long term symptoms (especially vertigo or dizziness), together with reports of persistence of a range of commonly experienced symptoms amongst some of the cases reported to adverse event databases.[46]

2.33 The RMA stated that in relation to the 'acute adverse effects of the drug' which are the effects which occur at the time of taking the drug or soon after it has been discontinued, 'there is undoubtedly evidence that mefloquine is associated with a range of symptoms, some of which can be quite distressing…that evidence has been translated into 16 statements of principles as a causal factor in relation to particular diseases or injuries.'[47] However, the evidence shows that 'these reactions are not experienced by the majority of people who take the drug':

> These are reactions that occur in a minority of people. The evidence shows that the vast majority of those reactions settle over weeks or months, or sometimes symptoms have continued into more than 12 months. So, there are these acute effects. They are uncommon. When they do occur they can be very distressing. In their extreme form, they can have disastrous outcomes in terms of psychotic episodes and the like, but they resolve after taking the drug.[48]

2.34 Adjunct Professor John Skerritt, Deputy Secretary, Health Products Regulation, Department of Health provided his view on the safety profile of mefloquine:

> Used in patients or individuals who do not suffer from psychiatric disorders, mefloquine, as antimalarials go, is quite a respectably safe medicine—I've taken it myself. Tafenoquine doesn't have as many adverse events in people with psych issues as does mefloquine. But, as antimalarials go, mefloquine definitely has a place.[49]

2.35 This view was supported by Professor Quail:

> Sure, mefloquine, as we've said, has this side effect profile, but it really is reasonably clear of side effects in about 90 per cent of cases. If it's taken, mefloquine is taken at a dose of 25 milligrams per kilogram, which is a standard dose. The incidence of severe neurotoxicity is less than one in 1,500. As I said, in almost every case that clears away unless there's a pre-existing psychiatric problem.[50]

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46 *Submission 4*, p. 9.

47 Professor Nick Saunders, *Committee Hansard*, 15 October 2018, p. 2.

48 Professor Nick Saunders, *Committee Hansard*, 15 October 2018, p. 2.

49 *Committee Hansard*, 11 October 2018, p. 40.

50 *Committee Hansard*, 30 August 2018, p. 42.

2.36 Adjunct Professor Skerritt emphasised the need for second or third line drugs due to antimalarial resistance in parts of Asia and Africa and because some people cannot tolerate doxycycline.[51]

2.37 Responding to concerns about whether a public health danger is being missed, Associate Professor Karunajeewa stated:

> The scale of this is that we're talking about 200 million people a year. Most of those people are being treated with some form of quinoline antimalarial of one type or another, and this has been going on for decades—hundreds of tonnes per year. The quinoline antimalarial drugs are probably the most-used drugs in human history, just to keep that in perspective. 'Are we missing something actually causing long-term harm?'…I go back to the evidence that we have. I don't think there's anything particular to suggest that that is the case. We're in the business of trying to limit sickness and death from one of the most serious illnesses that has ever affected humans. It has killed 300 million people over the history of humankind, and we're trying to put a stop to that. We're trying to put a stop to that, and we've had, I think, not insignificant successes over the last 15 years or so. There have been profound advances in the control of malaria which we think have saved about six million lives over the last 15 years. The improvements in malaria control are related to the use of bed nets but also to these new quinoline drugs that we're using for malaria. Six million people we think are alive today who wouldn't be if we hadn't been instituting those measures. We can't just sit around and watch it all happen; we have to try to do something about it, and that involves some risks. Nothing is achieved without risks, but our job is to try to manage those risks and minimise them.[52]

Defence approach

2.38 The potential side-effects of mefloquine were known and taken into consideration by Defence and are reflected in their cautious approach:

> Defence has always acknowledged that mefloquine can cause side effects, including neuropsychiatric problems, while individuals are taking the drug. Our conservative approach is a direct acknowledgement of these potential side effects. Generally, symptoms will disappear when the individual stops taking the drug but they can persist for some time afterwards due to the drug's long half-life of two to four weeks. Defence also acknowledges that neuropsychiatric side effects have been known to continue and become long term in a small number of individuals.[53]

2.39 Defence emphasised to the committee that at the time of the trials in the late 1990s and early 2000s, mefloquine was approved by the TGA, however Defence recognised:

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51 *Committee Hansard*, 11 October 2018, p. 40.

52 *Committee Hansard*, 11 October 2018, pp. 33-34.

53 *Submission 1*, p. 2. See also Defence, *Supplementary submission 1.1*, pp. 22-23.

> …mefloquine should not be taken for malaria prevention by people who have, or have had, a psychiatric condition, seizures, kidney disease or liver disease. For these reasons, Defence health policy requires that ADF members be properly informed of the potential side effects of mefloquine and that the drug only be prescribed by a qualified medical practitioner after the member has been provided information about the drug's side effects.[54]

2.40 Defence indicated that the known possible side-effects are outlined in the patient information:

> Mefloquine is known to cause unusual dreams and can cause psychiatric symptoms in some people, including disturbed sleep, anxiety, paranoia, depression, hallucinations and psychosis. Dizziness and loss of balance have also been reported as side effects from the use of mefloquine. For this reason, the medication is not used in ADF aircrew.[55]

2.41 The committee received a number of submissions from individuals recalling the vivid dreams they experienced while taking mefloquine.[56] This was addressed by Professor McCarthy who explained:

> When you take it, the levels of the drug go up in your blood very quickly and then they go down quite quickly. During that phase of 12 hours or so when the drugs are at high levels in the blood, people very frequently describe how, in the evening after they take their mefloquine, they would have a disturbed night's sleep or vivid dreams. But that is not a dangerous effect, and that's an effect that does disappear. I would always warn somebody that they should expect to have perhaps some disturbances in their sleep the night they take their mefloquine.[57]

2.42 Professor Sandy McFarlane AO, Director of the Centre for Traumatic Stress Studies at the University of Adelaide was asked by Defence to conduct a literature review on the adverse effects of mefloquine. The major findings of this review were:

- there are various theories on how mefloquine might cause neuropsychiatric effects based on its underlying action.
- there are varying conclusions about its potential toxicity.
- these variations are, in part, explained by the differences of the methodology used in the published reports.

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54 *Submission 1*, p. 12

55 *Submission 1*, p. 12.

56 See for example, Name withheld, *Submission 53*, p. 1; Mr Benjamin Fleming, *Submission 72*, p. 2; Name Withheld, *Submission 76*, p. 3; Name withheld, *Submission 97*, p. 1; Name Withheld, *Submission 101*, p. 1.

57 *Committee Hansard*, 11 October 2018, pp. 24-25. See also Associate Professor Harin Karunajeewa, *Committee Hansard*, 11 October 2018, p. 32; Defence, *Supplementary submission 1.1*, p. 22.

- the serious side effects of mefloquine have been known for many years, but continuation of effects after ceasing medication is a concern raised in recent years.
- there is no specific way to diagnose chronic mefloquine effects as many symptoms are shared with other conditions such as PTSD.
- there is no specific treatment except to cease the drug when symptoms develop and to treat the symptoms.
- the literature available at the time of this review does not address some questions, including:
    - Are some individuals pre-disposed to adverse effects?
    - Does mefloquine modify the response to trauma?[58]

Duration of side effects

2.43 Regarding the length of any side effects, the committee was told that they normally resolve after the medication is stopped. Defence indicated:

> Normally side effects, including neuropsychiatric side effects, resolve within days to weeks after stopping mefloquine. Mefloquine has a half-life (persistence in the bloodstream) of two to four weeks, which is longer than other antimalarials, therefore side effects that emerge while taking mefloquine have been reported to persist after cessation of the medication and sometimes for several months.[59]

2.44 Roche provided further detail on how long the medication takes to be eliminated from the body:

> …the half-life of the drug is quite long—it's 21 days—so that allows people not to have to take it daily—hence the weekly dosing regime that I described. That is, of course, an advantage when one looks at compliance and how well people adhere to medicines that have been prescribed to them. So the fact that the drug itself and its metabolites have half-lives of about 21 days means that, after 21 days, half the drug is eliminated from the body. The general understanding is that, in five times the half-life for the drug, it will be eliminated, which would be maximally 100 days. But they would be very low doses at that time, very low concentrations.[60]

2.45 Associate Professor Karunajeewa pointed to data from numerous clinical studies which have consistently found that any mefloquine side effects:

- develop early on in the drug's use;
- are more likely to occur in those with pre-existing psychiatric illnesses;

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58 Defence, *Submission 1*, p. 45; Defence, *Supplementary submission 1.1*, p. 25.

59 *Submission 1*, p. 12.

60 Dr Peter Stewart, Roche, *Proof Committee Hansard*, 8 November 2018, p. 4.

- are dose-related (therefore more likely to occur or be more severe if higher doses are used); and
- generally resolve following cessation of the drug.[61]

2.46 Associate Professor Karunajeewa emphasised that these findings have been reinforced by the clinical experience with many millions of people treated with mefloquine throughout the world.[62]

2.47 Further explanation was provided:

> …mefloquine, like virtually all drugs, can cause toxicity that encompasses a spectrum from none at all on one side, to very severe on the other. The key question then becomes, in practice, how many people taking the drug fall into the "very severe" category with lasting or permanent significant side effects. Is this likely to be very rare or quite common? To answer this question, our best available approach is to draw on the results of carefully constructed studies that apply the best statistical methods to compare the prevalence of these symptoms in humans who have taken these drugs, with a suitable group for comparison (often referred to as a control group).[63]

2.48 Associate Professor Karunajeewa discussed the possible length of side effects with the committee:

> To actually understand whether that does occur or not [that side effects are generally resolved following cessation of the drug] is the difficult process that we need really good evidence for, and I believe that large study of 360,000 is probably the best that we've got. There certainly have been reports, case reports, of people who have had persisting dizziness, persisting problems with ringing in the ears and that sort of thing, but it's still hard to be absolutely sure that it's mefloquine that's the cause of the problem. But, look, I'm perhaps a little bit more sanguine than some people in terms of being absolutely on one side of the barge or the other. I still think it's possible that in some rare, unlucky individuals that they do experience longstanding effects from mefloquine. I still think that's possible. But my reading of the literature and of the accumulated evidence is that, if that does occur, it's highly likely that it's actually quite a rare event.[64]

2.49 He further responded that these rare events are more likely to occur in those who have a pre-existing psychiatric illness.[65]

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61 *Submission 15*, p. 4. See also Professor Geoffrey Quail, President, Australian College of Tropical Medicine, *Committee Hansard*, 30 August 2018, pp. 44-45.

62 *Submission 15*, p. 4.

63 *Submission 15*, p. 8.

64 *Committee Hansard*, 11 October 2018, pp. 32-33.

65 *Committee Hansard*, 11 October 2018, p. 33. See also The Australasian Society for Infectious Diseases, *Submission 6*, p. 2.

International and domestic studies

2.50 The committee was told about the international and domestic studies involving mefloquine. Although the next section is not exhaustive, relevant submissions contain further details.

2.51 Associate Professor Karunajeewa directed the committee to a large and well-designed study published in 2017 of 367 840 US military personnel[66] which compared the incidence of neuropsychiatric diagnoses occurring up to a year following drug exposure in 36 568 individuals who took mefloquine with 331 272 who took an alternative malaria drug such as doxycycline or Malarone.[67] Following analysis of the findings in his submission Associate Professor Karunajeewa concluded:

> Based on these findings, we cannot absolutely with 100% [certainty] disprove the theory that mefloquine causes long-term toxicity in humans. In fact we can never do this - that's just not how science works. However, based on the study's findings, we can say, that if mefloquine did cause long-term toxicity (and that is still a very big "if"), then this is likely to occur as a fairly uncommon event and would only contribute to a very small proportion of the background rates of psychiatric disease in the population.[68]

2.52 Associate Professor Karunjeewa indicated that this US study '[b]y nature of this [the use of appropriate methods] and its very large size, it effectively constitutes the best evidence on this subject we currently have, and probably the best evidence we are ever likely to have'.[69] However, he also pointed to a smaller study conducted by the US CDC in 2016 which invited former Peace Corps volunteers (from 1995 to 2014) to participate in an internet based survey related to malaria prophylaxis and medical diagnosis. Noting the methodological problems (only 11 per cent participation) and recall bias, the overall conclusions were that:

> (1)'Malaria prophylaxis use by Peace Corps Volunteers is safe', (2) 'When excluding those with prior psychiatric illness there were no difference in psychiatric diagnosis rates' in mefloquine users and (3) In those with pre-existing psychiatric diagnoses, 'certain psychiatric diagnoses were more likely among Mefloquine users'. This last point is consistent with existing knowledge regarding risk factors for neuropsychiatric effects of mefloquine and emphasizes the importance of good screening for these contraindications prior to prescribing.[70]

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66 Eick-Cost et al, Neuropsychiatric outcomes after Mefloquine exposure among U.S. military service members, *American Journal of Tropical Medicine and Hygiene* 2017; 96: 159-166. See also Professor James McCarthy, *Committee Hansard*, 11 October 2018, p. 25.

67 Atovaquone-proguanil.

68 *Submission 15*, p. 9.

69 *Submission 15*, p. 8; *Committee Hansard*, 11 October 2018, p. 29. See also Professor James McCarthy, *Committee Hansard*, 11 October 2018, p. 27.

70 *Submission 15*, p. 9.

2.53 Associate Professor Karunajeewa stated that '[o]verall I think their findings were consistent with and supported by the larger and more rigorous subsequent [2017] study'.[71]

2.54 Responding to a question about taking mefloquine long-term, Professor McCarthy also referred to the study of US Peace Corps volunteers who took mefloquine for years while working in sub-Saharan Africa and that 'the rate of these side effects went down as people took the mefloquine for longer'.[72]

2.55 Associate Professor Karunajeewa emphasised that the results of these studies:

> …are also borne out by the now very extensive clinical experience with mefloquine. Until as recently as 2011, up to 17,000 Australian travelers were being prescribed mefloquine by GPs and travel clinics. As many as 35 million people a year receive the drug (mostly in much higher treatment doses than are used for prophylaxis). This represents the very large 'denominator' of total mefloquine use in the community and suggests that the isolated reports of serious side effects represent an extremely small fraction of the total users.[73]

2.56 Professor McCarthy also spoke about his own research involving mefloquine in small groups in three different doses:

> With the people on the highest dose, I think three or four of the eight people had what I would consider to be unacceptable side effects of the mefloquine when given very high doses to cure their malaria. So, without a doubt, the mefloquine did cause those transient side effects that went away once the mefloquine went out of their system.[74]

2.57 Defence also pointed to a 2006 study[75] which was a retrospective analysis of US military health records between 2002 and 2004 to examine the adverse effects of antimalarials. The study compared numbers of hospitalisations of military personnel who had been prescribed mefloquine and were deployed to active duty in malarial areas with those who had not and resided in Europe or Japan and those who were otherwise deployed. It found that '[m]efloquine users were statistically less likely to be hospitalised (after deployment) with mood disorders, or for any cause, than military personnel who did not receive any antimalarial agents but who were deployed to a war zone'.[76]

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71 *Submission 15*, p. 9. See also Defence, *Supplementary submission 1.1*, p. 21.

72 *Committee Hansard*, 11 October 2018, p. 22.

73 *Submission 15*, pp. 9-10.

74 *Committee Hansard*, 11 October 2018, p. 23.

75 Wells TS, Smith TC, Smith B, Wang LZ, Hansen CJ, Reed RJ, et al. Mefloquine use and hospitlaizations among US service members, 2002-2004, *American Journal of Tropical Medicine and Hygiene 2006*; 74(5): 744-9.

76 *Submission 1*, p. 47.

2.58 Dr Nevin criticised the studies cited, saying they have not been informed by 'methods of modern psychiatric epidemiology'.[77] This was not supported in evidence to the committee.[78] Adjunct Professor Skerritt commented that in general, 'neuropsychiatric tools are used to determine fairly subtle changes…You don't need a neuropsychiatric tool to say you've had severe insomnia or bad dreams or bad depression…so I'm not sure that that's necessarily required if you're looking for a serious adverse event'.[79]

2.59 Dr Peter Stewart, Roche, told the committee that 'mefloquine is the most studied of all the antimalarials' and '[t]here is a very large volume of evidence that has been collected around the safety and efficacy of this drug'.[80] He referred the committee to the most recent publication on the safety of efficacy published in 2017 by the Cochrane Collaboration[81] which is 'one of the most respected, independent, evidence based scientific bodies in the world'.[82] It reviewed a million patients using a variety of information sources including clinical trials, non-clinical trials, hospital records, and health authority records. It found that the 'risk benefit profile is very well understood and very well described and remains positive'.[83] Dr Stewart pointed to some of the findings of the Cochrane Collaboration that 'mefloquine does not have more frequent serious side effects overall than the two commonly used other antimalarials, doxycycline and atovaquone-proguanil [Malarone]'. 'They [the Cochrane Collaboration] did note, as we know, that people taking mefloquine are more likely to have [transient] abnormal dreams, insomnia, anxiety and a depressed mood for the period during travel than those who take doxycycline or atovaquone'.[84]

2.60 Dr Stewart also noted the large volume of clinical research data and real world data collected over 32 years and stated that this body of evidence does not support the hypothesis of brain injury from antimalarial treatment generally or mefloquine specifically.[85] He pointed to one of the conclusions of the Cochrane Collaboration which was:

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77 *Committee Hansard*, 11 October 2018, p. 8.

78 Associate Professor Harin Karunajeewa, *Committee Hansard*, 11 October 2018, p. 33; Professor James McCarthy, *Committee Hansard*, 11 October 2018, p. 26.

79 *Committee Hansard*, 11 October 2018, p. 44.

80 *Proof Committee Hansard*, 8 November 2018, p. 3.

81 See https://cidg.cochrane.org/news/cochrane-review-update-mefloquine-preventing-malaria-during-travel-endemic-areas, accessed 19 November 2018. Tickell-Painter M et al, Melfoquine for preventing malaria during travel to endemic areas, Cochrane database of Systemic Reviews, 2017, Issue 10:CD006491; See also, Roche Products Pty Ltd, Answers to questions on notice from 8 November 2018 hearing, received 19 November 2018.

82 *Proof Committee Hansard*, 8 November 2018, p. 3.

83 Dr Stewart, *Proof Committee Hansard*, 8 November 2018, p. 8.

84 *Proof Committee Hansard*, 8 November 2018, p. 4.

85 *Proof Committee Hansard*, 8 November 2018, pp. 8-9.

> We believe it is important that the large retrospective healthcare record analyses did not demonstrate a clear quantitative association between mefloquine use and formal mental health disorders.[86]

Metabolisation

2.61 As the AQVFA points to metabolisation of the drugs as a possible reason for potential adverse reactivity,[87] the committee discussed the metabolisation of mefloquine with Roche which advised that metabolisation occurs through a class of enzymes called the cytochrome P450 enzymes. While there are more than 50 types of cytochrome P450 enzymes, the two most common are CYP3A4 and CYP2D6 and mefloquine is metabolised by CYP3A4. Dr Stewart noted the hypothesis that if a patient has a low level of CYP3A4 then potentially the body might not be able to metabolise mefloquine as well as others or it might not be cleared as rapidly. He explained that all medicines are metabolised by one of these enzymes and it has not been determined that routine use of testing to discover genetic variations in people would improve outcomes. He also pointed to the large body of evidence in relation to mefloquine which does not support the hypothesis that mefloquine causes brain injury[88] or long term mental health disease or conditions.[89] See below for further discussion of metabolisation in relation to tafenoquine.

PTSD

2.62 Professor McFarlane speculated about the role of antimalarials which may modify the risk of developing a range of psychiatric disorders including PTSD.[90] This was addressed by Dr Dow from 60 Degrees Pharmaceuticals:

> It is not disputed by most travel physicians that mefloquine at prophylactic doses statistically increases the risk of the following adverse events relative to doxycycline and atovaquone-proguanil: insomnia, abnormal dreams, anxiety and depression. Professor McFarlane speculates that antimalarial drugs that are "psychotropic" and cause such events in some individuals might increase the risk of rarer and more severe post-deployment psychiatric events, particularly in stressful situations. However, he neglects to mention that, at a population level, the scientific literature does not support such a causal association in practice. In fact, recent reports from reputable U.S. government agencies have demonstrated that (i) deployment and combat experience not antimalarials increases the risk of PTSD and other serious psychiatric events, (ii) mefloquine and atovaquone-proguanil result in a similar increase in the total burden of neuropsychiatric illness during deployment and (iii) the long term risk of serious psychiatric events

86 *Proof Committee Hansard,* 8 November 2018, p. 9.

87 *Submission 16*, pp. 51-52.

88 *Proof Committee Hansard,* 8 November 2018, pp. 8-9.

89 *Proof Committee Hansard,* 8 November 2018, p. 6.

90 *Submission 58,* p. 2.

is not increased for mefloquine relative to other antimalarial prophylactics if prescribing information is followed.[91]

Use by the civilian population

2.63 Defence advised that its use of mefloquine has been conservative compared to its use in other militaries around the world and in the civilian population. It is commonly prescribed in the broader Australian community.[92]

Estimated Australian Civilian Prescription Data[93]

Anti-malarial	2010	2011	2012	2013	2014	2015	2016
Mefloquine	14,149	16,512	13,674	14,030	13,770	12,713	11,457

Source: Australian statistics on medicines/Roche Products Pty Ltd

2.64 Roche advised that 8,810 scripts for mefloquine were issued in Australia in 2017[94] with approximately 40 million patients treated with mefloquine globally since it was made available.[95] Approximately 300,000 Australian patients have been prescribed mefloquine.[96]

2.65 The RMA noted that mefloquine has been used by more than 35 million travellers for chemoprophyaxis worldwide since 1985 in Europe and 1990 in the USA and therefore 'there is a strong likelihood that even rare effects would be able to be detected with reasonable frequency if a causal relationship existed. Nevertheless, there are relatively few case reports of long term adverse effects given the high level of usage'.[97]

2.66 The committee spoke to Dr Penny Burns, GP representative of the Royal Australian College of General Practitioners to discuss the use of mefloquine in the civilian population. Emphasising that 'malaria is a very serious and deadly disease', she confirmed that 'GPs are still regularly prescribing mefloquine and the '[c]urrent evidence based resources used by many GPs as reference on best management of

91 *Supplementary Submission 9.1*, p. 5.

92 Defence, *Submission 1*, p. 2.

93 See http://www.defence.gov.au/Health/HealthPortal/Malaria/Anti-malarial_medications/Mefloquine/, accessed 4 July 2018.

94 *Submission 12*, p. 10.

95 *Submission 12*, p. 6. Mr Svend Peterson, Managing Director Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 1.

96 Dr Stewart, Medical Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 3.

97 Australian Government, Repatriation Medical Authority, Statement of Reasons Re: Decision not to make Statements of Principles for chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine, pp. 10-11.

patients, including therapeutic guidelines up to date, still include mefloquine as an option for malarial prophylaxis'.[98] Dr Burns spoke about her personal experience:

> …I've seen a lot of patients prescribed mefloquine with minimal percentage, in my experience, having had side effects. I've probably only seen about three people with side effects from mefloquine that have been impacted over that period of time.[99]

Tafenoquine

Potential to assist the region

2.67 It was noted that the approval of tafenoquine would be the first new medicine for the prevention of relapse of P. vivax malaria in more than 60 years, addressing the need for a single dose, effective medicine.[100] Evidence noted the potential public health value of tafenoquine for the Asia Pacific region.[101] The Asia Pacific Leaders Malaria Alliance reported:

> As expressed during the recent Malaria World Congress in Melbourne (1-5 July 2018) by world experts on P. vivax, the promise of Tafenoquine as a single dose radical cure is revolutionary. Not only will Tafenoquine improve patient adherence by reducing a current standard regimen from 14 days, but will also reduce the risks of resistance, because of its single-dose formulation as a radical cure. This is particularly relevant in settings where regular follow-up with patients is a challenge due to poor geographic accessibility to public health services.[102]

2.68 It also advised that:

> In addition, Tafenoquine as a preventive treatment is crucial from a public health perspective to mitigate the risk of malaria spreading beyond borders, as well as to reduce the number of imported malaria cases, which could reverse efforts to eliminate malaria. What is more, Tafenoquine as a prophylaxis could support efforts to prevent transmission from asymptomatic carriers.[103]

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98 *Committee Hansard*, 11 October 2018, p. 15.

99 *Committee Hansard*, 11 October 2018, p. 15.

100 See Medicines for Malaria Venture, 'GSK submits US regulatory application for single-dose tafenoquine for Plasmodium vivax malaria', M*edia Release*, 28 November 2017. Note: For radical cure, primaquine needs to be administered daily over 2 weeks but there can be poor compliance which can lead to a 3 to 4 fold reduction in efficacy. See MMV, *Submission 10*, p. 3. See also GSK, *Supplementary submission 8.1*, p.1; Australasian Society for Infectious Diseases, *Submission 6*, p. 1. See also Geoffrey S. Dow et al, Tafenoquine is not neurotoxic following supertherapeutic dosing in rates, *Travel Medicine and Infectious Disease*, 17 (2017) 28-34, see Introduction.

101 See for example Mr Karl Herz, Managing Director, Biocelect Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 17.

102 *Submission 5*, p. 1.

103 *Submission 5*, p. 1.

2.69 Professor McCarthy also supported the approval of tafenoquine:

> I think it's a really useful drug and will protect lots of people from catching malaria—as long as we've got adequate mechanisms in place to give surveillance for these unusual side effects, which are of uncertain relationship to tafenoquine. Certainly if I was to go to one of these malaria areas I would be wanting to have tafenoquine available. I think it will be a fantastic drug for the prevention of malaria, if we can continue to monitor for the unusual outcomes.[104]

2.70 Mr David Herd, Director, Market Access and Communications and Government Affairs, GlaxoSmithKline Australia Pty Ltd emphasised the importance of the radical cure[105] treatment as a 'critical step towards the effective elimination of P. vivax malaria globally'.[106] GSK spoke about their work with Medicines for Malaria Venture (MMV)[107] to address the 'very significant unmet medical need in malaria-endemic countries for an alternative treatment to the current standard of care, which you have to give for 14 days'.[108]

2.71 Responding to concerns raised by Dr Nevin about the safety of tafenoquine, and the effect in poorer countries[109] Professor McCarthy responded:

> It's obviously morally really important that we don't relegate drugs as 'second class' so, therefore, they can be tested or deployed in populations where they will never be accepted in Australia. But you've got to remember that these drugs have been approved for use in the US on US citizens, so I don't believe that we can do any better than that. As long as we've got a robust process in place for surveillance after licensing these drugs, I think, to turn it on its head, it would be unethical and immoral to deprive the people who are most at risk of malaria of getting a new drug that's going to be the first prophylactic drug available for many years. I think that you could turn that around and say that it would be inappropriate to deny them access to this drug.[110]

2.72 At the time of the ADF trials tafenoquine was not registered in Australia. However, in July 2018 it was approved by the US FDA for malaria radical cure

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104 *Committee Hansard*. 11 October 2018, p. 26.

105 Prevention of relapse, or eradication.

106 *Proof Committee Hansard*, 8 November 2018, pp. 10, 15.

107 MMV works closely with the World Health Organization, and is funded by donors including the governments of Australia, Ireland, Japan, the Netherlands, Norway, Switzerland, the UK and the USA; the Bill and Melinda Gates Foundation and the Wellcome Trust. MMV, *Submission 10*, p. 2.

108 Dr Webster, *Proof Committee Hansard*, 8 November 2018, p. 12.

109 See *Committee Hansard*, 11 October 2018, p. 9.

110 *Committee Hansard*, 11 October 2018, pp. 27-28.

(prevention of relapse)[111] of liver-stage infections under the trade name Krintafel.[112] On 8 August 2018 it was approved by the US FDA for malaria prevention under the trade name Arakoda.[113] In September 2018 it was also approved by the Australian TGA for prevention under the trade name Kodatef[114] and radical cure under the trade name Kozenis.[115]

2.73 Dr Geoffrey Dow, CEO and Chairman, 60 Degrees Pharmaceuticals explained the relationships between GSK, 60 Degrees Pharmaceuticals and Biocelect in relation to tafenoquine in evidence to the committee.[116]

Safety profile

2.74 The committee was told that there is no compelling evidence that tafenoquine causes long term adverse effects.

2.75 Dr Dow addressed the assertions made by some groups:

> Activist groups such as the Quinism Foundation, in common cause with some veterans' groups, (hereafter referred to as the 'anti-tafenoquine activist community') bluntly assert that all quinoline antimalarials are neurotoxic. This is false. Primaquine…is an 8-aminoquinoline. It is activated in the body to form unknown oxidative intermediates that confer an indirect antimalarial effect on hepatic stages without causing neurologic deficits….In contrast, mefloquine is a 4-aminoalcohol with a side chain and confers both a potent and direct effect only on blood stage malaria parasites, while inducing an increased rate of some specific neuropsychiatric events relative to the standard of care in travelers. Since tafenoquine is an 8-aminoquinoline analog of primaquine, and is not structurally related to

111 For a more detailed explanation of radical cure see Mr David Herd, Director, Market Access and Communications and Government Affairs, GlaxoSmithKline Australia Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 10.

112 US FDA approved single-dose 300mg tafenoquine for the radical sure of P. vivax malaria. This was sponsored by GSK and MMV.

113 It provides effective protection against both the major types of malaria (P. vivax and P. falciparum) killing the parasites in the blood and the liver. This was sponsored by 60 Degrees Pharmaceuticals. Dr Geoff Dow, Chief Executive Officer and Chief Scientific Officer, 60 Degrees Pharmaceuticals, *Proof Committee Hansard*, 8 November 2018, p. 17. See Also Mr Mark Reid, *Submission 71*, p. 9.

114 Sponsor Biocelect. Dr Dow, 60 Degrees Pharmaceuticals, *Proof Committee Hansard*, 8 November 2018, p. 17

115 Sponsor, GSK. See Defence, *Supplementary Submission 1.1*, pp. 4-5.

116 See *Proof Committee Hansard*, 8 November 2018, p. 20. Note: Biocelect have been helping 60 Degrees Pharmaceuticals with the commercialisation of tafenoquine since 2013. This assistance was provided by the consulting company Biointelect Pty Ltd of which Mr Herz, Managing Director of Biocelect, is a director, employee and one of the owners. Biocelect Pty Ltd licenced tafenoquine from 60 Degrees Pharmaceuticals under a Supply and Distribution Agreement executed 22 September 2016 for Australia, NZ, PNG and various Pacific Islands. See Biocelect, additional information, received 19 November 2018.

> mefloquine, there is no reason, a priori, to expect it to exhibit the same adverse event profile as mefloquine.[117]

2.76 Biocelect also addressed the claims:

> We are aware of a small group of veterans and their supporters who attribute their mental health issues to having been given Tafenoquine in trials conducted within the Australian Defence Force during their deployment in East Timor. We wholeheartedly sympathise with these veterans and while we recognize and appreciate that they have served our country, based on the evidence available we do not attribute these mental health issues experienced by the veterans to Tafenoquine….We believe that this position has been confirmed by the recent approval for Tafenoquine as a treatment (radical cure) for malaria by the U.S. Food and Drug Administration (FDA) and the recent recommendation by the U.S. FDA expert Advisory Committee for the approval of Tafenoquine for the prevention of malaria. This recent FDA approval for treatment and FDA expert Advisory Committee recommendation, for approval by the FDA for prevention, was conducted by highly qualified scientific and medical experts based on their review of the scientific evidence.[118]

2.77 GSK emphasised to the committee that they take safety very seriously. 'We have been fully transparent with all of the safety data that we've gathered across all of the studies that were done—not just the ones done more recently—that are relevant to a radical cure. They have been evaluated very thoroughly by the regulators'.[119] GSK advised that they will continue to review the safety profile as tafenoquine is rolled out in the US and working with WHO when it is available for radical cure in endemic countries.[120]

2.78 GSK advised that the full report of safety data was submitted to the FDA and TGA for review. GSK added 'there is no evidence that tafenoquine concentrates at toxic levels in the brain causing permanent brain injury'.[121] GSK advised that 13 clinical trials were submitted to US and Australian regulatory authorities involving more than 800 patients.[122] GSK noted that the FDA and its Antimicrobial Drugs Advisory Committee were aware of the concerns raised by ADF veterans.[123] Dr Nevin

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117 *Submission 9*, p. 2. See also Biocelect, *Submission 11*, p. 2; Jonathan Berman et al, Tafenoquine and primaquine do not exhibit clinical neurologic signs associated with central nervous system lesions in the same manner as earlier 8-animoquinolines, *Malaria Journal*, (2018) 17:407.

118 *Submission 11*, p. 2.

119 Dr Webster, GSK, *Proof* Committee Hansard, 8 November 2018, p. 14.

120 Dr Webster, GSK, *Proof Committee Hansard*, 8 November 2018, p. 15.

121 *Supplementary submission 8.1*, p. 1.

122 *Submission 8*, p. 3.

123 *Supplementary submission 8.1*, p. 3.

confirmed that he was the only submittor to the FDA against approval of tafenoquine.[124]

2.79 MMV, a product development partnership in the field of antimalarial drug research and development, reported:

> …it should be noted that no serious neurological or psychiatric adverse events (AEs) were noted in the clinical efficacy & safety studies that investigated the single 300mg tafenoquine treatment dose (GSK-MMV clinical trials program for TQ), and no subjects withdrew from the studies or discontinued treatment due to central nervous system (CNS) AEs. All CNS events seen in these studies were mild to moderate in severity and were self-limiting.
>
> …
>
> We therefore conclude that in the >800 subjects who have received a total single-dose of 300mg TQ, no serious CNS events have been reported and the observed events have been mild to moderate and self-limiting. Therefore, the single 300 mg TQ dose + [chloroquine] CQ for radical cure of P. vivax malaria is anticipated to have a low risk of significant CNS effects in patients without an active or past history of serious psychiatric disorders.[125]

2.80 The Australasian Society for Infectious Diseases said that the extensive experience with the structurally similar primaquine is reassuring:

> In more than 36 million exposures, there has only been 1 report of neurotoxicity in a 55 year old man who developed depression and psychosis after the 2nd dose of primaquine which resolved within 24 hours on stopping the drug.[126]

2.81 Dr Dow noted that the US prescribing information for Arakoda includes a contraindication for those with psychotic illness and explained this as precautionary because three clinical trial participants with an undisclosed history of psychosis experienced psychotic events at doses which were not the approved dose.[127]

2.82 MMV provided information on non-clinical animal studies which do not suggest a signal for CNS toxicity with tafenoquine.[128] MMV concluded:

> We believe its use will transform case-management of P. vivax infection, improve compliance, help achieve improved rates of radical cure and

124 *Committee Hansard*, 11 October 2018, p. 4.

125 *Submission 10*, pp. 4-5.

126 *Submission 6*, pp. 2-3. See also 60P, *Submission 9*, p. 2; Dr Webster, GSK, *Proof Committee Hansard*, 8 November 2018, p. 12.

127 60 Degrees Pharmaceuticals, *Supplementary Submission 9.1*, p. 4.

128 *Submission 10*, p. 4.

> contribute to achieving both the Sustainable Development Goals and malaria elimination targets set by WHO.[129]

2.83 Professor McCarthy spoke about his clinical trials using small groups of people. He reported that in the case of tafenoquine, '[a]ll of the subjects who were given tafenoquine had no neurologic side effects at all'.[130]

2.84 Dr Dow confirmed that during its review of tafenoquine, the US FDA included specialists from their division of psychiatry as well as the pharmacovigilance and epidemiology areas to review the data.[131] He also outlined the additional work undertaken in an attempt to address the concerns of some advocates.[132]

2.85 The Department of Health took the committee through the approval process for drugs which tafenoquine has just been through and the ongoing safety monitoring of drugs.[133] Adjunct Professor John Skerritt, Deputy Secretary, Health Products Regulation, Department of Health, confirmed that experts within the TGA include medical doctors, toxicologists and pharmaceutical chemists. He also advised that the TGA sought external advice 'from an advisory committee of doctors, community representatives, epidemiologists, statisticians'.[134]

2.86 Adjunct Professor Tim Greenaway, Chief Medical Adviser, Health Products Regulation, Department of Health, pointed out that there is much more data available than just the ADF trial involving tafenoquine. He pointed to a review of 22 trials of tafenoquine where 'the safety profile of tafenoquine was very, very good and the risk-benefit analysis was favourable' and this was considered by Australia's Advisory Committee on Medicines (ACM)[135] and the US FDA independently.[136]

2.87 The US FDA and TGA approval processes included an audit of the Defence studies involving tafenoquine:

> The U.S. FDA, with TGA observing, audited study records for Study 033 and 049. The auditor, commented…that the level of oversight by ADF

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129 *Submission 10*, p. 4.

130 *Committee Hansard*, 11 October 2018, p. 23.

131 *Proof Committee Hansard*, 8 November 2018, p. 19. See Also Mr Mark Reid, *Supplementary Submission 71.3*, p. 3.

132 *Proof Committee Hansard*, 8 November 2018, p. 21. GSK also outlined the steps they have taken to address concerns, see Answers to questions taken on notice at 8 November 2018 hearing in Canberra, received 21 November 2018.

133 Adjunct Professor John Skerritt, Deputy Secretary, Health Products Regulation, Department of Health, *Committee Hansard*, 11 October 2018, pp. 35, 37.

134 *Committee Hansard*, 11 October 2018, p. 37. Dr Dow also spoke of the wide range of specialists accumulating and analysing medical data, *Proof Committee Hansard*, 8 November 2018, p. 19.

135 Providing independent medical and scientific advice to the Minister for Health and the TGA.

136 *Committee Hansard*, 11 October 2018, p. 37; Adjunct Professor Skerritt, *Committee Hansard*, 11 October 2018, p. 42.

> medical officers, in particular Lieutenant Colonel Peter Nasveld, [of soldiers] receiving tafenoquine and mefloquine in these studies was of a very high standard.[137]

2.88 Dr Dow stressed:

> The 'bottom line up front' of the testimony contained herein, is that scientific studies in animals and humans do not suggest that tafenoquine is neurotoxic. Furthermore, the suggestion by advocacy organizations that a causal relationship exists between tafenoquine administration and anecdotal reports of adverse events on social media 15+ years later is not supported by the facts. The U.S. FDA has concluded in regulatory briefing documents that tafenoquine is effective and reasonably safe.[138]

Animal studies

2.89 Professor McCarthy responded to the view put forward by Dr Nevin that tafenoquine had not been tested on monkeys:[139]

> There are good reasons not to do studies on monkeys. I'm sure you're aware of the, obviously, ethical issue about doing studies on monkeys. In the drug-development community, which I'm very closely involved in, we would require two non-human mammal species to be tested. Monkey studies are almost never done these days because of all of the problems that you'd be well aware of. I don't believe it would be appropriate to do a monkey study with tafenoquine when we've got clear evidence from some of the other species, and we've got good guidelines from the USFDA about what studies need to be done for licensing a drug. The USFDA, as you know, recently licensed tafenoquine for both prophylaxis of malaria and clearing the liver of malaria parasites. That was done based upon all the scientific information available to the FDA.[140]

2.90 Professor McCarthy spoke further about the findings in rat studies:

> Going back to some of the rat studies that were done, if you give a rat a really high dose of mefloquine, that rat looks very dizzy and doesn't do well neurologically. You can't replicate that when you give tafenoquine to the rat. To me, that says that we've got good information that the neurotoxicity of tafenoquine is much lower than mefloquine.[141]

Long term study

2.91 Dr Dow from 60 Degrees Pharmaceuticals advised that prior to marketing approval in the US, 60P and its partners 'committed to conducting a long-term study in

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137 Mr Mark Reid, *Submission 71*, p. 11. See also 60 Degrees Pharmaceuticals, *Submission 9.1*, pp. 3-4; Defence, *Supplementary Submission 1.1*, p. 5.

138 *Submission 9*, p. 1.

139 See *Committee Hansard*, 11 October 2018, p. 3.

140 *Committee Hansard*, 11 October 2018, p. 27. See also GSK, *Supplementary submission 8.1*, p. 2.

141 *Committee Hansard*, 11 October 2018, p. 27.

which the safety and tolerability of the drug is being evaluated following 12 months exposure (current safety database is six months)'. Dr Dow provided further information:

> This study will take several years and is being conducted at considerable expense. This study includes, as secondary endpoints, specific and validated neuropsychiatric assessments to monitor those events which were elevated in incidence in the ADF Timor deployment (general psychiatric events, insomnia and motion sickness/dizziness). Since we attribute the higher incidence of such effects to the operational environment, not tafenoquine, we expect a similarly low incidence of psychiatric events to be reported in the placebo and tafenoquine arms of this study. More details of the study can be found at www.clinicaltrials.gov (reference number NCT03320174). Additional studies in pediatric subjects and travelers are being planned with regulatory input from FDA.[142]

Defence view

2.92 Regarding possible side effects Defence advised:

> Tafenoquine has not been shown to have any serious neuropsychiatric side effects, including in the long term. Like primaquine, the main concern regarding tafenoquine relates to people who are deficient in the G6PD enzyme. In those people, tafenoquine can cause red blood cell problems, potentially leading to anaemia.[143]

2.93 Defence added:

> Defence acknowledges that mild and moderate neuropsychiatric side effects have been reported in individuals participating in tafenoquine studies, including in Defence studies. These include vertigo, sleepiness, abnormal dreams, dizziness and insomia.
>
> Defence is not aware of any clear evidence that tafenoquine produces serious neuropsychiatric side effects, including in the long term.[144]

G6PD deficiency

2.94 GSK advised that tafenoquine is contraindicated in the following: G6PD deficiency (see below); pregnancy; breastfeeding an infant who is G6PD-deficient or if the G6PD status of the infant is unknown; and patients with known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any component of the formulation. These contraindications have been fully reviewed by the US FDA and TGA and appropriate labelling describing the warnings and precautions has been agreed.[145]

2.95 Tafenoquine and primaquine share a key safety concern which is the potential to cause hemolysis (destruction of red blood cells) in individuals with a hereditary

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142 *Supplementary Submission 9.2*, p. 1.

143 *Submission 1*, pp. 2-3.

144 *Submission 1*, p. 17.

145 *Supplementary submission 16.1*, p. 2.

disorder, deficiency of Glucose-6-Phosphate-Dehydrogenase (G6PD) enzyme. Individuals must be tested for this deficiency before receiving either of these drugs.[146]

2.96 All ADF members are checked for this deficiency before being administered such medications.[147] The committee discussed with 60 Degrees Pharmaceuticals the test that could be made available in developing countries in the context of a sponsored aid program to undertake the G6PD testing.[148]

Vortex keratopathy

2.97 Some ADF trial participants experienced the benign, reversible eye condition vortex keratopathy (small deposits in the cornea) while taking tafenoquine.[149] This is covered in further detail in Chapter 3.

Metabolisation

2.98 The AQVFA calls for 'CYP450 pharmacogenomic profiling' to be implemented for current ADF members and veterans involved in the trials contending that of those experiencing long term adverse health effects and volunteering the information, 92 per cent were poor or intermediate metabolisers of the CYP2D6 enzyme.[150]

2.99 In relation to the claims that the absence or poor functioning of an enzyme called CYP2D6 has implications for the efficacy and safety of tafenoquine, Defence responded:

> While the CYP2D6 metaboliser status of individuals may be significant in terms of the effectiveness of the medication, it has no known relationship to adverse events. If anything, failure to generate active metabolites would be expected to stop/limit adverse events.[151]

2.100 GSK also responded to these claims:

> The Committee has been advised in other submissions to this Senate Inquiry that tafenoquine requires activation by the CYP 2D6 enzyme to be effective (as is the case for primaquine), and two studies in mice are referenced in support of this. Clinical trials of tafenoquine for radical cure

146 GSK, *Submission 8*, p. 2; Defence, *Submission 1*, p. 15. See also Australasian Society for Infectious Diseases, *Submission 6*, p. 2; Dr Webster, GSK, *Proof Committee Hansard*, 8 November 2018, p. 12; Dr Dow and Mr Herz, *Proof Committee Hansard*, 8 November 2018, p. 22.

147 Defence, 'Response to Fairfax reporting on the use of tafenoquine in the ADF', *Media release*, 2 May 2016.

148 *Proof Committee Hansard*, 8 November 2018, p. 23.

149 Defence, *Submission 1*, pp. 2-3; Defence, *Supplementary submission 1.1*, pp. 10, 14.

150 *Submission 16*, pp. 6, 52-54. See also Mr Stuart McCarthy, *Submission 94*, p. 4. Note: Cytochrome P450 enzymes are essential for the metabolism of many medications. CYP2D6 is one of the CYP450 enzymes.

151 *Submission 1*, p. 21. See also Professor Dennis Shanks, Director, ADF MIDI, *Committee Hansard*, 11 October 2018, p. 57.

> of P. vivax malaria show no difference in efficacy resulting from CYP 2D6 metabolizer status (extensive, intermediate or poor) [St Jean 2016]. The results of the mice studies are likely accounted for by differences in substrate metabolism and tissue expression between the CYP2D orthologues (mouse and human) [Miksys 2005, Scheer 2012]. The Committee has also been advised in Submission 16[152] that CYP alleles have been linked to treatment failure for antimalarials, which is documented in the case of primaquine, however, GSK has found no evidence that this is the case for tafenoquine.[153]

2.101 AVM Tracy Smart AM, Commander Joint Health, Defence, added that the US FDA and TGA did not recommend that CYP2D6 enzyme testing be conducted before administering tafenoquine.[154]

TGA database of adverse events

2.102 The TGA is Australia's regulatory authority for therapeutic goods, including prescription medications. As it is not possible to know all potential adverse events of a medicine before it is approved for use, the TGA monitors adverse events (such as side effects) related to medicines to safeguard the health of the Australian community. Most adverse events reports are made by sponsors such as pharmaceutical companies or medical device suppliers, others by state and territory health department, hospitals, health professionals and consumers.[155]

Mefloquine

2.103 Roche advised that following registration, 'sponsors such as Roche are required[156] to collect and evaluate safety information about the product continuously, in order to report serious adverse reactions and significant safety issues to the TGA, identify any changes to the benefit-risk balance of the product and to take action where necessary'.[157]

2.104 The Department of Health advised that the TGA receives adverse event reports associated with medicines and medical devices which come from a wide variety of sources including members of the public, general practitioners, nurses, other health professionals and the therapeutic goods industry. It maintains a public database of suspected adverse events. The Department of Health indicated at the 11 October

152 AQVFA.

153 *Supplementary Submission 8.1*, p. 2. See also 60 Degrees Pharmaceuticals, *Submission 9.2*, Presentation of Clinical Safety, p. 81.

154 *Committee Hansard*, 11 October 2018, p. 57.

155 See www.tga.gov.au, accessed 13 November 2018.

156 A legal requirement.

157 *Submission 12*, p. 3.

2018 hearing that for the period January 1971 (when the adverse event database started) to 20 June 2018, 242 adverse events were received.[158] It noted:

> The most commonly-reported events are neuropsychiatric (depression 55 reports, dizziness 53, anxiety 51, headache 29, nightmare 28, insomnia 24, agitation 22) and gastrointestinal (nausea 52 reports, abdominal pain 19, diarrhoea 17). This is in keeping with the known adverse effect profile of the drug.
>
> In that…period there were 11 reports of suicidal ideation, and 4 reports of completed suicide, with no other reports of fatalities. The database does not contain any reports describing adverse events arising from the use of mefloquine in a clinical trial. The four cases of suicide reported in the database contained insufficient information to determine cause-and-effect.[159]

2.105 In relation to the TGA database of suspected adverse events, the Department of Health emphasised:

> It is important to emphasise that the search results cannot be used to determine the incidence of an adverse event (that is, how often the adverse event has occurred in patients taking a particular medicine), or the likelihood of a patient experiencing that reaction, as they do not include information on the total number of patients who have taken the medication or the total number of adverse events occurring (because reporting of adverse events is not mandatory, other than for industry sponsors). As a result the search results cannot be used to make accurate numerical comparisons between adverse events associated with different medicines.[160]

2.106 Adjunct Professor Skerritt emphasised that the adverse reports received up until the last few years were largely related to the short term impacts of the drug or the 'immediate psychological and psychiatric adverse events'. This resulted in the warnings being updated.[161]

2.107 Roche confirmed to the committee that there are robust mechanisms in place to capture and act on adverse event reports and that the risk benefit profile of mefloquine remains positive:

> We are very, very confident that the mechanisms in place to capture, record and analyse adverse events associated with all our medicines, including mefloquine, are very robust. It's not only what we as a company do.

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158 Adjunct Professor Skerritt, *Proof Committee Hansard*, 11 October 2018, p. 36. Note: the submission from the Department of Health refers to the database containing 242 adverse reports for mefloquine submitted from 1993 to 2018. See *Submission 3*, p. 4. The committee understands the reference to 1993 in the submission is incorrect.

159 *Submission 3*, p. 4.

160 *Submission 3*, p. 4. See also Adjunct Professor Skerritt and Adjunct Professor Greenaway, *Committee Hansard*, 11 October 2018, p. 39.

161 *Committee Hansard*, 11 October 2018, pp. 41, 44.

> Just to illustrate this to you, in my medical department in Australia alone, there is a department of drug safety of 20 professional people, whose role it is to monitor, review, follow up and discuss with people who have reported adverse events, to ensure that we understand things fully. This happens in every single country around the world.
>
> Globally, Roche has a drug safety department that specifically looks at this daily for all of our medicines. We very closely monitor the safety profile of all of our medicines. Our safety department produces documents called PBRERs, or periodic benefit-risk evaluation reports. They run to hundreds of pages. The most recent one was completed on 17 April 2018, and it essentially concluded that there was no new information: 'The risk-benefit profile of mefloquine remains positive and favours its use in the approved indications and adheres to the prescribing information.'[162]

Tafenoquine

2.108 Chapter 3 details the adverse events reported during the tafenoquine trials involving ADF members. Following the trials, Defence noted:

> An administrative error by TGA allowed entry of adverse events to the database subsequent to the study period. This was unusual as this would normally only be possible for a registered medication on the market in Australia. The remaining 26 of the 32 total entries relating to the use of tafenoquine have been entered into the database since 2016, some 15 years after the study. 18 of these were entered in a ten day period following a social media campaign in early in 2017. The entries related to tafenoquine have since been removed from the online [Database of Adverse Event Notifications] DAEN by the TGA.[163]

2.109 Defence emphasised:

> There is no way to establish definitive links between the symptoms recorded in the anonymous entries made to the DAEN since 2016 and tafenoquine use. Indeed, there could be many other causes for these symptoms. As such this is does not constitute clear evidence of long term tafenoquine-related effects.[164]

2.110 60P advised that these more recent reports were examined and 'in all instances but one, contemporaneous accounts of adverse events could not be verified as actually having occurred'. 60P noted that 'GSK reached broadly the same conclusion as did the FDA in an independent audit of ADF records'.[165] Biocelect provided further detail:

> For events alleged to have occurred during or after 2017, it is not scientifically plausible based on the available evidence that Tafenoquine could have been a causative factor. It is implausible for Tafenoquine to cause long term psychiatric events if (i) there is no drug in the patient's

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162 Dr Stewart, *Proof Committee Hansard*, 8 November 2018, p. 7.

163 *Submission 1*, pp. 17-18. See also Annex C.

164 *Submission 1*, p. 18. See also Defence, *Supplementary submission 1.1*, p. 23.

165 *Submission 9*, pp. 3-4.

> system when the events occur and (ii) it does not cause meaningful increases in the risk of psychiatric adverse events compared to placebo over the shorter term following administration of drug when drug levels are at their highest. In other words you would need an initial psychiatric event to plausibly claim a later psychiatric event was related. Therefore, with the greatest respect to the veterans affected, their adverse experiences cannot, in 60P's view, be reasonably attributed to Tafenoquine. Biocelect supports the position of 60P in this matter.[166]

2.111 GSK reported that it has followed up with those who have recently reported adverse events. The recent reports 'prompted a thorough evaluation by GSK of all available clinical data and literature. To date it has not been possible to make a connection between the mild to moderate side effects reported during the ADF study and any permanent, serious long-term effects with onset after completion of the study'.[167]

2.112 Biocelect emphasised that it takes seriously its 'commitment to the TGA to collect further safety information and provide it to the regulators in a timely manner for their analysis'.[168]

Labelling

2.113 Adjunct Professor Skerritt told the committee that with new drugs such as tafenoquine, a black triangle is placed on the patient leaflet which is to make sure health professionals and consumers are encouraged to report adverse events.[169]

Related medical inquiries

2.114 The AQVFA is calling for a single Statement of Principles (SOP) covering the condition they term 'quinoline poisoning' to inform decisions made regarding support available for veterans.[170] The AQVFA points out that without a single SOP for 'quinoline poisoning' veterans have to lodge multiple claims which is an administrative challenge to those who are unwell.[171] Administrative barriers are addressed in more detail in Chapter 4.

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166 *Submission 11*, p. 3. See also 60 Degrees Pharmaceuticals, *Submission 9*, p. 3. Note: the 60P submission reference to 2007 refers to the adverse events made to the TGA in 2017 or later which were reported to have occurred many years after the drugs were taken with the earliest such onset being 2007 (see case 2 in Appendix A to Briefing Document for the Antimicrobial Drugs Advisory Committee, p. 139, available in *Submission 9*, Attachment 1)

167 Mr Herd, *Proof Committee Hansard*, 8 November 2018, pp. 10, 13.

168 Mr Herz, *Proof Committee Hansard* 8 November 2018, p. 17.

169 *Committee Hansard*, 11 October 2018, pp. 41, 42; Dr Carolyn Tucek-Szabo, Head, Regulatory Affairs, Australasia, GSK Australia, *Proof Committee Hansard*, 8 November 2018, p. 15. See also: https://www.tga.gov.au/black-triangle-scheme, accessed 29 October 2018.

170 *Submission 16*, pp. 40-42.

171 *Submission 16*, pp. 41- 42. Associate Professor Quinn, *Proof Committee Hansard*, 5 November 2018, p. 42.

2.115 Serving and ex-serving ADF members can claim compensation at any time for conditions they believe are related to their service. For DVA to accept liability for compensation there has to be a causal link determined between the person's service and their medical conditions. Under the *Veterans' Entitlements Act 1986* (VEA) and the *Military Rehabilitation and Compensation Act 2004* (MRCA) the potential link between a medical condition and service is assessed using SOPs.[172]

2.116 The main function of the Repatriation Medical Authority (RMA) is to determine SOPs for the purposes of the VEA and the MCRA. SOPs determined by the RMA are legislative instruments and apply to decisions about liability for injuries, diseases and deaths made under both the VEA and the MCRA.[173]

2.117 The RMA clarified that SOPs are made for diseases or injuries, not for exposures:

> If an exposure can be causally related to a disease or injury then it can become a factor within a statement of principles, but we do not make statements of principles relating to exposures to drugs, toxins or those sorts of things.[174]

2.118 The RMA stressed that the VEA is 'beneficial legislation' 'and is intended to be generous'.[175] This point was further emphasised by Professor Nick Saunders, Chairperson, RMA, who stated 'we take a very generous view of the evidence when we write the statements of principles'.[176]

RMA

2.119 The claim that taking mefloquine or tafenoquine causes chemically-acquired brain injury has been raised with the RMA.

2.120 The RMA received a request dated 6 February 2017 from the President of the Repatriation Commission and Chair of the Military Rehabilitation and Compensation Commission seeking an investigation of chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine in order to find out whether SOPs may be determined concerning the claimed condition. This was agreed by the Authority on

172 DVA Information Paper: Mefloquine, p. 3. Note: SOPs are legal instruments, based on sound medical-scientific evidence (SMSE) which state the factors that must exist for a particular disease, injury or death to the linked causally to prior service. See RMA, *Submission 4*, Attachment 1, p. 4.

173 See http://www.rma.gov.au/sops/, accessed 27 June 2018. Note: the RMA determines SOPs at two standards of proof: reasonable hypothesis, where the SMSE has to indicate or point to a reasonable hypothesis of a causal association between the factor and the disease; and balance of probability, where the SMSE has to show that it is more probable than not that the factor is causally related to the disease. RMA, *Submission 4*, Attachment 1, p. 5.

174 Professor Saunders, Chairperson, RMA, *Committee Hansard*, 15 October 2018, p. 1.

175 RMA, *Submission 4*, Attachment 1, p. 4.

176 *Committee Hansard*, 15 October 2018, p. 8.

7 February 2017 and an investigation notice placed in the Commonwealth of Australia Gazette on 14 February 2017.[177]

2.121 On 18 August 2017, the RMA declared that it 'does not propose to make a Statement of Principles concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine for the purposes of subsection 196B(2) or (3) of the [Veterans' Entitlements Act 1986]'.[178] It noted:

> The Authority is of the view that there is insufficient sound medical-scientific evidence that exposure to mefloquine, tafenoquine or primaquine causes chronic brain injury. Further, there is insufficient sound medical-scientific evidence that there is a characteristic and persisting pattern of signs and symptoms following exposure to mefloquine, tafenoquine or primaquine that could be determined to be a particular kind of disease of, or injury to, the brain.[179]

2.122 The RMA provided further detail for this finding in its submission:

> The hypothesis that mefloquine causes permanent brain damage is based on proposed causal mechanisms and pathology identified in high dose animal studies mostly conducted shortly after World War II. There is no direct evidence that it causes permanent brain damage in humans given therapeutic doses.
>
> The claim that there are persistent symptoms that are due to mefloquine is based on a small number of case reports and adverse event reports of a variety of commonly experienced symptoms in a widely prescribed medication. These same animal studies and human case reports are cited repeatedly as the basis for the contention of a syndrome resulting from permanent brain injury.
>
> Animal studies and case reports are considered "hypothesis generating", since the associations they suggest need to be evaluated in well-conducted comparative studies in humans. Human studies of this type are considered higher quality evidence. Because of the lack of supporting evidence from such studies, the RMA found that the evidence was not persuasive when critical appraisal of the total body of SMSE [sound medical-scientific evidence] was taken into account.[180]

177 Australian Government, Repatriation Medical Authority, Statement of Reasons Re: Decision not to make Statements of Principles for chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine, p. 3.

178 Australian Government, Repatriation Medical Authority, Declaration under subsection 196B(6) of the *Veterans' Entitlements Act 1986*, 18 August 2017.

179 Australian Government, Repatriation Medical Authority, Statement of Reasons Re: Decision not to make Statements of Principles for chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine, p. 3. See also Defence, *Supplementary submission 1.1*, pp. 24-25.

180 *Submission 4*, p. 8. See also Professor Nick Saunders, *Committee Hansard*, 15 October 2018, p. 2.

2.123 Professor Saunders told the committee that for a chronic brain injury to be caused by a particular agent, damage to the brain needs to be demonstrated. While this can be done through imaging of the brain and other tests in relation to sniffing solvents or lead poisoning for example:

> There is no evidence of that in terms of the quinoline class of drugs—there is no evidence of that in relationship to mefloquine or tafenoquine. Nobody has been able to demonstrate in humans that there are imaging abnormalities or other evidence of structural abnormality of the brain. The only evidence that we have for structural changes relates to animal experiments. Also, I think there was one case where a massive overdose of a drug was taken, which killed the person, and autopsy evidence showed that there was damage of the brain. I think the person took twenty-fold times the prescribed dose. So, we have no evidence that is sufficient to allow us to define a particular condition, be that in terms of the constellation of symptoms and signs that might be present, or indeed other evidence of structural abnormality.[181]

2.124 The RMA emphasised the lack of evidence of harm despite widespread and long term use of mefloquine and the inclusion of mefloquine by the WHO in its Model List of Essential Medicines.[182]

2.125 Professor Saunders summarised that with the millions of doses of mefloquine worldwide:

> One would have thought that even a rare adverse effect causing chronic brain injury would have become evident given the scope of the usage of this particular agent. There has been no defined syndrome or clinical entity that one could recognise as chronic brain injury from the civilian use of this drug.[183]

2.126 Mr Paul Murdoch, Registrar, RMA advised that when individuals attempt to link conditions to eligible service, it needs to be on the basis of a diagnosed disease or injury, not symptom by symptom. Therefore getting a clear diagnosis is key as a diagnosed injury or disease 'can then be matched very quickly to a statement of principle, [which] is the key from a compensation point of view'.[184] Professor Saunders further explained that:

> Although a range of symptoms have been reported following the use of these drugs, the timing of these symptoms, their duration and severity, and the set of individual symptoms which could define a condition have not really been established.[185]

2.127 Professor Saunders continued his explanation:

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181 *Committee Hansard*, 15 October 2018, p. 2.

182 *Submission 4*, p. 9.

183 *Committee Hansard*, 15 October 2018, p. 3.

184 *Committee Hansard*, 15 October 2018, p. 5.

185 *Committee Hansard*, 15 October 2018, p. 2.

> In 1994 the government of the day introduced this current system, which, really, I think, has served the veteran community very well, because the government felt that one would have greater transparency and greater equity if decisions were based on sound scientific medical evidence. So passionate opinion does not trump objective evidence in the system we have at the moment. The fact that somebody has been given a drug and now they are claiming to have a chronic brain injury from that drug is not sufficient in the system we have today. Indeed, it would undermine the system if one were to carve out exemptions to the system as a whole.[186]

SMRC review

2.128 The AQVFA noted that a review of the RMA's decision was underway at the time of lodging their submission.[187] In November 2017 the Specialist Medical Review Council[188] gave notice that it had been asked under section 196Y of the VEA to review the decision of the RMA which should be finalised before the end of 2018.[189] The RMA indicated that the review was requested by the AQVFA.[190]

2.129 On 17 September 2018 the SMRC announced that it had completed its review and affirmed the RMA's decision not to make a SOP for 'chemically acquired brain injury'.[191]

2.130 Professor Saunders spoke about the composition of the RMA and the SMRC:

> The council's composition is different from ours in terms of the people who do the assessment. In our case the RMA is made up of five medical academics, or epidemiological academics, who have their own specialties but, as well as that, have a broad general experience. When this decision was reviewed by the Specialist Medical Review Council, their committee was an expert committee; it contained people who understood epidemiology but also were drawn from pharmacology, neurology, mental health and neuropsychology. These were expert people. They considered the same evidence that we considered, and drew the same conclusions that we drew.[192]

2.131 Professor Saunders answered assertions[193] about the evidence being relied upon:

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186 *Committee Hansard*, 15 October 2018, p. 5.

187 *Submission 16*, p. 42.

188 An independent statutory body, established by the VEA, responsible to the Minister for Veterans' Affairs.

189 DVA, *Submission 2*, p. 8.

190 Mr Paul Murdoch, Registrar, RMA, *Committee Hansard*, 15 October 2018, p. 3.

191 Commonwealth of Australia Gazette, Specialist Medical Review Council Declarations, Request for Review Declaration no. 34, 17 September 2018. See also Professor Nick Saunders, *Committee Hansard*, 15 October 2018, p. 2.

192 *Committee Hansard*, 15 October 2018, p. 3.

193 See Dr Remington Nevin, *Committee Hansard*, 11 October 2018, pp. 7-9.

> …the evidence that we place highest reliance on—sound, epidemiological evidence—is not being driven by the pharmaceutical industry or the malarial specialists. These are people who are interested in population based studies and who look at the evidence in an impartial way.[194]

Inclusion of mefloquine and tafenoquine in SOPs

2.132 The RMA has included mefloquine and tafenoquine, either by name or in more general terms, as a potential causal factor in the SOPs for a total of 16 conditions – 15 for mefloquine and six for tafenoquine where there was a least a reasonable hypothesis that the relevant condition can occur.[195] The RMA notes that 'the wording of the mefloquine- or tefenoquine-related factors in these SOPs requires a close temporal link between the taking of the drug and the onset of the condition…reflecting the well-accepted evidence that these agents can have acute neuropsychiatric effects'.[196]

2.133 The RMA told the committee that they 'are confident that we have included mefloquine or tafenoquine in statements of principle for all diseases or injuries which could be linked to taking these drugs based upon sound medical scientific evidence that meets standard epidemiological criteria when examining things for causation'.[197]

2.134 Acknowledging the chronic and complex symptoms being presented to the committee, Professor Saunders mentioned the SOP concerning 'chronic multisymptom illness'[198] determined in 2014:

> We have a statement of principle on an illness called chronic multisymptom illness. This arose out of an inquiry that we conducted in relation to Gulf War syndrome. Although this did not satisfy the Gulf War advocate group that was presenting to us, it became quite clear to us that there were a significant number of veterans who had quite debilitating symptoms that fitted into particular patterns of illness, but this wasn't related just to serving in the Gulf War. In fact, it was related more broadly to deployment into hazardous environments. So we wrote a statement of principle called 'Chronic multisymptom illness'. That statement of principle is available today for those people who were deployed to, say, East Timor, took antimalarial drugs and now have debilitating symptoms that are broad-ranging.[199]

2.135 Professor Saunders again emphasised that the RMA takes a very generous view of evidence when they write the SOPs.[200] Therefore in his view the key for many

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194 *Committee Hansard*, 15 October 2018, p. 7.

195 DVA *Submission 2*, p. 7. See also RMA, *Submission 4*, Attachment 2.

196 RMA, *Submission 4*, p. 6.

197 *Committee Hansard*, 15 October 2018, pp. 1-2.

198 See Statement of Principles concerning chronic multisymptom illness No. 55 of 2014.

199 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 5.

200 *Committee Hansard*, 15 October 2018, p. 8.

veterans is getting assistance from an advocate for example to establish a causal link between their service and their health today.[201]

Review processes and ongoing monitoring

2.136 The RMA specifically searches for 'new evidence in relation to factors that have a particular association with the veteran community'.[202] The RMA regularly reviews the evidence through a comprehensive evidence-gathering process, using standard scientific methods and recognised epidemiological criteria.[203] It reviews 'the entire literature that is available on the large public databases in the English language'.[204] Each SOP is reviewed at least every ten years, with an aim of reviewing them more frequently.[205] RMA experts can identify new evidence from their fields, and SOP reviews can be initiated through the authority's own motion.[206] Individuals outside the RMA can also request reviews, as was the case for the recent reviews completed by the RMA and Specialist Medication Review Council.[207] The committee also understands that consultation between the RMA and a range of stakeholder organisations including Joint Health Command (JHC) in Defence, DVA, and the RSL occurs regularly on a range of topics relating to the health of veterans.[208]

2.137 The JHC seeks to ensure the health preparedness of ADF members by developing evidence-based health policy. Among other things, it is responsible for 'participating in research to inform and improve health policy, programs and services', 'developing strategic health policy and programs' and 'reviewing and assuring health policy, programs and services to drive continuous improvement'.[209] ADF clinical and medical policy is developed with clinical medical input.[210] Defence also undertakes and supports a range of research activities, including through the Mental Health Research and Evaluation section.[211]

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201 *Committee Hansard*, 15 October 2018, p. 5.

202 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 1.

203 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 1.

204 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 3.

205 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 4.

206 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 4; Mr Murdoch, *Committee Hansard*, 15 October 2018, p. 4.

207 Mr Murdoch, *Committee Hansard*, 15 October 2018, p. 3.

208 See http://www.rma.gov.au/consultation/, (accessed 30 November 2018).

209 Australian Government, Joint Health Command, *Annual Review 2016–17*, 2017, p. 4.

210 Australian Government, Defence, 'Directorate of Military Medicine', http://www.defence.gov.au/Health/SHC/militaryMedicine.asp, (accessed 29 November 2018).

211 Australian Government, Defence, 'Mental Health Research and Evaluation (MHR&E)', http://www.defence.gov.au/Health/DMH/ResearchSurveillancePlan.asp, (accessed 29 November 2018).

Searching for an explanation

2.138 As the concerns expressed by individuals appear to be manifested in military and not civilian populations, the committee discussed possible explanations for this with witnesses. Mr Mark Reid indicated that in his view:

> I contend that these soldiers raising concerns about chemically acquired brain injury resulting from use of tafenoquine have PTSD. The PTSD has arisen more than 16 years after taking tafenoquine and mefloquine, but the PTSD is not related to these anti-malarial drugs.[212]

2.139 Professor Graham Brown, Australian College of Tropical Medicine posited:

> I was explaining this to a layperson. For example, let's say, you were trying a new flu vaccine in New South Wales two months ago. You did a three-month review, and people had nightmares and couldn't sleep and were anxious and depressed. You'd say, 'That's the flu vaccine.' Perhaps it was, but the fact that they were firefighters fighting bushfires with people dying could surely have contributed to the symptoms. We couldn't say, 'It's not the flu vaccine,' but most of us would think it's highly unlikely. That's the sort of example. It's a coincidence of things and trying to work out the underlying cause. So, I would say that that's the importance of controlled trial evidence that we look at. Many of the symptoms reported are found in other conditions. I'm also aware of certain unproved hypotheses about what might cause these problems, and I think it's important to start with the evidence based information and separate this away from ideas or options or hypotheses, which are terribly important in science but they need to be proved and not confused with opinion.[213]

2.140 Professor Shanks pointed out the many potential contributors to a veteran's current health:

> Trying to assign any single cause to various post-military, veteran's illnesses does not accurately reflect the many potential contributors to a soldier's mental and physical health.[214]

2.141 When asked his view on the issues raised with the committee, Professor Shanks responded:

> It's multifactorial…Mental illness is a broad category and a very frequent one, but trying to blame a drug 20 years after the fact, when it's long, long been cleared, isn't plausible. That isn't how drugs work.[215]

2.142 Associate Professor Karunajeewa also emphasised the difficulty of attributing causality to taking a drug nearly 20 years ago:

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212 *Submission 71*, p. 5.

213 *Committee Hansard*, 30 August 2018, p. 44.

214 Professor Shanks, *Submission 13*, p. 2.

215 *Committee Hansard*, 11 October 2018, p. 58.

> I suppose the first thing to say is that we want to avoid at all costs being at all dismissive or belittling about their experiences and their symptoms, and they should be regarded as real. Essentially the difficulty comes down to the fact that a lot of the symptoms and a lot of the illnesses being described, unfortunately, as you know, are highly prevalent in the general Australian community. For example, I think the statistics are that two or three million Australians are out there suffering from depression, and a similar number have anxiety. The most common cause of death now in young people under the age of 44 is suicide. So this mental health crisis that we have in the country is obviously highly prevalent. There are an awful lot of other people out there who haven't taken mefloquine, of course, who are dealing with very, very similar problems. So the difficulty comes in ascribing causality when you have conditions and symptoms that are very, very common throughout the general community. So actually ascribing causality to something that happened 20 years ago becomes very difficult.[216]

2.143 Vice Admiral David Johnston AO, VCDF, acknowledged the challenges of dealing with PTSD:

> There are many other possible causes of the symptoms that these people are suffering. Indeed, many admit that they have been diagnosed with PTSD but are frustrated that the treatment does not seem to be working. The challenge for some people with PTSD to recover is a known problem, but it doesn't mean that the diagnosis is wrong. Even if it were possible to connect the use of mefloquine with these symptoms, it's unlikely to alter the individual's treatment or management.[217]

2.144 AVM Tracy Smart put forward that:

> It's very hard to distinguish or diagnose what could be the problem of someone who develops a health problem many years after an event. We've heard today that there is some evidence—and certainly there have been some reports—that people can get long-term effects from mefloquine. There are no reports that someone can take the drug, get some symptoms, stop the drug, have the symptoms stop and then get symptoms a long way down the track. There is no evidence to suggest that. That's not been recorded in the literature. You've also got to look at someone who is this many years down the track; what other events have occurred in their life, including on deployment, in terms of both traumatic events and the stressors in deployment, because there are many: away from home, poor living conditions—all of these things can contribute to having health problems.
>
> I think this is one of the main problems we have got here: what is the cause of this problem? The overwhelming evidence suggests that, in the majority of cases, it is not the antimalarials. As some of the presenters today have

216 *Committee Hansard*, 11 October 2018, p. 30.

217 *Committee Hansard*, 11 October 2018, p. 46. See also Defence, *Supplementary submission 1.1*, p. 27.

> said, it's rare or very rare at best to see long-term symptoms of mefloquine.[218]

2.145 AVM Smart continued:

> Being exposed over a military career over a life to a number of stressors can cause neuropsychiatric problems, can cause psychiatric problems or can cause brain injury. Things like traumatic brain injury, which you've heard about—a number of things can cause acquired brain injury down the track. The important thing is that I can't tell you sitting here that someone has or hasn't got a particular diagnosis. That is something that a doctor needs to do one-on-one with the individual, looking at their symptoms. When did they come on and when did they finish? That's what a diagnosis is all about. I would say, though, that some of the people who've written to us through our malaria email address have really told us they are suffering from severe problems similar to the ones in the submission[s]. When we look back at their documents, some of those have continued to deploy many time[s] after Timor, including to the Middle East. To then say this condition was caused by this drug we took at that time is very problematic.[219]

Influence of social media

2.146 Many witnesses referenced social media as the catalyst for bringing them together. An individual listing 32 symptoms[220] reported the following:

> I read an article published by Stuart McCarthy in December 2015. After reading this article I realised that everything I had experienced, physically and mentally, were very real. For the first time in 11 years there was a diagnoses to 'fit' my medical situation.[221]

2.147 Many others also referred to Mr Stuart McCarthy and his facebook page as did a number of confidential submissions. A few of those that are public are listed below:

> I came across a Facebook group started by fellow veterans, namely Stuart McCarthy, who was also suffering. This was a God send for me. I was not alone and was not the only one with these symptoms.[222]

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218 *Committee Hansard*, 11 October 2018, p. 54.

219 *Committee Hansard*, 11 October 2018, pp. 54-55. See also Defence, *Supplementary submission 1.1*, pp. 23-24.

220 Loss of sight/visual disturbances; Encephalitis; Swelling of the brain; Demyelination; Chronic diarrhoea, Irritable Bowel Syndrome (IBS); Body Rashes; Migraines; Photosensitivity; Chronic infections caused by Low Immunity; Allergies; Suicidal; PTSD; Chronic fatigue; Major Depression/Withdrawal; Fibromyalgia; Chemical sensitivities; Low immunity; Weight gain (BMI over 30); Memory loss; Chronic reflux; Aggressive Explosive Anger; Impatient; Overwhelmed; Psoriasis; Hearing loss (not noise related); Auto-immune (blood); Herpes simplex (Compromised Immunity); Vertigo; Daily Nausea; Light headedness; Tinnitus. Name withheld, *Submission 67*, pp. 2-3.

221 Name withheld, *Submission 67*, p. 3.

222 Mr Colin Brock, *Submission 69*, p. 2.

> …in February, 2018 I became aware of Retired Major Stuart McCarthy, who has been of great comfort and assistance to my family.[223]
>
> Well several years ago information started to appear from fellow Vets, especially on Facebook. We started talking and finally telling each other what had happened, how we felt etc.[224]
>
> For almost twenty years I felt isolated and alone with my 'creeping madness' until I stumbled across a Facebook group for soldiers who had suffered from Mefloquine poisoning. There in front of me were men and women detailing strikingly similar symptoms that I had experienced.[225]

2.148 Mr David Madsen also listed a number of diagnoses[226] and referred to the facebook page of Mr Stuart McCarthy:

> I [knew] nothing about [mefloquine] toxicity or any potential side effects prior to and after all of this until [I] saw Major McCarthy's Face book page after being invited by an old army Friend.
>
> Over time I have started to see the GLARING similarities between where I am at and what many studies are showing now.[227]

Conclusion

2.149 The committee was very concerned to hear the stories from individual veterans and their families outlining their health and other challenges. Though there may be disagreement between them and the medical professionals on the cause or causes of their health conditions there was no disagreement that their physical and mental symptoms are real and that they require assistance. This is the focus of Chapter 4.

223 Mr Syd Carter, *Submission 108*, p. 3.

224 Name withheld, *Submission 75*, p. 3.

225 Name withheld, *Submission 61*, p. 6.

226 Mr David Madsen, *Submission 91*, p. 1.

227 Mr David Madsen, *Submission 91*, p. 2.

Chapter 3

Antimalarial drug trials involving the ADF

3.1 This chapter considers the extent to which ADF members can provide informed consent to participate in research, and presents information on ADF antimalarial policy. It summarises the consent process undertaken for the antimalarial drug trials during the late 1990s and early 2000s, as well as outlining perspectives on the screening processes, responses to adverse events and participant follow up.

Consenting to participate in research

3.2 The ethics of human research in military populations is addressed in the National Health and Medical Research Council (NHMRC) *National Statement on Ethical Conduct in Human Research* (National Statement).[1] This outlines the general requirements for seeking individuals' consent to participate in research:

> …consent should be a voluntary choice, and should be based on sufficient information and adequate understanding of both the proposed research and the implications of participation in it.[2]

3.3 Pre-existing relationships between prospective research participants and those involved in facilitating or implementing the research 'may compromise the voluntary character of participants' decisions, as they typically involve unequal status, where one party has or has had a position of influence or authority over the other'.[3] The relationship between a soldier occupying a subordinate position and their senior officer is an example of an unequal relationship.[4]

3.4 The National Statement suggests that an unequal relationship 'always constitutes a reason to pay particular attention to the process through which consent is negotiated'.[5] However, it is not automatically sufficient to prevent research being undertaken, rather, 'you have to think about extra ethical considerations when approving and conducting that research'.[6]

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1 NHMRC, Australian Research Council (ARC) and Universities Australia, *National Statement*, 2007 (updated 2018), Chapter 4.3: People in dependent or unequal relationships, p. 68.

2 *National Statement*, p. 16.

3 *National Statement*, p. 68.

4 Inspector-General of the ADF (IGADF), *Inquiry report into issues concerning anti-malarial trials of the drug mefloquine between 2000 and 2002 involving Australian Defence members deploying to East Timor*, 2016, p. 23; Australian Government Therapeutic Goods Administration, *Note for Guidance on Good Clinical Practice*, 2000, p. 13.

5 *National Statement*, p. 68.

6 Ms Jillian Barr, Ethics and Integrity, Research Quality and Priorities Branch, NHMRC, *Committee Hansard*, 11 October 2018, p. 13.

Views on whether the ADF should participate in medical research

3.5 The committee heard different perspectives on whether ADF members can truly consent to participate in research.

Opposition to ADF participation

3.6 The participation of ADF members in research was viewed by some submitters, such as Mr Greg Jose, as 'cruel and unethical'.[7] Some veterans suggested that drug trials on ADF members should be prohibited.[8] This was echoed by others including the Royal Australian Regiment (RAR) Association and the wife of a veteran.[9] Colonel Ray Martin (Rtd) opposed mass drug trials as members cannot:

> …give truly informed and voluntary consent and…drug trials with untested or potentially harmful drugs will likely detract from operational effectiveness of the ADF, and or produce ineffective results.[10]

3.7 Mr Benjamin Fleming proposed 'legislation be put to parliament that prevents the testing of drugs on deployed personnel, who, by the mere fact of the environment they are working in, have enough to deal with'.[11] The submission by Associate Professor Quinn on behalf of the Australian Quinoline Veterans and Families Association (AQVFA) further recommended that 'veterans are precluded by law from being engaged as subjects in clinical trials'.[12]

Support for ADF participation

3.8 Other submitters argued that ADF members should not be prohibited from participating in research, because it is vital for advancing medical science and force protection measures, and because members should have the right to choose and to access higher levels of care through trials. Vice Admiral David Johnston AO, Vice Chief of the Defence Force, explained Defence needs to retain:

> ...the ability to conduct clinical studies for improved and emerging medications to be evaluated to ensure they are effective and safe in military populations. It's an accepted scientific fact that studies of therapeutic agents need to be conducted in the population in which they will be used.[13]

3.9 The committee heard from doctors and scientists who agreed, such as Associate Professor Harin Karunajeewa, who stated that the ADF:

> …has both a duty of care to protect and maintain the health of its personnel, and a strategic imperative to maintain the fitness and battle-readiness of its

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7 Mr Greg Jose, *Committee Hansard*, 31 August 2018, p. 2.

8 See Mr Stuart McCarthy, *Submission 94*, p. 11; Name withheld, *Submission 59*, [p. 5].

9 *Submission 96*, [p. 1]; Mrs Susan Armstrong, *Committee Hansard*, 30 August 2018, p. 15.

10 *Submission 92*, [p. 4].

11 *Committee Hansard*, 30 August 2018, p. 32.

12 *Submission 16*, p. 6.

13 *Committee Hansard*, 11 October 2018, p. 45.

> troops. It is therefore perfectly logical and ethically appropriate that the ADF should endeavour to understand what the most effective and safest ways are to protect its troops from the high risks of a potentially debilitating and lethal disease…the best way to find out what works best is to actually perform a test in the population for which the treatment is intended. Clinical trials in the military have done a great deal to improve the health, safety and effectiveness of soldiers throughout modern history. It is in the best interest of all soldiers that they continue.[14]

3.10 Based on evidence from hospitals in the United Kingdom and his own experience conducting trials, Associate Professor Karunajeewa noted that 'clinical trial participants are likely to receive better medical care and have better outcomes to patients receiving routine care'.[15] Mr Mark Reid, coordinator of one of the trials involving the ADF, reiterated this point and noted this trial involved the:

> …only infantry battalion that has ever deployed into a malarious area with no clinical cases [of malaria] in the field. And it wasn't just the drugs that achieved that; it was the actual awareness of having people there with a specific mandate of force protection under a controlled clinical trial.[16]

3.11 Defence rejected 'claims that informed consent is not possible in military populations and the assertion that clinical studies should not be conducted on these personnel'.[17] It underscored its support for individuals' rights to decide whether to participate or not in research, and cautioned any constraints on research:

> …must be balanced against the considerable direct benefits that have been obtained by participants in clinical studies of novel drugs to treat a variety of medical conditions. While some research may not infer direct benefit to the individual, everyone has the right to choose whether or not to participate for their own future benefit, or the benefit of others.[18]

Considerations for future research involving ADF members

3.12 The National Statement identifies that people in unequal relationships 'are vulnerable to being over-researched because of the relative ease of access to them as research populations'.[19] Therefore, it suggested that researchers 'should take account of this vulnerability in deciding whether to seek out members of these populations as

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14 For other examples see: Professor James McCarthy, Professor of Tropical Medicine and Infectious Diseases, Royal Brisbane Hospital and QIMR Berghofer Medical Research Institute, *Submission 15*, [p. 12]; Professor Geoffrey Quail, President of the Australian College of Tropical Medicine; *Committee Hansard*, 30 August 2018, p. 44.

15 *Submission 15*, [pp. 12–13].

16 *Committee Hansard*, 30 August 2018, p. 21. This trial compared tafenoquine and mefloquine use in 1 RAR in Timor-Leste in 2000 to 2001.

17 *Submission 1*, p. 27.

18 *Supplementary submission 1.1*, pp. 15–16.

19 NHMRC, ARC and Universities Australia, *National Statement*, p. 68.

research participants'.[20] Similarly, a report by the Inspector-General of the Australian Defence Force (IGADF) into issues concerning some of the trials recommended:

> The ready acceptance by soldiers of advice or encouragement provided to them by military persons in authority, combined with a potential belief that participation in the trial was expected is an issue worthy of further consideration in the conduct of any future medical trials, particularly in the context of a pre-deployment for an overseas operation.[21]

3.13 Defence noted that each time the Departments of Defence and Veterans' Affairs Human Research Ethics Committee (DDVA HREC) examines a research proposal it considers the issue of informed consent in military populations.[22] DDVA HREC is 'acutely aware' that military personnel may be vulnerable due to their unequal relationships 'and is very stringent in its review of research proposals to ensure that there is no coercion, real or perceived, in the recruitment of participants from the ADF'.[23] Membership of the current DDVA HREC includes a contemporary veteran, Defence health graduate, a lawyer, lay people, a pastoral care member, a civilian clinical care provider and others with experience in the types of research being considered by the DDVA HREC.[24] The DDVA HREC terms of reference establish that 'at least one third of the members are to be external to Defence and DVA'.[25]

3.14 The National Statement further suggests that researchers should:

> …invite potential participants to discuss their participation with someone who is able to support them in making their decision. Where potential participants are especially vulnerable or powerless, consideration should be given to the appointment of a participant advocate.[26]

3.15 The committee did not hear evidence on examples of where participant advocates have been appointed elsewhere.[27]

3.16 AVM Tracy Smart AM recently wrote to DDVA HREC to request that it 'consider additional measures to ensure participants in clinical studies, and particularly

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20 *National Statement*, p. 68.

21 IGADF, *Inquiry report*, 2016, p. vi.

22 Defence, *Submission 1*, p. 33. When the research is deemed to be of low- or negligible-risk, reviews are undertaken by the Joint Health Command Low Risk Ethics Panel, People Research Low Risk Ethics Panel or Defence Science and Technology Low Risk Ethics Panel. Defence and Department of Veterans' Affairs, *The Departments of Defence and Veterans' Affairs Human Research Ethics Committee Terms of Reference*, p. 2, http://www.defence.gov.au/health/hrec/ (accessed 11 October 2018).

23 Defence, *Supplementary submission 1.1*, p. 15.

24 Defence, *Supplementary submission 1.1*, p. 15.

25 *DDVA HREC Terms of Reference*, pp. 2–4,

26 NHMRC, ARC and Universities Australia, *National Statement*, p. 68.

27 Ms Barr, *Committee Hansard*, 11 October 2018, pp. 13–14.

Phase 3 clinical trials, are fully informed of all aspects of the studies and that there is no belief created that Command is endorsing or actively encouraging the study'.[28] AVM Smart suggested initiatives could include providing a standard script to Command and standard briefing materials to prospective participants, and having an external agency observe, monitor, evaluate and report on the consent process.[29]

ADF antimalarial prescribing policies and practices

3.17 Defence provided a summary of its malaria policies since 1990.[30] The committee heard the claim that some ADF members had been prescribed mefloquine as a first-line antimalarial.[31] However, Defence indicated that doxycycline has been the antimalarial medication of choice for prevention since the early 1990s.[32] During the start of the trials, doxycycline was the first line antimalarial, and mefloquine was the next option if doxycycline was contraindicated.[33] If both doxycycline and mefloquine were contraindicated, Atovaquone/proguanil (Malarone™) was the third option. However, at that time Malarone had not been approved for malarial prophylaxis by the Therapeutic Goods Administration (TGA).[34] Defence stated that its 'health policy regarding malaria has consistently provided guidance regarding potential side effects of each antimalarial medication, based on what was known at the time, and on reporting of adverse events'.[35] Guidance on monitoring and reporting adverse effects has been 'refined and expanded over the years'.[36]

3.18 The committee's inquiry largely focused on mefloquine and tafenoquine. VCDF Johnston emphasised that Defence has been cautious in its use of mefloquine, noting it 'has always acknowledged that this drug has side effects and has never used it as a first-line antimalarial medication'.[37] Tafenoquine was only registered in 2018, and, to date, Defence has only permitted its use during the trials.[38]

Loading doses

3.19 The term 'loading dose' refers to the practice of prescribing a higher dose of a medication for a short period at the beginning of a course, before reducing the dose to maintain the level of protection. Defence noted that:

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28 Defence, *Letter form AVM Tracy Smart AM to Mr Ian Tindall, Chair DDVA HREC,* 4 October 2018, [p. 1] (tabled 11 October 2018).

29 *Letter form AVM Tracy Smart AM to Mr Ian Tindall*, [pp. 1–2].

30 Defence, *Submission 1*, Annex R, [pp. 229–233].

31 For example, see Mr Brian McCarthy, *Submission 73*, pp. 3–5.

32 *Submission 1*, p. 36.

33 *Submission 1*, pp. 10, 36. See Defence, *Submission 1*, Annex S, [pp. 234–249].

34 Defence, *Submission 1*, Annex S, [p. 239].

35 Defence, *Submission 1*, p. 39.

36 Defence, *Submission 1*, p. 39.

37 *Committee Hansard*, 11 October 2018, p. 45.

38 Defence, *Submission 1*, p. 37.

> Taking a three day loading dose at the start of a course of mefloquine when used for prevention is standard Defence practice. A three day loading dose was also used for those taking tafenoquine during the studies.[39]

3.20 The committee heard that a 1985 study sponsored by the World Health Organization found a mefloquine loading dose for the treatment of malaria caused some mild and transient side effects, but concluded the drug was highly effective, well tolerated and safe.[40] It also heard that another study[41] compared 250 milligrams (mg) weekly versus 250 mg daily for three days (loading dose), and found:

> …more sleep disturbances, vivid dreams and depressive feelings in the patients who took the loading dose, which diminished over time. The authors concluded that the loading dose should be considered as an option for short-term travellers or military personnel...[42]

3.21 The committee heard some concerns that ADF members took loading doses inappropriately, including during the trials.[43] Defence responded that:

> Mefloquine and tafenoquine both have a long half-life and therefore it can take several weeks for sustained protective levels of the drug to be reached. This is a problem when preparing forces for deployment at short notice as it could mean that soldiers are unprotected for periods during the initial deployment period. A loading dose prior to deployment achieves protective levels more quickly… [and] allows any side effects to be identified before deployment and for the medication to be stopped if necessary.[44]

3.22 The product information for Lariam™ (mefloquine) in Australia does not specifically recommend a loading dose, though the product information for New Zealand recommends a loading dose for 'lastminute' travellers.[45] Mefloquine loading doses were found to be tolerable in the United States (US) Marine Corp in the early 1990s.[46] Other militaries experienced malaria outbreaks when mefloquine was used during deployment without a loading dose, including the British in Sierra Leone and the US in Somalia.[47] Professor Dennis Shanks, Director of ADFMIDI, reasoned that if

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39 The new product information for the use of tafenoquine for the prevention of malaria also recommends a loading dose. *Submission 1.1*, pp. 11–12.

40 Dr Peter Stewart, Medical Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 3.

41 Boudreau. E. et al., Tolerability of Prophylactic Lariam® Regimes; Trop. Med. Parasitol. 44(1993) 257-265.

42 Dr Stewart, *Proof Committee Hansard*, 8 November 2018, p. 3.

43 For example, see Ms Anne-Maree Baker, *Proof Committee Hansard*, 5 November 2018, p. 36; Associate Professor Jane Quinn, *Proof Committee Hansard*, 5 November 2018, p. 41.

44 Defence, *Supplementary submission 1.1*, p. 12.

45 Defence, *Submission 1*, pp. 36–37.

46 Professor Dennis Shanks, Director, ADFMIDI, *Committee Hansard*, 11 October 2018, p. 55. See also Defence, *Supplementary submission 1.1*, p. 12.

47 Professor Shanks, *Committee Hansard*, 11 October 2018, p. 55; Defence, *Supplementary submission 1.1*, p. 12.

the ADF had not provided loading doses it 'would be doing something that we knew had not worked operationally at least twice instead of what we knew was tolerable based on actual testing'.[48]

Period of time taking antimalarial drugs

3.23 The committee heard concerns that some ADF members took antimalarials for too long and negatively affected their health.[49] However, the American Centers for Disease Control and Prevention 'recommends that mefloquine be started two or more weeks before entering a malarious area and does not specify a maximum duration of treatment, judging it to be suitable for long term prevention'.[50] Moreover:

> Mefloquine had been successfully used for long periods in Africa by the US Peace Corps prior to the Timor-Leste studies with no evidence of long term health effects. Long term follow-up of the US Peace Corps, a majority of whom took mefloquine, showed no serious adverse effects attributable to the medication after more than 10 years.[51]

3.24 Also referring to evidence from the Peace Corps, Professor James McCarthy, Royal Brisbane Hospital and QIMR Berghofer Medical Research Institute, noted the rate of side effects went down as people took mefloquine for longer.[52] Some people could not tolerate mefloquine so stopped taking it very quickly, however another group were able to take it for a very long time without side effects.[53]

Use of antimalarial drugs outside the trials

3.25 At the time of the trials, mefloquine was registered by the TGA, so personnel could take it if they had issues tolerating doxycycline, as was the case for some submitters.[54] Personnel who were deployed at the time of the tafenoquine prevention trial, but not actually participating in the trial, could choose to take doxycycline or mefloquine.[55] Defence explained that '[t]he exact number of individuals who were prescribed mefloquine during Timor-Leste deployments outside of the studies is unknown as Defence did not have a complete electronic dispensing record until 2001'.[56]

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48 *Committee Hansard*, 11 October 2018, p. 55.

49 See *Proof Committee Hansard*, 5 November 2018, p. 36.

50 Defence, *Submission 1*, pp. 36–37.

51 Defence, *Supplementary submission 1.1*, p. 21.

52 *Committee Hansard*, 11 October 2018, p. 22.

53 *Committee Hansard*, 11 October 2018, p. 22.

54 See, for example, Name withheld, *Submission 48*, p. 1.

55 Defence noted that this was 'to simplify health surveillance activities by aligning dosage requirements with the rest of the group', and Mr Reid also noted that it was to prevent 'an inducement for the soldiers to go into the trial unnecessarily'. Defence, *Supplementary submission 1.1*, p. 9; *Committee Hansard*, 30 August 2018, p. 21.

56 *Supplementary submission 1.1*, p. 9.

3.26 Excluding trial participants, 664 ADF personnel were prescribed mefloquine from 2001 to 20 June 2018.[57] Prescriptions have decreased in recent years:

> …on average 76 members being prescribed the drug each year during 2001–2005, 33 members each year during 2006–2010 and 19 members each year during 2011 to 2015. In the past two years, the figure has been five and two respectively.[58]

Current ADF antimalarial policy

3.27 Defence provided its current policy, which lists doxycycline as the first line antimalarial, Malarone™ second and mefloquine third.[59] The Defence submission indicated that tafenoquine would be considered for use if it was registered by the TGA (as it has been), and a new Defence policy is expected to be released in late 2018.[60]

Details of the antimalarial drug trials

3.28 Defence stated:

> The maximum number of Defence personnel who have taken mefloquine and tafenoquine in the ADFMIDI [ADF Malaria and Infectious Disease Institute] studies, and the number of prescriptions of mefloquine outside of these studies since 2001, is 3,523. It is likely that this is an overestimate as there may be some overlap in these groups.[61]

3.29 This 3,523 comprises a maximum of 1,983 people who took mefloquine and 1,540 who took tafenoquine.[62]

3.30 The following table presents information on the trials, though it 'does not include every single unit that made up the deploying Battalion Group', and the tafenoquine 'eradication and treatment studies included personnel from a large number of units in addition to those listed'.[63]

57 Defence, *Submission 1*, pp. 14, 20.

58 Defence, *Submission 1*, p. 14.

59 *Submission 1*, p. 36, Annex T.

60 *Submission 1*, pp. 2, 36.

61 *Submission 1*, p. 20.

62 Defence, *Submission 1*, Annex E, [p. 149].

63 Defence, *Supplementary submission 1.1*, p. 8.

Table 1: ADF antimalarial studies 1999 to 2002

Trial	Number of participants taking antimalarial	Approximate dates	Location	Personnel involved	Dosages
Tafenoquine eradication[64]	Tafenoquine 1017 (378/639) Primaquine 464	February 1999 to April 2000	Bougainville (1999)/ Timor-Leste (2000)	3 RAR, 5/7 RAR, others	Tafenoquine: over 3 days either: 400mg daily; 200mg twice daily; or in Timor-Leste only, 200mg daily
Tafenoquine prevention[65]	Tafenoquine 492 Mefloquine 162	October 2000 to April 2001	Timor-Leste	1 RAR	Tafenoquine: 200mg daily for 3 days then 200mg weekly Mefloquine: 250mg daily for 3 days then 250mg weekly
Mefloquine prevention[66]	Mefloquine 1157 Doxycycline 388	2001–2002	Timor-Leste	2 RAR and 4 RAR	Mefloquine: 250mg every other day on 3 occasions, then a 250mg weekly dose
Tafenoquine treatment[67]	Tafenoquine 31	2000–2001	Australia	Various	Tafenoquine: 200mg daily for 3 days then 200mg weekly for 8 weeks

Sources: Defence, *Submission 1*, pp. 20–21; *Submission 1.1*, p. 8; papers listed in footnotes to the table.

64 See N Elmes, P Nasveld, S Kitchener, D Kocisko, M Edstein, 'The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of Plasmodium vivax malaria in the Southwest Pacific', *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 102, no. 11, November 2008, pp. 1095–101.

65 See P Nasveld, M Edstein, M Reid, L Brennan, I Harris, S Kitchener, P Leggat, P Pickford, C Kerr, C Ohrt, W Prescott et al, 'Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects', *Antimicrobial Agents and Chemotherapy*, vol. 54, no. 2, 2010, pp. 792–8.

66 See S Kitchener, P Nasveld, R Gregory, M Edstein, 'Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor', *Medical Journal of Australia*, vol. 182, no. 4, 2005, pp. 168–171.

67 See S Kitchener, P Nasveld, M Edstein, 'Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria', *American Journal of Tropical Medicine and Hygiene*, vol. 76, no. 3, 2007, pp. 494–6.

Reasons for ADF involvement

3.31 Defence indicated that the broad purpose of the trials was to consider the use of alternatives to the standard medications in use at the time, including primaquine and doxycycline.[68] Prior to the trials there were cases of relapsing malaria during deployments, and it was not known whether this was due to compliance problems with primaquine or if the malaria parasite was developing resistance.[69] Moreover, during the 1999 INTERFET operation, 64 cases of malaria were recorded while using doxycycline, and 212 soldiers experienced the onset of malaria after returning to Australia.[70] Defence noted this could have been due to poor compliance or possible resistance to doxycycline, so sought to assess the use of other medications.[71]

3.32 Some submitters suggested the mefloquine prevention trial was unnecessary, as 'studies of long-term mefloquine prophylaxis had by this time already been conducted involving military personnel…providing seemingly ample evidence to adequately inform ADF policy'.[72] Compared to other militaries, 'the ADF has been conservative in its use of mefloquine',[73] and sought to define the safety and tolerability of mefloquine and assess its effectiveness under operational conditions.[74]

Allegations regarding conflicts of interest

3.33 Some submitters claimed there were conflicts of interest during the trials, such as Associate Professor Quinn, who pointed out 'the doctors, the medical officials and the senior ADF members who are managing that deployed cohort are also invested in the development and delivery of a third-party pharmaceutical-funded drug trial'.[75] She suggested the 'close interdependency' between organisations and:

> The implicit pressures on the AMI [Army Malaria Institute] staff carrying out the trial to deliver positive outcomes for these agencies likely biased results an[d] resulted in drug continuation for some participants where withdrawal from treatment was indicated.[76]

3.34 As another example, Mrs Mary Bush told the committee that she perceived the trials involving tafenoquine to be unethical as she alleged participants 'were used as human guinea pigs for the government's own gain, namely money and greed'.[77]

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68 *Supplementary submission 1.1*, p. 6.

69 Defence, *Supplementary submission 1.1*, p. 6.

70 Defence, *Supplementary submission 1.1*, p. 6.

71 *Supplementary submission 1.1*, p. 6.

72 The Quinism Foundation, *Submission 17*, p. 9.

73 Vice Admiral David Johnston AO, *Committee Hansard*, 11 October 2018, p. 45.

74 AQVFA, *Submission 16.3*, Annex 1, [p. 15].

75 *Proof Committee Hansard*, 5 November 2018, p. 40.

76 The Australian Malaria Institute has been renamed the ADF Malaria and Infectious Disease Institute. AQVFA, *Submission 16*, pp. 19, 45–47.

77 *Proof Committee Hansard*, 5 November 2018, p. 11.

3.35 The conduct of the trials has been scrutinised several times. It was reported in 2015 that the chair of the ethics committee that preceded the DDVA HREC reviewed documentation available at the time of the trials and the conduct of the researchers.[78] It determined that Defence and the ethics committee applied appropriately rigorous scientific and ethical evaluation of the trials.[79] The 2016 IGADF report found the trials undertaken from 2000 to 2002 in East Timor involving mefloquine 'were conducted ethically and lawfully'.[80] More details on the IGADF report are included later in this chapter. In 2018, the US Food and Drug Administration (FDA) conducted an audit of Defence's tafenoquine trials, and 'confirmed compliance with the approved protocols and conformity with the Declaration of Helsinki (1996) and International Conference of Harmonisation Guidelines for Good Clinical Practice'.[81] The audit found 'no conclusion of impropriety' and 'no indication that good clinical practice was not followed'.[82] Defence characterised the audit as representing 'a thorough, independent validation of all aspects of the conduct of the studies'.[83]

3.36 Allegations of misconduct were also refuted by pharmaceutical companies and Defence. Organisations such as ADFMIDI, the US Army's Walter Reed Army Institute of Research and Medicines for Malaria Venture (MMV) collaborate, but Defence emphasised it does not have 'direct financial relationships with the drug companies associated with the development of tafenoquine'.[84] Associate Professor Karunajeewa, who was not involved in the trials, stated:

> …AMI and its members are very well-respected as scientists and academics and their contributions to this effort are genuinely very highly valued throughout our small community. We all do our best to co-operatively draw on a wide variety of resources including government, academia, public-private partnerships, non-government organizations and industry…I am not aware of any evidence to support suggestions that clinical trials in Bougainville and Timor Leste were ethically compromised by pecuniary interests or collusion with the pharmaceutical industry.[85]

3.37 In its submission, Defence noted that malaria is more prevalent in poorer countries, so it is difficult for pharmaceutical companies to recoup the development costs of antimalarials.[86] While not directly involved in the trials, the pharmaceutical

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78 The Australian Defence Human Research Ethics Committee (ADHREC), *Annual Report 2015*, Department of Defence, 2016, p. 7.

79 ADHREC, *Annual Report 2015*, Department of Defence, 2016, p. 7.

80 IGADF, *Inquiry report*, 2016, pp. ii–iii.

81 Defence, *Supplementary submission 1.1*, p. 5.

82 The FDA considered 'study 033' (the tafenoquine prevention trial) and 'study 049' (the tafenoquine eradication trial). *Proof Committee Hansard*, 8 November 2018, p. 18.

83 *Supplementary submission 1.1*, p. 5.

84 *Submission 1*, p. 17.

85 *Submission 15*, [p. 12].

86 *Submission 1*, p. 16.

company Roche confirmed that mefloquine represents a very small portion of their business at less than $1 million per year and less than one per cent of turnover.[87] The pharmaceutical company GlaxoSmithKline (GSK), sponsor of some tafenoquine studies, emphasised that its 'aim is to make that drug available in malaria-endemic countries at an affordable price' and reiterated that this 'is not a commercial opportunity for GSK'.[88] Defence also refuted the claim that pharmaceutical companies stand to make millions of dollars from the registration of tafenoquine, pointing out that its global roll out will cost more than an estimated US$100 million, and probably require continued subsidy.[89] The US military 'also continues to invest a great deal of money in tafenoquine because it is required for force health protection'.[90]

3.38 Tafenoquine was not registered for nearly two decades following the trials, a length of time described as 'unusual' by Adjunct Professor John Skerrit, Deputy Secretary, Health Products Regulation, Department of Health.[91] However, GSK explained that it initially worked with the US Army in the early 2000s, and then changed direction to focus on developing a radical cure with MMV, noting 'a 10-year time frame to develop the medicine for that setting is not that unusual'.[92]

Concerns about access to research data

3.39 The AQVFA expressed concerns that data from the tafenoquine prevention trial were provided to 60P without the re-consent of trial participants.[93] 60P responded that its use of de-identified data in regulatory dossiers and for pharmacovigilance reporting was appropriate. The original information and consent form signed by participants informed them that 'data collected as part of the studies would be kept for 75 years'.[94]

3.40 Professor Sandy McFarlane AO, Director, Centre for Traumatic Stress Studies, University of Adelaide, raised the broader issue of how to 'allow access to and use of data collected in Defence and DVA sponsored research programs' to ensure it is used optimally while protecting the privacy of participants.[95]

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87 Mr Svend Peterson, Managing Director, Roche Products Pty Ltd, *Proof Committee Hansard*, 8 November 2018, p. 5.

88 Dr Alison Webster, Head, Global Health Clinical Research and Development, GSK, *Proof Committee Hansard*, 8 November 2018, p. 12.

89 *Supplementary submission 1.1*, p. 18.

90 Defence, *Supplementary submission 1.1*, p. 18.

91 *Proof Committee Hansard*, 11 October 2018, p. 37.

92 Dr Webster, *Proof Committee Hansard*, 8 November 2018, p. 14.

93 60P is also referred to as 60 Degrees Pharmaceuticals LLC. AQVFA, *Submission 16.1*, p. 3.

94 60P, *Supplementary submission 9.1*, p. 2.

95 *Submission 58*, [p. 5].

The consent process during the trials

3.41 This section summarises the trial consent process, including ethics committee approval and the provision of information and choice to prospective participants. In its submission, Defence provided the consent forms and information sheets for most of the trials.[96] Defence also provided the original and amended study protocols relating to the tafenoquine prevention trial (study 033) as well as related documentation in its supplementary submission.[97] The AQVFA provided some documentation related to the mefloquine prevention trial.[98]

3.42 The Australian Defence Medical Ethics Committee (ADMEC) was created in 1988 to be a committee of impartial experts responsible for ensuring trials are 'both ethically permissible and scientifically correct'.[99] It was called the Australian Defence Human Research Ethics Committee (ADHREC) from 2001–2017, and then replaced by DDVA HREC. ADMEC considered research protocols in line with a precursor to the current National Statement, the 1999 *National Statement on Ethical Conduct in Research Involving Humans* (National Guidelines).[100] The provisions pertinent to research involving ADF members are almost directly the same in the 1999 National Guidelines and as the current National Statement.[101] ADMEC reviewed and approved the protocols for the antimalarial trials.[102]

Disclosure of risks and provision of information

3.43 Providing sufficient information to prospective participants involves giving them 'an adequate understanding of the purpose, methods, demands, risks and potential benefits of the research'.[103] Some submitters suggested that though participants were provided with information and signed consent forms, this did not constitute consent because they did not understand the information. Lieutenant General John Caligari AO DSC (Rtd) explained:

> Informed consent for a lot of these soldiers would have been: 'Hey, it's all right for the boss. He thinks it's okay. It's in the army newspaper. It must be okay. Someone's let them on the base to describe it. It must be okay.'…they've probably walked in and the doctor started explaining it to them, and they're not really listening…That's not informed consent, because they're not listening. They don't understand what they're reading.[104]

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96 The forms are for the mefloquine prevention, tafenoquine prevention and tafenoquine eradication trials. See *Submission 1*, Annexes F to H.

97 *Supplementary submission 1.1*, Annex C, [p. 78].

98 *Supplementary submission 16.3*, Annexes 1 and 2.

99 IGADF, *Inquiry report*, p. i.

100 IGADF, *Inquiry report*, p. 7.

101 Ms Barr, *Committee Hansard*, 11 October 2018, p. 13.

102 Defence, *Submission 1*, pp. 22, 25.

103 NHMRC, ARC and Universities Australia, *National Statement*, p. 16.

104 *Committee Hansard*, 31 August 2018, p. 25.

3.44 A veteran described that prior to the tafenoquine prevention trial they were too focused on preparation for deployment to 'fully understand medical terminology used or the drugs that we were being exposed to'.[105] Another veteran told the committee: 'Truthfully, I didn't even read it. The sergeant just gave out a piece of paper and we all just signed it so that we [could] go to Timor'.[106]

Inspector-General of the Australian Defence Force investigation

3.45 The statutory role of IGADF was established to 'provide a means for review and audit of the military justice system independent of the ordinary chain of command'.[107] In 2015, then Major Stuart McCarthy lodged a wide-ranging submission with the IGADF alleging 'unethical, unlawful and negligent use by Defence of the anti-malarial drug mefloquine' during the trials held between 2000 and 2002 involving members deploying to East Timor.[108] He claimed that Defence failed to comply with National Guidelines because members were compelled to participate in one of the trials as a condition of deployment and there was a lack of informed consent in both trials.[109] Major McCarthy's complaint also focused on the purported 'neurotoxic' effects of mefloquine and the claim that the AMI failed to ensure prospective participants were 'informed of the foreseeable likelihood of permanent brain injury with long term or permanent side effects'.[110] Similar allegations were outlined in submissions to this inquiry from Mr McCarthy, the AQVFA, the American Quinism Foundation and some individuals.[111]

3.46 The IGADF concluded that Defence and AMI investigators did not accept the claim that mefloquine caused 'mefloquine neurotoxicity'.[112] As noted above, the IGADF also found that the trials undertaken by the AMI from 2000 to 2002 in East Timor involving mefloquine 'were conducted ethically and lawfully by the AMI, in accordance with the National Guidelines issued by the NHMRC and the TGA'.[113] Details on the provision of information in specific trials are below.

Tafenoquine prevention trial

3.47 This trial compared tafenoquine and mefloquine. The Quinism Foundation, led by Dr Remington Nevin, raised concerns that:

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105 Name withheld, *Submission 67*, p. 1.

106 Mr Warren Goodchild, *Committee Hansard*, 31 August 2018, p. 31.

107 Defence, *Military Justice: Organisations*, http://www.defence.gov.au/mjs/organisations.asp#1 (accessed 2 October 2018).

108 IGADF, *Inquiry report*, pp. 1–2.

109 IGADF, *Inquiry report*, 2.

110 IGADF, *Inquiry report*, p. 24, [original emphasis removed].

111 Mr Stuart McCarthy, *Submission 94*; AQVFA, *Submission 16.3*; Quinism Foundation, *Submission 17*, pp. 5–10.

112 IGADF, *Inquiry report*, p. 49.

113 IGADF, *Inquiry report*, 2016, pp. ii–iii.

> …guidance in the then-current Australian mefloquine Patient Information to stop taking the drug and to 'tell your doctor immediately or go to casualty at your nearest hospital' for 'change in mood, for example, depression, restlessness, confusion, feeling anxious or nervous' do not appear to have been communicated to subjects.[114]

3.48 However, the consent form and information sheet stated:

> Should you experience any medical problems, including suspected side effects to the study drugs, you should report these promptly to your Company medic, RAP or study investigator. If you want any further information on the study, please contact the study investigator…[115]

3.49 Fourteen witnesses were interviewed as part of the IGADF inquiry, and while most of them 'had a limited and vague memory of the informed consent process', almost all accepted that 'the medical briefings dealt with the potential side effects of both drugs and that the trial was voluntary'.[116] The IGADF reported that participants:

> …undertook a comprehensive three phase medical briefing process culminating in a witnessed consent form being signed before a medical officer. This process ensured that participants were aware of the potential side effects of both drugs and that the trial was a voluntary trial, without detriment to deployment, and they could withdraw at any time.[117]

3.50 The IGADF was 'satisfied the trial participants were appropriately informed by the medical investigators of the potential side effects of both tafenoquine and mefloquine, and understood that participation in the trial was voluntary without detriment to deployment or future career'.[118] Lieutenant General Caligari (Rtd) said participants were:

> …individually briefed by a doctor, and a witness with the doctor, and signed the documents after they were asked, 'Do you believe you understand enough about the trial?' I was very satisfied with the way the AMI conducted the introduction of everyone into the trial...There were also group sessions that were held which I made them all attend. They received briefings on whiteboards and PowerPoint presentations on what this drug was all about, what the purpose of the trial was and what the possible implications of it were….every soldier signed in front of a doctor, or at least the RAP sergeant, with a witness.[119]

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114 *Submission 17*, p. 9.

115 Defence, *Submission 1*, Annex G, [p. 159].

116 IGADF, *Inquiry report*, p. iii.

117 IGADF, *Inquiry report*, p. iii.

118 IGADF, *Inquiry report*, p. 49.

119 *Committee Hansard*, 31 August 2018, pp. 21, 23.

Mefloquine prevention trial

3.51 This trial compared mefloquine and doxycycline. Mefloquine had already been approved and registered in Australia at the time of the trial.[120] On direction from the ethics committee of the time, the information and consent form for the trial were amended to 'clearly outline in quantitative terms the side effects of the medication'.[121] The information on mefloquine's potential side effects provided in the 4 RAR and 2 RAR trial medical briefings and consent form was consistent with the detailed 1998 Lariam (mefloquine) product information.[122]

3.52 The IGADF judged that this 'provided sufficient relevant information in a form comprehensible to participants, to allow them to make an informed decision whether or not to participate in the trial'.[123] The IGADF inquiry found:

> Participants in the 4 RAR and 2 RAR mefloquine anti-malarial drug trials received a comprehensive medical briefing, during which they were informed of the side effects of mefloquine, that the trial was completely voluntary, and non-participation would have no effect on deployment or career. These aspects were reinforced at individual doctor/participant consultations when mefloquine was prescribed to the soldiers taking part in the trial. After the loading dose was administered in Australia and prior to deployment, the soldier had a further opportunity to discuss any side effects with a medical officer and to withdraw from the trial.[124]

3.53 Some submitters recounted memories of receiving briefings about the trial.[125]

Tafenoquine eradication trial

3.54 This trial compared tafenoquine and primaquine. Mr McCarthy recalled receiving a briefing from trial investigator Colonel Peter Nasveld, but noted:

> …In Bougainville there was no internet. We literally wrote letters home. We had a satellite phone there. We were given one two-minute phone call home per week. So there was absolutely no way to check the veracity of the information we were told.[126]

3.55 Mr Stuart McCarthy and Mr Brian McCarthy also expressed concerns that they had not viewed evidence that the TGA approved the export of tafenoquine to East

120 IGADF, *Inquiry report*, 2016, p. vi.

121 The protocol appears to have been amended during 2001. AQVFA, *Submission 16.3*, pp. 4, 121–122.

122 This was more detailed than the 1998 Lariam consumer medicine information normally provided to patients on prescription. IGADF, *Inquiry report*, 2016, p. vi.

123 IGADF, *Inquiry report*, 2016, p. vi.

124 IGADF, *Inquiry report*, 2016, p. vi.

125 See, for example, name withheld, *Submission 76*, p. 3.

126 Mr Stuart McCarthy, *Committee Hansard*, 30 August 2018, p. 6.

Timor for use by 3 RAR participants in the tafenoquine eradication trial.[127] Defence reiterated that tafenoquine 'was administered in accordance with ADMEC approved study protocols and participation was voluntary'.[128] It stated:

> These personnel were briefed about the study, given a written information sheet and the opportunity to ask questions. Those who chose to participate then signed the study consent form and were provided a copy. The consent form included information on their right to withdraw from the study at any time without any consequences. Those who chose not to participate received the standard primaquine eradication course.[129]

3.56 A participant from 3 RAR recalled being briefed, but stated: '[d]uring the enrolment in this clinical trial I was not examined by a doctor'.[130] The study requirement was for 'all individuals to be briefed and consented by a doctor', but perhaps not physically examined as the participant appeared to expect.[131] The committee understands that ADF members underwent pre-deployment medicals as part of the usual preparation process external to the trials.[132]

Tafenoquine treatment trial

3.57 Defence noted giving tafenoquine to 31 members with relapsing malaria 'was not a study per se but a quality assurance activity'.[133] Tafenoquine was not registered at the time of the trials, so TGA approval was required to import the medication under the Special Access Scheme.[134] An academic paper stated:

> The proposal to conduct this treatment trial was reviewed and approved by the [ADHREC], and each individual patient signed an informed consent and information sheet and their treatment was approved by the Australian Therapeutic Goods under the auspices of the Therapeutics Goods Act (1989), Section 19(1).[135]

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127 Mr Brian McCarthy, *Supplementary submission 73.2*, pp. 7–8; Mr Stuart McCarthy, *Submission 94*, pp. 9–10.

128 *Submission 1*, p. 25.

129 Annex G of the Defence submission includes four versions of the information sheet and consent form. Defence, 'Tafenoquine Eradication and Treatment Trials', http://www.defence.gov.au/Health/HealthPortal/Malaria/AMI_research/tafenoquine-trials/eradication-treatment-trials.asp (accessed 8 October 2018).

130 Name withheld, *Submission 59*, [p. 1].

131 Defence, *Supplementary submission 1.1*, p. 12.

132 Defence, *Supplementary submission 1.1*, p. 29.

133 *Submission 1*, p. 24.

134 IGADF, *Inquiry report*, p. 9; Defence, *Submission 1*, p. 25. The TGA manages the Special Access Scheme in recognition that there are circumstances where patients need access to unregistered therapeutic goods. See TGA, 'Special Access Scheme' https://www.tga.gov.au/form/special-access-scheme (accessed 24 July 2018).

135 Kitchener et al, 'Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria', p. 494.

3.58 Defence reiterated that participation was 'voluntary and those who agreed to take tafenoquine to treat their relapsing malaria provided consent'.[136]

Voluntary participation

3.59 There are two conditions for consent: the provision of sufficient information and voluntary choice to prospective participants. Consent must be able to be withdrawn even once the trial has started, and prospective participants should be informed of the consequences of this as part of the consent process.[137] The National Statement explains that someone 'declining to participate in, or deciding to withdraw from, research should not suffer any negative consequences'.[138]

3.60 The committee heard concerns that the unequal relationships within the ADF prevented members fully exercising their right to choose whether or not to participate in the trials. The following extract from a submission exemplifies these issues:

> I was 19 years old, have been in the army for approx 7–8 months at this stage, new to the battalion and would be deploying overseas in approx 2 month's time. Who am I to be questioning anything we are taught, trained or advised of especially in an organisation like the Australian Defence Force. From the moment you get off that bus at Kapooka for basic training you now or soon learn very quickly to shut your mouth, do what you are told and don't ask questions.[139]

3.61 The wife of a veteran reiterated that the military 'culture doesn't allow them [soldiers] to say no'.[140]

3.62 Some submitters suggested even though members signed consent forms, this could not be understood to be voluntary consent because they felt pressured to participate. Mr Kel Ryan, National President of the Defence Force Welfare Association, told the committee 'I suppose they've consented, and I suppose they've agreed with it—they've been informed—but it might be based on a degree of peer pressure'.[141] Mr Mark Armstrong, a veteran who did not participate in the trials, stated:

> Nothing is consensual in the military. Once you sign, if you're going to be a good soldier you say yes. You don't get a choice. If you do, you get hammered…It's a team and you don't want to let that team down.[142]

3.63 Lieutenant General Caligari (Rtd) shared his view that:

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136 Defence, *Submission 1*, p. 25.

137 NHMRC, ARC and Universities Australia, *National Statement*, p. 18.

138 *National Statement*, p. 69.

139 Confidential, *Submission 103*, p. 1.

140 *Committee Hansard*, 30 August 2018, p. 15.

141 *Committee Hansard*, 30 August 2018, p. 29.

142 *Committee Hansard*, 30 August 2018, p. 11. See also Mr Eveille, Returned and Services League of Australia, *Committee Hansard*, 11 October 2018, p. 20.

> I don't think there is any such thing as informed consent in the military. We do things because we are ordered to do things; we don't have the opportunity to say yes or no to some things; we shouldn't have a say in anything….People signed a form and that is what was considered by the trial conductors as informed consent—which was a requirement of the human research and ethics committee.[143]

3.64 In contrast, Vice Admiral Johnston stated:

> My view is that informed consent is available, and important, for military people…on the general comment by General Caligari that it's impossible to have informed consent: we exercise informed consent over a range of our career choices, not just limited to our participation in medical practice.[144]

3.65 He conceded 'these people's recollections now are such that they don't believe they were given informed consent' and 'that's very concerning'.[145] The IGADF found:

> In compliance with NHMRC guidelines, participants in the 2000 to 2002 anti-malarial drug trials conducted by AMI were required to voluntarily confirm their willingness to participate in the trial, that is, exercise a voluntary choice, after having been informed at their level of comprehension of relevant aspects of the trial including the risks and discomforts (side effects) associated with taking the drugs. There were not to be any adverse consequences for failing to participate in the trial.[146]

3.66 Details on the voluntary nature of consent in specific trials are noted below.

Tafenoquine prevention trial

3.67 Principal investigator Colonel Nasveld was responsible for obtaining informed consent from participants and 'was personally present for all of it'.[147] He assured the committee that the consent process:

> …was done according to the best practice and in fact at a level that probably had greater rigour than that generally experienced in the civilian community…they were consented in pairs, at matched ranks, was so there could be no suggestion that there was coercion from a senior person because he said yes and a junior person still had doubt. That briefing period, that consenting period, ran over several weeks. The implication that it was done on the spur of the moment is incorrect…I understand that many, many years later the recollection of that 10 or 20 minutes while you're preparing to go on your first deployment may not flag as strongly as it does with those who have to actually deliver the consenting process. I am

143 *Committee Hansard*, 31 August 2018, p. 20.

144 *Committee Hansard*, 11 October 2018, p. 47.

145 *Committee Hansard*, 11 October 2018, p. 47.

146 IGADF, *Inquiry report*, 2016, p. iii.

147 *Committee Hansard*, 11 October 2018, p. 48.

> extremely comfortable—as was the FDA, the TGA and our internal audits by the ethics committee—in the activities undertaken.[148]

3.68 He explained the regimental medical officer firstly provided an outline of the trial as part of a briefing to companies about general health risks.[149] In smaller groups, members were given information and consent forms and briefed by medical officers as part of their general health screening, which included the opportunity to ask questions about the trial.[150] Members did not return their signed forms until at least two days later, to enable them to consider their choice and consult with friends and family.[151]

3.69 Defence has a duty of care to ensure its members are protected from malaria when they deploy to malarious areas.[152] Colonel Nasveld acknowledged that ADF members would not deploy in such situations without taking an antimalarial, but stressed that this is 'not the same as saying, 'You must be on this study'.'[153] The IGADF investigated the allegation that the Commanding Officer (CO), then Lieutenant Colonel Caligari, told 1 RAR troops they would not deploy if they did not participate in the trial.[154] This claim was made in then Major McCarthy's submission to the IGADF, and in information provided to the committee's inquiry.[155] Lieutenant General Caligari (Rtd) denied the allegation.[156]

3.70 The IGADF inquiry found witnesses' 'overall memory of events surrounding the anti-malarial drug trial, conducted during a busy pre-deployment 16 years ago is generally poor and lacking in detail'.[157] The IGADF concluded:

> There is differing but credible evidence provided by the six witnesses identified by MAJ McCarthy, and the former command group officers and LTGEN Caligari concerning voluntary participation in the trial. The sufficiency and quality of the evidence does not satisfy the required standard of proof to make an adverse finding that the CO used the alleged words (or a similar threat or direction) to the effect that participation in the trial was required in order to deploy to East Timor.[158]

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148 *Committee Hansard*, 11 October 2018, p. 48. See also Mr Reid, *Submission 71*, p. 12.

149 *Committee Hansard*, 11 October 2018, p. 49.

150 *Committee Hansard*, 11 October 2018, p. 49.

151 *Committee Hansard*, 11 October 2018, p. 50.

152 Defence, *Supplementary submission 1.1*, p. 16.

153 *Committee Hansard*, 11 October 2018, p. 50.

154 IGADF, *Inquiry report*, 2016, p. iii.

155 See, for example, Mr Brock, *Committee Hansard*, 31 August 2018, p. 9; Mr Chris Ellicott, *Submission 105*, p. 1; Mr Todd Connors, *Submission 99*, [p. 1]; Mr Glen Norton, *Submission 80*, [p. 1].

156 IGADF, *Inquiry report*, p. 50; LTGEN Caligari, *Committee Hansard*, 31 August 2018, p. 25.

157 IGADF, *Inquiry report*, p. 50.

158 IGADF, *Inquiry report*, p. 56.

3.71 ADF members did not have to participate in the trial, and could deploy while taking other antimalarial drugs such as doxycycline. Colonel Nasveld noted:

> …we had people who would come up and say, 'Listen, I'm not comfortable with being part of the study.' They all knew they had an option of not being there or commencing on another antimalarial. They even had a choice of taking any of the antimalarials that were available, having had a discussion on what the side-effect profiles of those were.[159]

3.72 The IGADF inquiry heard that over 400 deployed members of the battalion group did not participate in the trial and were taking doxycycline.[160] It was noted that such large numbers of non-participants was not consistent with the CO threatening that those who refused to participate would not deploy.[161] The AQVFA suggested that the majority of these would have been excluded from the trial for medical or administrative reasons, because they were due to be posted in or out of 1 RAR partway through the deployment, or because they were not initially members of 1 RAR.[162] Colonel Nasveld noted that, in addition to these reasons for not participating, some prospective participants 'basically just said no'.[163] According to trial records, '95 personnel were recorded as being unwilling or unable to enrol and another 24 were excluded as they were found unsuitable on screening'.[164] Defence stated that '[n]o evidence has been presented that anyone was stopped from deploying because they refused to participate'.[165] The IGADF report was criticised by veterans and commentators who did not accept the findings.[166]

Mefloquine prevention trial

3.73 The IGADF noted 'investigators went to some lengths to ensure voluntary participation', including offering soldiers opportunities to withdraw.[167] This 'may not have impacted on the soldiers' decision to automatically participate', as they perceived the trial as just 'one of the many pre-deployment matters that had to be completed in order to deploy'.[168] For example, Mr Fleming recalled the trial was not:

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159 *Committee Hansard*, 11 October 2018, p. 49. See also Mr Reid, *Committee Hansard*, 30 August 2018, p. 21.

160 IGADF, *Inquiry report*, pp. 37–38, 51. See also Defence, *Submission 1*, p. 23.

161 IGADF, *Inquiry report*, p. 51.

162 AQVFA, *Supplementary submission 16.6*, pp. 3–4.

163 *Committee Hansard*, 11 October 2018, p. 50.

164 Defence, *Supplementary submission 1.1*, p. 11.

165 *Supplementary submission 1.1*, p. 11.

166 For example, Mr Brian McCarthy, *Submission 73*, pp. 6–8, Mr Stuart McCarthy, *Committee Hansard*, 30 August 2018, pp. 3–4; Associate Professor Jane Quinn, *Proof Committee Hansard*, 5 November 2018, pp. 39–40.

167 IGADF, *Inquiry report*, pp. 70–71.

168 IGADF, *Inquiry report*, pp. 71, 73.

> …high on my priority list with fitness and preparation for deployment taking higher priorities. It very much sounded like it made sense at the time, having to take one tablet a week instead of daily and in general as soldiers we trusted that our medical support had our best interest in mind.[169]

3.74 Nevertheless, the IGADF concluded members 'were not compelled or coerced by command to participate in the 4 RAR and 2 RAR anti-malarial drug trials and to take mefloquine'.[170]

Tafenoquine eradication and treatment trials

3.75 The committee did not receive as much evidence on voluntary consent for these trials, but it appears that consent was provided.[171] For instance, Major Phillip Chapman (Rtd) described his experience of the tafenoquine eradication trial:

> …I was a volunteer for this trial and volunteered because the benefits of taking Tafenoquine as a post-deployment eradication were 'sold' to us, at the briefing for the trial (three days pre-departure for Tafenoquine), as the being a far better option than the arduous task of taking the alternative 'standard' 14 day post-departure eradication program.[172]

Screening processes

3.76 Colonel Nasveld explained that the 'screening process was different for each of the trials'.[173] Generally, ADF members could be excluded from the trials by choice or for reasons including pregnancy, allergic reactions, enzyme G6PD deficiencies or previous experiences of mental illness such as serious depression.[174] The committee heard some concerns that the mental health of prospective participants was not checked prior to them consenting to participate. For example, Ms Anne-Maree Baker noted '[w]e had no specific psych testing prior to deployment as part of this trial'.[175] Defence:

> …uncovered a small number of cases of other individuals who were included in the mefloquine studies despite having a history of mental health issues…Defence acknowledged the error, apologised, and offered to provide assistance to help access support services and engage with DVA.[176]

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169 *Submission 72*, [p. 1].

170 IGADF, *Inquiry report*, 2016, p. viii.

171 See Defence, *Submission 1*, Annex H, [pp. 161–179]; Kitchener et al, 'Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria', p. 494.

172 *Submission 87*, [p. 1].

173 *Committee Hansard*, 11 October 2018, p. 53.

174 See the information and consent forms for details on specific trials. Defence, *Submission 1*, *Submission 1*, Annexes F to H.

175 *Proof Committee Hansard*, 5 November 2018, p. 36.

176 Defence, *Submission 1*, p. 40.

3.77 For example, AVM Smart wrote to apologise to a veteran whose previous history of depression was not identified prior to participating in a trial, partly due to the reliance on paper records.[177] It was noted that such a situation would 'not happen today as Defence introduced an electronic Health System in 2014 making it easier for health providers to access documentation'.[178]

Tafenoquine and mefloquine prevention trials

3.78 Colonel Nasveld explained the tafenoquine prevention trial screening entailed:

> …going into the health records and reviewing what was written inside them. That's not to say that with doctors handwriting we might not have missed one or two, but certainly that was the focus. That was also secondarily checked by an audit team from USAMMDA, the United States Army Medical Materiel Development Activity. They had independent people come over and confirm that we were fairly well on the mark.[179]

3.79 Mr Fleming recounted his experience prior to participating in the mefloquine prevention trial: 'There was certainly no review of suitability to take the medication, no examination by a doctor or medic etc other than signing the waiver form and self-assessing your own suitability'.[180] However, Defence stated that each participant of that trial 'was medically assessed prior to starting the study, during deployment and before return to Australia'.[181] This discrepancy may be due to the expectation that prospective participants would have undergone a physical medical examination specifically to assess their suitability for the trial, compared to the approach described by Colonel Nasveld above.

Response to adverse events

3.80 The Defence submission included a summary of the adverse events experienced by ADF members while participating in the trials.[182] Defence defined an adverse event as 'an untoward occurrence associated with (but not necessarily caused by) a medication'.[183] These included events that had not been causally linked to the medication, for example, trial records 'include adverse events such as 'spider bites' which are obviously not related to the use of medication'.[184] Colonel Nasveld stressed that the details of any adverse events were recorded, including when they started and ended.[185] Members could report:

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177 *Committee Hansard*, 11 October 2018, p. 53.

178 Defence, *Supplementary submission 1.1*, p. 29; *Committee Hansard*, 11 October 2018, p. 53.

179 *Committee Hansard*, 11 October 2018, p. 53.

180 *Submission 72*, [p. 2].

181 *Submission 1*, p. 23.

182 *Submission 1*, Annex V, Adverse Event Reporting in AMI Studies 1999–2002.

183 *Submission 1*, p. 38.

184 Defence, *Submission 1*, p. 38.

185 *Committee Hansard*, 11 October 2018, p. 56.

> …to the study team doctors through the structured interviews conducted at programmed intervals during the study, or by reporting to their supporting health element. If reported by the former, individuals were referred to the supporting health element…If symptoms were severe and thought to be associated with the antimalarial medication being taken, or if requested by the individual, the medication was ceased and an alternative provided.[186]

3.81 Adverse events reported by participants were recorded in both the study Case Record Form to gather data for the trial, and the health treatment data forms for individuals, which were later filed in individuals' medical documents.[187] Some submitters agreed that adverse events were documented in their records, such as Major Chapman (Rtd) and Mr King.[188]

3.82 Some submitters claimed that adverse events were systematically underreported during the trials. The committee heard various reasons for this, including differing perceptions or memories of the events. For instance, Ms Baker indicated that while the adverse events she experienced during the trial were documented as 'mild', she felt that they should have been recorded as more serious.[189] Another potential reason for the claimed underreporting was that participants were reluctant to report their experiences. Mr Ben Whiley explained:

> The minute you show any kind of weakness or anything, there's the mental stigma and your career is over. So many guys have had to hide what was going on to continue with their careers.[190]

3.83 Mr Michael Kruizinga suggested that participants were unlikely to disclose issues when they were about to deploy, go on leave or go home:

> When the soldiers hit the ground back in Townsville, the psych comes up to them and says, 'How was the deployment?' They say, 'Great,' because they are just about to go on post-deployment leave…I think these psych sessions were specifically designed to receive the answers that they got.[191]

3.84 Dr Nevin posited that confusion could also cause underreporting:

> …the user will confuse or misattribute side effects from the drug to the stresses of travel, to the effects of crossing time zones and to the effects of stress on deployment…Because of the tendency to misattribute adverse effects from mefloquine to the environment, it's inherently unsafe to use mefloquine and, I believe, tafenoquine, in a military environment.[192]

3.85 Mr Kruizinga made a similar point:

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186 Defence, *Supplementary submission 1.1*, p. 13.

187 Defence, *Supplementary submission 1.1*, p. 13.

188 *Proof Committee Hansard*, 5 November 2018, p. 37.

189 *Proof Committee Hansard*, 5 November 2018, p. 37.

190 *Committee Hansard*, 30 August 2018, p. 32.

191 *Proof Committee Hansard*, 5 November 2018, p. 5.

192 *Committee Hansard*, 11 October 2018, p. 5.

> Are there negative side effects? Yes. But does the soldier equate them with the drugs that they're taking when the doctor, who tells them that they're going to be taking these drugs, says, 'This drug is safe'? No, the soldier doesn't. When the psych says, 'Was there anything wrong?' they say, 'No, there's nothing wrong at all,' because then the soldier's thinking: 'Maybe it's all in my head. Maybe it's because I've been deployed. This is the first time I deployed. Maybe it's negative side effects. Maybe I've got PTSD.[193]

3.86 A few submitters alleged that the trial investigators themselves underreported adverse events. Dr Nevin compared the reports of psychiatric symptoms including abnormal dreams and insomnia in the trials to those indicated in the most recent meta-analysis of published data, and found rates of reported adverse events for mefloquine during the tafenoquine prevention trial were significantly lower than those reported in the meta-analysis.[194] He alleged this represented 'strong and compelling evidence that adverse drug reactions to mefloquine and tafenoquine, particularly neuropsychiatric adverse reactions, were significantly underreported among ADF personnel by the [AMI]'.[195] The AQVFA also made a range of allegations of systematic underreporting of adverse events by researchers.[196] For example, it raised concerns that not all instances of adverse events identified in the tafenoquine prevention trial were reported to the TGA separately.[197] However, as summarised in the next section, the committee heard that this was because there was no clinical reason to do so as it would not change the course of the follow up for participants, rather than due to clinical malpractice.[198]

3.87 When asked broadly about allegations of underreporting of adverse events by researchers, Professor Shanks, responded:

> It's not true. You can't do that and get your drug registered. The reporting of adverse events is quite detailed, and you don't know what you're going to get till the end. These clinical research forms are filled out as you go, and you report what you find. What that basically says is that we've been conducting fraudulent trials. We reject that assertion and say that the FDA and the TGA also assert that our trials were valid.[199]

3.88 Other witnesses including Mr Reid reiterated that there was no 'underreporting of adverse events during ADF studies; and these studies were audited

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193 *Proof Committee Hansard*, 5 November 2018, p. 5.

194 The Quinism Foundation, *Submission 17*, p. 10. Dr Nevin identified the following meta-analysis: M Tickell-Painter, N Maayan, R Saunders, C Pace, D Sinclair, 'Mefloquine for preventing malaria during travel to endemic areas', Cochrane Database of Systematic Reviews, 2017(10):CD006491.

195 The Quinism Foundation, *Submission 17*, p. 10.

196 *Submission 16*, pp. 18–24; *Supplementary submission 16.1*, pp. 5–10.

197 *Submission 16*, p. 21.

198 Mr Reid, *Supplementary submission 71.3*, p. 3.

199 *Committee Hansard*, 11 October 2018, p. 58. As noted above, the FDA audited the tafenoquine prevention and eradication trials.

by both the TGA and the FDA, including the consenting process'.[200] He noted the tafenoquine prevention trial involved a high rate of adverse reporting when compared to other tafenoquine studies.[201] Details on responses to adverse events in specific trials are summarised below.

Tafenoquine prevention trial

3.89 Some participants in this trial stopped taking the trial medication in response to adverse events.[202] For instance, a corporal who reported an adverse event to Mr Reid saw a psychologist, was put on anti-depressive treatment and was taken off the study drugs.[203] Defence summarised the adverse events during the trial as follows:

> The most common side effects of the tafenoquine prevention study were nausea, vertigo, diarrhoea, abdominal pain, abnormal dreaming and somnolence (drowsiness). 18 (4%) severe adverse events were recorded in the prevention study. These were not all necessarily drug related; for example three were injuries and six were gastroenteritis. No major side effects were observed in the eradication study and no severe neuropsychiatric adverse events were observed in any individuals taking tafenoquine in Defence.[204]

Vortex keratopathy

3.90 Some participants taking tafenoquine experienced benign, reversible 'changes on the surface of the eye (cornea) called vortex keratopathy'.[205] This did not affect participants' vision:

> …and would probably not have been found if the additional eye examination had not occurred. This reflects the high level of care afforded to the participants of the studies.[206]

3.91 The committee heard concerns that this finding was underreported, as only the first five cases were reported to ADHREC, TGA and the US Army Human Subject Research Review Board (HSRRB), rather than each of the 69 individual cases identified.[207] The trial study protocol required that:

> The [Ethics Review Committee] ERC/[Institutional Review Board] IRB must be informed by the investigator of all subsequent protocol amendments and of serious or unexpected adverse experiences occurring

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200 *Committee Hansard*, 30 August 2018, p. 19.

201 Mr Reid, *Supplementary submission 71.3*, pp. 5–6.

202 LTGEN Caligari, *Committee Hansard*, 31 August 2018, p. 22.

203 Mr Reid, *Committee Hansard*, 30 August 2018, p. 20.

204 *Submission 1*, p. 41.

205 Defence, *Submission 1*, p. 17; *Supplementary submission 1.1*, p. 10. See also GSK *Submission 8*, p. 4; GSK, *Supplementary submission 8.1*, p. 2.

206 Defence, *Supplementary submission 1.1*, p. 10.

207 AQVFA, *Submission 16*, p. 21; Mr Todd Connors, *Proof Committee Hansard*, 5 November 2018, p. 18.

> during the study which are likely to affect the safety of subjects or the conduct of the study'.[208]

3.92 However, Mr Reid explained that the corneal deposits did not constitute a Serious Adverse Event as they were 'asymptomatic findings'.[209] He added that a safety report was submitted to the US FDA and provided to the TGA. He emphasised that '[t]here was no clinical reason to submit all 69 reports to ADHREC initially as this did not change the course of the individual follow-up actions with the ADHREC, US Army HSRRB, US FDA and TGA for all subjects for this unexpected finding'.[210]

3.93 The study records of each of the 69 participants who were found to have experienced the corneal deposits were updated to include the findings.[211] At the direction of ADHREC, the follow up was extended from 6 to 12 months.[212] Defence noted that the 'volunteers were subsequently followed up by an ophthalmologist until the changes had fully resolved and all resolved within six months of return to Australia'.[213] Participants were also sent a letter with information on the vortex keratopathy.[214]

Tafenoquine treatment trial

3.94 Treatment was terminated early in four patients due to the finding of vortex keratopathy in the tafenoquine prevention trial.[215] However, no adverse events were reported during the treatment trial, and the medication was well tolerated.[216]

Mefloquine prevention trial

3.95 Participants 'who did not report side effects were still questioned about symptoms', and some received routine blood tests to check that there were no problems.[217] Participants experiencing significant adverse side effects:

> …were examined by medical and nursing officers, the medication was ceased, and the findings recorded while in Timor-Leste. 75 individuals (6.5%) were unable to tolerate the specific antimalarial they were assigned and had to be switched to an alternative…[218]

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208 Mr Reid, *Supplementary submission 71.5*, p. 3, (emphasis added).

209 *Supplementary submission 71.3*, p. 2.

210 *Supplementary submission 71.3*, p. 3. See also GSK, *Supplementary submission* 8.1, p. 2.

211 Defence, *Submission 1*, p. 38; Mr Reid, *Supplementary submission 71.3*, p. 3.

212 Mr Reid, *Supplementary submission 71.3*, p. 3.

213 Defence, *Supplementary submission 1.1*, p. 10.

214 A draft copy of the letter sent to participants with information on vortex keratopathy was included in the following submissions: Defence, *Submission 1*, Annex I, [pp. 180–181]; Name withheld, *Submission 47*, Annex B.

215 Defence, *Submission 1*, pp. 26, 38.

216 Defence, *Submission 1*, p. 26.

217 Defence, *Submission 1*, p. 23.

218 Defence, *Submission 1*, p. 23.

3.96 Defence stated that:

> 57%...of soldiers using mefloquine reported at least one adverse event, compared with 56% using doxycycline. The most commonly reported adverse effects of both drugs were sleep disturbance, headache, tiredness and nausea. There were three serious neuropsychiatric events reported in people taking mefloquine. Two of these individuals had undisclosed medical conditions that would have prevented the prescription of mefloquine if they had been known to medical staff.[219]

3.97 Defence 'has only identified two instances in which members may have had long term, continuing neuropsychiatric side effects after ceasing mefloquine, and no cases among those who took tafenoquine'.[220] Defence noted that it does not have details on the ongoing health of individuals once they leave the ADF.[221]

3.98 The IGADF investigation found that the:

> …medical support provided to the participants before, during and following the [mefloquine and tafenoquine prevention trials] was appropriate. There is no evidence any medical issue at the time was not followed up with appropriate and proper medical care.[222]

Follow up with trial participants

3.99 The AQVFA noted those who stopped participating in the trials early 'appear to have experienced little or no follow-up from the study team'.[223] Colonel Nasveld explained that some who withdrew 'would not have been in location in East Timor to go through the exact rigorous follow-up'.[224] A submitter from 4 RAR whose file was marked 'lost to follow up' stated:

> Due to my early return to Australia at no time did I have any contact from AMI staff in regards to the trial, I had received no debrief in regards to the trial…AMI had neglected in its duty of care to follow up on me...[225]

3.100 AVM Smart indicated that those who withdrew due to illness 'wouldn't have been followed up for the study purposes per se through the normal means', but they would have been 'followed up in terms of the most appropriate medical treatment'.[226]

3.101 In addition, the committee heard varying perspectives on the adequacy of follow up with participants who completed the trials. Defence described participants

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219 *Submission 1*, p. 23.

220 Defence, *Submission 1*, p. 41.

221 *Submission 1*, p. 41.

222 IGADF, *Inquiry report*, p. ii.

223 *Supplementary submission 16.3*, p. 5.

224 *Committee Hansard*, 11 October 2018, p. 54.

225 Name withheld, *Submission 76*, pp. 4, 7–8.

226 *Committee Hansard*, 11 October 2018, p. 54.

receiving 'intense monitoring and health support' during and after the trials, more regular health reviews and blood tests.[227] After the trials, participants:

> …were followed up for six to 12 months from the end of the studies, which was considered enough time for late onset side effects to present. Participants were also given a study card that advised them and their medical practitioner of what to do and who to contact if they were to develop fever during or in the six months after the study.[228]

3.102 While many submitters recalled experiencing something similar to Defence's description, they did not perceive this to be sufficient. For example, Mr Colin Brock reflected that the study card 'was the only thing we received ever, in 18 years, from them'.[229] Details on the follow up for specific trials are outlined below.

Tafenoquine prevention trial

3.103 Mr Wayne Karakyriacos recalled undergoing tests, providing blood samples and speaking with medics at the end of his deployment.[230] However, he viewed this as insufficient to address his ongoing challenges during subsequent years, stating: 'All that time I was untreated. I not once had Defence approach me or the AMI approach me to follow up to see how I was going. Not once did they come back'.[231]

3.104 Defence conveyed a different view of the adequacy of the follow up, noting that 'personnel were monitored closely during the study and for six months afterwards'.[232] Colonel Nasveld insisted the 'follow-up was conducted according to the protocol, and that's well documented in the case record forms for all the participants' apart from those who withdrew from the trial early.[233] The FDA audit only made a minor finding relating to the final telephone follow-up of the trial. Some participants were followed up two months late, however:

> The variance demonstrated the diligence of researchers in continuing to conduct telephone follow-up until all study participants could be contacted, even when outside the stated time limits of the protocol. It was acknowledged that this was indicative of the study team personnel doing all possible to ensure the ongoing welfare of the study participants.[234]

3.105 The committee understands that all participants in the trial received letters informing them that they had taken mefloquine, though 492 had taken tafenoquine.

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227 *Submission 1*, pp. 27–28.

228 Defence, *Submission 1*, p. 28.

229 *Committee Hansard*, 31 August 2018, pp. 16–17.

230 *Committee Hansard*, 31 August 2018, p. 10.

231 *Committee Hansard*, 31 August 2018, pp. 10–11.

232 *Submission 1*, p. 25.

233 *Committee Hansard*, 11 October 2018, p. 54.

234 Defence, *Supplementary submission 1.1*, p. 5.

This was corrected with subsequent correspondence.[235] As noted above, tafenoquine recipients were advised that some participants had developed vortex keratopathy.[236]

3.106 AVM Smart explained to the committee that:

> …as well as the actual specific follow-up that we did as part of the study and interactions during the study we had ongoing health surveillance activities happening. That included post-deployment psychological screening…conducted with proper psychological screening instruments. It is actually designed to pick up things like PTSD and other stressors.[237]

The '100 Club'

3.107 Approximately 100 participants were selected for additional testing and assessment before, during and after deployment.[238] This included 'eye and lung function tests that were done before (within three weeks) and after (within four weeks) deployment, and the taking of an additional 20mls of blood'.[239] Several submitters described this testing, such as Mr Aaron King, who recalled having blood, lung and eye tests.[240] A few submitters suggested that they were also anticipating other medical checks that did not occur.[241] For example, Mr Brock underwent tests after six or seven months on deployment, and recalled being 'told there would be follow-up tests in six months and in 12 months, but these never eventuated'.[242]

Mefloquine prevention and tafenoquine eradication trials

3.108 Submitters differed in their view of what adequate follow up entails. For example, Defence indicated that follow up, including the provision of an information card, was provided over several months following return to Australia.[243] However, Mr Fleming indicated that this was insufficient, recalling that a review was not undertaken following the mefloquine trial (other than a one-page survey), and noting that he was never spoken to by a doctor or a trial facilitator about his experience.[244] Similarly, Major Chapman (Rtd) described the follow up from the tafenoquine eradication trial as 'pretty poor', and stated:

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235 Defence, *Supplementary submission 1.1*, p. 14.

236 A draft copy of the letter sent to participants with information on vortex keratopathy was included in the following submissions: Defence, *Submission 1*, Annex I, [pp. 180–181]; Name withheld, *Submission 47*, Annex B.

237 *Committee Hansard*, 11 October 2018, p. 54.

238 Defence, *Supplementary submission 1.1*, p. 9.

239 Defence, *Supplementary submission 1.1*, p. 9. The submission provided additional details on the testing.

240 *Proof Committee Hansard*, 5 November 2018, p. 34.

241 Name withheld, *Submission 56*, [p. 1].

242 *Committee Hansard*, 31 August 2018, pp. 8, 16–17.

243 *Submission 1*, p. 24.

244 *Proof Committee Hansard*, 30 August 2018, p. 32; *Submission 72*, [p. 3].

> I completed the trial documents. They were forwarded away and that was it—I didn't hear a thing afterwards. No-one came to me and said, 'You've been reporting headaches and nausea; let's see what's going on with it.' That was it; it was up to me to look after myself.[245]

3.109 In contrast, Defence stated '[a]ll participants were followed up for 12 months after completion of the eradication course'.[246]

General healthcare available to ADF members

3.110 Submitters did not appear to consider general health services to count as trial follow up:

> There was no specific test or survey conducted for soldiers with regards to assessing their mental health following the drug trial…All soldiers returning from East Timor conducted post screening psychology interviews but I believe this was in no way linked to the drug trial...[247]

3.111 Nevertheless, trial participants (including those who ceased the trial early) would have had access to the range of healthcare services available to ADF members. Defence detailed the comprehensive health services available to all members (including trial participants) throughout their service careers, including:

- return to Australia medical examinations at the end of deployments;
- Return to Australia Psychological Screen (RtAPS) (questionnaire and screening interview);
- post-deployment assessments conducted three months after return to Australia;
- Post Operational Psychological Screening (questionnaire and screening interview) between three and six months after RtAPS;
- general GP services;
- access to psychology and mental health services;
- annual health assessments (prior to 2011), now periodic health assessments; and
- separation health assessments, including formal psychological screening.[248]

3.112 Following separation from the ADF, veterans can access the ADF post-discharge GP health assessment, and other services through DVA.[249] The next chapter includes more information on services available to veterans.

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245 *Proof Committee Hansard,* 5 November 2018, p. 27.

246 *Submission 1*, p. 25.

247 Name Withheld, *Submission 47*, p. 4.

248 *Submission 1*, pp. 28–29.

249 Defence, *Submission 1*, p. 29.

Chapter 4

Assistance and support for veterans

Introduction

4.1 An area of unanimous agreement in this inquiry is the utmost importance of individuals who are unwell being able to access appropriate support and assistance. The role of both the Department of Defence (Defence) and the Department of Veterans' Affairs (DVA) in offering and providing support and assistance was a key focus in much of the evidence received by the committee.

4.2 The committee spoke with some veterans who were clearly in need of immediate assistance and many of these individuals had been trying to access support for some time. As noted earlier in the report, the committee was pleased that representatives from DVA were in attendance at hearings and available to provide assistance and support to individuals and families in immediate need if they wished to speak with them.

4.3 This chapter discusses the matters raised with the committee in relation to the provision of assistance to veterans, with particular reference to assistance with their health concerns. It covers the actions taken to date by Defence and DVA; veterans' experiences with accessing assistance; barriers to accessing assistance; the assistance and support being sought; and addressing veterans' concerns moving forward.

Summary of Government actions to date

4.4 As noted in Chapter 1, this committee tabled the report, titled *Mental health of Australian Defence Force members and veterans*, on 17 March 2016. The report included two recommendations in relation to mefloquine.[1]

4.5 Responding to the committee's recommendations from the report, on 15 September 2016, the Minister for Veterans' Affairs, the Hon Dan Tehan MP announced that the government would:

- establish a formal community consultation mechanism to provide an open dialogue on issues concerning mefloquine between the Defence Links Committee and the serving and ex-serving ADF community;
- develop a more comprehensive online resource that will provide information on antimalarial medications;
- establish a dedicated DVA mefloquine support team to assist our serving and ex-serving ADF community with mefloquine-related claims, which will provide a specialised point of contact with DVA; and

1 Senate Foreign Affairs, Defence and Trade References Committee, *Mental health of ADF serving personnel*, 17 March 2016. See Recommendations 5 and 6.

- direct the inter-departmental DVA-Defence Links Committee to examine the issues raised, consider existing relevant medical evidence and provide advice to the Government by November 2016.[2]

4.6 With particular reference to these actions identified by the Minister for Veterans' Affairs, the committee asked witnesses at its public hearings in Brisbane and Townsville for their perspective on the progress of recommendations. While noting that witnesses would likely be unaware of the DVA-Defence Links Committee action, it was disappointing to note that several witnesses indicated they were completely unaware of the other actions.[3]

4.7 Following the hearing, Senator Alex Gallacher wrote to the Minister for Veterans' Affairs, the Hon Darren Chester MP, seeking advice on the progress of the announcements from the Government.

4.8 On 18 September 2018, the Minister wrote to the committee and included the following update:

> With respect to the commitments made by the then Minister for Veterans' Affairs, the Hon Dan Tehan MP, I can advise these have either been met or are ongoing. I draw the Committee's attention to the submission to the inquiry from DVA which provides more information about services and supports available to veterans and their families; and the future action plan involving further outreach, communications and research in this area.[4]

4.9 While it is disappointing that there was little awareness of the response to the recommendations within the community the actions were designed to assist, the committee is aware that Defence and DVA have both undertaken a series of key actions in response to the issues and concerns raised about antimalarial use which are outlined below and throughout the chapter.

Department of Defence response

Key message

4.10 Defence has indicated that its response to concerns about the use of antimalarial drugs has 'been designed to provide current and former serving members with information about the medications of concern, detail on the studies, and to encourage them to seek help'.[5] A key message from Defence has been to encourage

2 The Hon Dan Tehan MP, Minister for Veterans Affairs, 'Addressing mefloquine concerns', *Media Release*, 15 September 2016.

3 Mr Greg Jose, *Committee Hansard*, 31 August 2018, p. 3; Mr Colin Brock, *Committee Hansard*, 31 August 2018, p. 8; Mr Wayne Karakyriacos, *Committee Hansard*, 31 August 2018, p. 8.

4 Correspondence from Minister for Veterans' Affairs, The Hon Darren Chester MP, response to Committee Chair, received 18 September 2018.

5 *Submission 1*, p. 30.

individuals with concerns to consult their treating medical practitioner and to consider putting in a claim with DVA.[6]

4.11 On 30 November 2015, Defence issued a statement on the use of mefloquine in the ADF and advised that 'if any ADF member, past or present is concerned that they might be suffering side-effects from the use of mefloquine defence encourages them to raise their concerns with a medical practitioner so they may receive a proper diagnosis and treatment'.[7]

Comprehensive website

4.12 In February 2016, VADM Griggs told the Senate Foreign Affairs, Defence and Trade Legislation Committee about the need for their actions to balance the provision of information with the need to avoid causing undue concern for people who are well:

> I would like to make the point that we are now in about month 7 of a pretty sustained media campaign about mefloquine. What we have been trying to do is to get out as much information as possible in as transparent a manner as possible to allay the fears of serving and former serving members of the ADF about the use of this drug, because the nature of the reporting and the nature of this campaign has elevated concern levels amongst people who do not need to be as concerned as they now are. We are actually quite concerned about that. One of the things we have just completed is a series of web pages, which is now available on the Defence internet site, which I think is a very comprehensive and transparent articulation of all the issues around antimalarials, not just mefloquine, in use in the ADF.[8]

4.13 In order to provide information to concerned veterans and their families, Defence developed a comprehensive external website on malaria, mefloquine and the ADF and established an email address where individuals can request further information.[9]

Information for families

4.14 Defence advised that information for families concerned about antimalarial use continues to be available by contacting the dedicated email address as well as accessing information from their website.[10]

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6 Department of Defence, *Submission 1*, p. 3.

7 See https://news.defence.gov.au/media/media-releases/statement-use-mefloquine-adf, accessed 27 June 2018.

8 VADM Ray Griggs, VCDF, Senate Foreign Affairs, Defence and Trade Legislation Committee, *Estimates Hansard*, 10 February 2016, pp. 173-174.

9 See http://www.defence.gov.au/health/healthportal/malaria/default.asp, accessed 16 July 2018. See also http://www.defence.gov.au/Health/HealthPortal/Malaria/Documents/160402%20-%20Townsville%20forum.pdf, accessed 16 July 2018.

10 *Submission 1*, p. 43.

4.15 In its submission Defence also described other support services available to families for a variety of reasons and not specifically related to concerns about antimalarial use such as the ADF Family Health Program, the All-hours Support Line, the Defence Family Helpline and the Veterans and Veterans Families Counselling Service (VVCS).[11]

Research

4.16 To inform its ongoing response to these issues, Defence has undertaken or commissioned research into a number of matters relating to its use of antimalarials and in particular mefloquine, including:

- a review of Medical Employment Classification outcomes of those who participated in the Timor-Leste trials. This has shown no significant differences in the incidence of becoming medically unfit for service, or diagnosis of PTSD between those who were prescribed mefloquine and those prescribed other anti-malarial medications;[12]
- a comprehensive literature review on mefloquine commissioned from Professor Sandy McFarlane AO, Director of the University of Adelaide Centre for Traumatic Stress Studies;[13] and
- commissioned (jointly with DVA) the University of Queensland to undertake a research study involving the re-analysis of health study data on anti-malarial use from the 2007-2008 Centre for Military and Veterans' Health deployment health studies.[14] Further information on this is outlined below.

Department of Veterans' Affairs response

Mefloquine support team

4.17 In accordance with the government commitment announced in September 2016, DVA established a dedicated mefloquine support team within their claims area to respond to inquiries about mefloquine. DVA advised the committee that the team 'did not receive many calls' and that team was subsequently put onto other duties within the claims area. In September 2018, DVA added information to their phone line, prompting callers to dial zero to speak to someone in relation to mefloquine but again they did not receive many calls.[15]

Support for GPs

4.18 DVA has provided information to general practitioners (GPs) to assist them to provide support to veterans who may have concerns about mefloquine:

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11 *Submission 1*, p. 44. VVCS is now called Open Arms—Veterans and Families Counselling.

12 Defence, *Submission 1*, p.42.

13 http://www.defence.gov.au/Health/HealthPortal/Malaria/Documents/160822-Mefloquine-and-suicide.pdf, accessed 16 July 2018.

14 DVA, *Submission 2*, p. 6.

15 Ms Cosson, *Committee Hansard*, 11 October 2018, p. 63.

- DVA's Principal Medical Adviser wrote to all GPs on 30 September 2016 and to the Primary Health Network in October 2016 to bring information about mefloquine to their attention;[16] and
- DVA organised and hosted a briefing with GPs in Townsville on 29 November 2016.[17]

Information event

4.19 In December 2016, DVA held an event, referred to as an 'outreach program',[18] in Townsville which was attended by more than 90 members of the community concerned about antimalarial medications such as mefloquine. Defence supported this event.[19] As noted earlier, the government committed to establishing a formal community consultation mechanism on issues concerning mefloquine and the Townsville 'outreach program' was the first step.[20]

Support for families

4.20 DVA provides support to veterans' partners and families through funding a range of health services as well as the front line mental health services provided through Open Arms—Veterans and Families Counselling (formerly VVCS).[21]

DVA's Future Action Plan

4.21 In its submission, DVA noted it has 'prepared an action plan to address [veteran] community concerns about potential effects of mefloquine that includes outreach activities, communications and research'.[22] Following the outreach program conducted in Townsville in December 2016 (in collaboration with the Repatriation Medical Authority (RMA), VVCS and with the support of Defence), DVA is conducting consultation forums across other capital cities. The submission noted that these will be publicised through advertisements in newspapers and services newspapers, as well as direct invitations to relevant organisations, and individuals where possible.[23]

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16 DVA, *Submission 2*, p. 5.

17 Defence, response to journalist, 6 December 2016, http://www.defence.gov.au/Health/HealthPortal/Malaria/Resources/media-statements.asp, accessed 16 July 2018.

18 Note: Veterans were very clear with the committee that they did not see this event as fitting their definition of 'outreach'. Detailed later in this chapter the committee heard about the next series of consultation forums being held by DVA.

19 *Submission 1*, pp. 31, 35.

20 See https://www.dva.gov.au/about-dva/publications/vetaffairs/vol-33-no1-autumn-2017/townsville-mefloquine-outreach-program, accessed 19 July 2018.

21 *Submission 2*, pp. 45.

22 *Submission 2*, p. 5.

23 *Submission 2*, p. 5.

4.22 Ms Liz Cosson AO CSC, Secretary, DVA, provided further detail about these consultation sessions at the hearing in Canberra. A series of sessions were planned in different locations throughout October and November. Further sessions in different locations would be considered should there be sufficient demand.[24] These consultation forums are further discussed later in the chapter.

DVA funded health treatment and compensation claims

4.23 The support provided to veterans who have been injured or suffered illness as a result of their service (including illness or injuries related to antimalarial medication) fall broadly into three categories—compensation, income support and health treatment. To access compensation and income support, a veteran needs to make a claim and show to the relevant standard of proof that they have suffered an illness or injury, and demonstrate that this condition was related to their service.[25]

4.24 In relation to health treatment, there are two pathways by which veterans may access DVA-funded services:

- Under the *non-liability pathway*, veterans can apply for access to treatment for mental health conditions without the need to show that the condition is related to service.
- Under the *liability pathway*, veterans can make a claim which DVA will then assess to establish whether the condition was related to service. If the claim is accepted, the veteran's entitlement to compensation and income support will then be assessed, and the veteran will be eligible for DVA-funded health treatment for the condition.[26]

4.25 In addition, all former serving personnel can access a comprehensive health assessment from their GP.[27] Independent of the claims process, mental health services are also available from Open Arms—Veterans and Families Counselling to all current and former serving personnel.[28]

4.26 Serving and ex-serving ADF members can claim compensation at any time for medical conditions they believe are related to their service. For DVA to accept liability for compensation there has to be a causal link determined between the person's service and their medical conditions. Under the *Veterans' Entitlements Act 1986* (VEA) and the *Military Rehabilitation and Compensation Act 2004* (MRCA) the potential link between a medical condition and service is assessed using Statements of Principles (SOPs).[29] SOPs are discussed later in this chapter.

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24 *Committee Hansard*, 11 October 2018, p. 64.

25 DVA, *Submission 2*, p. 2.

26 DVA, *Submission 2*, pp. 2–3.

27 DVA, *Submission 2*, p. 3.

28 DVA, *Submission 2*, p. 4.

29 RMA, *Submission 4*, p. 4.

Veterans' experiences with accessing assistance

4.27 The committee explored with individuals their experiences of accessing assistance; whether they had tried to access assistance, and if so, the details of that experience. The committee also spoke to veterans who had not accessed assistance and explored the reasons why not, as well as the assistance they are seeking.

Veterans who are accessing services and receiving help

4.28 Some individuals appeared to be accessing assistance. While acknowledging it had taken some time to access, Mr Mark Armstrong described the services he is receiving:

> I have access to a neurologist and a neuropsychologist, a psychiatrist and a psychologist because of my PTSD tag, so I'm able to get certain treatments through that. Other things like my brain injury—my eighth cranial nerve is 31 per cent more damaged on my right-hand side than on my left-hand side. As I was walking, I'd fall to my right, so I went and got that tested. That was through the PTSD as well. I suppose I'm one of the lucky ones—because I have a TPI [Totally and Permanently Incapacitated] gold card I have access to a lot of different medical things that other people don't.[30]

4.29 Another submitter explained their experience as follows:

> My health conditions are accepted by DVA and I consider I have been well looked after with treatment, hospitalisation and incapacity payments. My military super was converted to an invalidity pension at discharge. None of my accepted conditions contain reference to Mefloquine although my medical documents do so.[31]

Families/partners

4.30 A small number of partners and family members also advised that they have accessed some support services through DVA, including counselling services from Open Arms.[32] While some indicated that support had been of some assistance, others reported that the experience had not been helpful.[33]

4.31 However, Mrs Susan Armstrong spoke positively about her participation in the Female Veterans and Families Forum. While she noted there is limited opportunity to discuss personal circumstances in detail due to the number of issues in these forums, it did provide an opportunity 'to get to [speak to] someone in a meeting break'.[34]

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30 *Committee Hansard*, 30 August 2018, p. 12.

31 Name withheld, *Submission 61*, p. 1.

32 See for example Mrs Mary Bush, *Proof Committee Hansard*, 5 November 2018, p. 15.

33 See for example Mrs Susan Armstrong, *Committee Hansard*, 30 August 2018, p. 17.

34 *Committee Hansard*, 30 August 2018, p. 16.

Veterans who are getting assistance but believe it is not working

4.32 Some veterans explained that while they are receiving help, their current treatment and support has not been very successful in improving their health.[35]

4.33 Mr Stuart McCarthy explained that although some of his claims to DVA for issues such as depression and anxiety have been accepted, the available treatment predominately consisted of medication which has not been of great benefit.[36]

4.34 Mr Aaron King advised that he was classified as Totally and Permanently Incapacitated (TPI) some years ago and been diagnosed with PTSD but that the treatment he has received to date has not been effective:

> I'm TPI. I was made TPI years ago, not as a part of this [use of antimalarials]. We only just found out about this a couple of years ago, about the symptoms. It was put down to PTSD for me. I've got lots of side effects and problems. It's always just been put down to PTSD. Treatment-wise, there's Ward 17 at Heidelberg. Now they don't really want me to go, because they've exhausted all avenues. There's no treatment. I've had [Electroconvulsive Therapy and Transcranial Magnetic Stimulation] ECT, TMS [Transcranial Magnetic Stimulation] and pretty much every medication. I've been in and out of psych wards. I've been thrown in jail because they felt there was no other safe place for me at times.[37]

4.35 Mrs Naomi Kruizinga explained that the medications given to her husband, Mr Michael Kruizinga, have not helped:

> Many times before, Michael has been given a bandaid, or a temporary fix, to stop his suicidal ideation—more mood stabilisers under the PTSD umbrella—with most of his network of psychologists and psychiatrists linking it to just severe depression. Yet he suffers from the neurotoxic properties of these drugs that were given. None of the medications have worked since he commenced them over a year ago. If anything, they have made him worse.[38]

Veterans who are not receiving or seeking assistance

4.36 Worryingly, some veterans told the committee that they are not accessing help from DVA. In some cases, this was due to a lack of trust in the process. In other cases, it was suggested that veterans do not have a diagnosis and/or have not been able to access treatment and support because the effects of antimalarial medications are not recognised under a single SOP. This is further discussed later in the chapter.

4.37 Ms Anne-Maree Baker explained:

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35 Mr Chris Ellicott, *Proof Committee Hansard*, 5 November 2018, p. 49; Mr Aaron King, *Proof Committee Hansard*, 5 November 2018, p. 29; Mr Michael Bush, *Proof Committee Hansard*, 5 November 2018, p. 15.

36 *Committee Hansard*, 30 August 2018, p. 8.

37 *Proof Committee Hansard*, 5 November 2018, p. 29.

38 *Proof Committee Hansard*, 5 November 2018, p. 1.

> I have not used the phone lines and made claims for compensation with DVA because I am undiagnosed. None of my illnesses are attributed or connected to this trial because nothing has been reported correctly.[39]

4.38 Mr Stuart McCarthy told the committee that he has submitted claims for cognitive impairment which have not been accepted. Further to this, Mr McCarthy stated:

> …What's not happening—we are being refused the support (a) that we need and (b) that we have actually asked for. And that's exactly the situation that I'm in.[40]

4.39 Other veterans also discussed this issue. Mr Wayne Karakyriacos reported that '[a] lot of veterans have gone bush and a lot of them are hiding'.[41] Mr Desmond Rose told the committee that 'most of us don't contact DVA about tafenoquine anyway…'.[42]

4.40 One veteran, Mr Brian Carlon, is receiving assistance but reported that dealing with DVA is difficult:

> Everything I've done with DVA is a fight, and that fight takes its toll. I have nothing to do with DVA except: when they send me a letter, I will send it back. I don't ring them. I don't contact them. It's too hard on me, because it is a fight.[43]

Barriers to accessing assistance

4.41 As the committee was told that assistance is available and some witnesses described their experiences of positive support, the committee explored the reasons why some veterans are not accessing support. These include: ADF cultural issues, lack of information and difficulties navigating the claims process.

Cultural issues

4.42 As briefly noted in Chapter 3, some veterans suggested that the nature of the ADF environment means it is difficult to report health concerns or to question authority for fear of showing weakness and the potential impact on career progression.

4.43 On a similar theme, some veterans reported that it is difficult to ask for assistance. Colonel Ray Martin (Rtd) explained as follows:

> Certainly in my experience, and you've heard it today, men and women in the ADF are self-reliant and very well trained. They're kind of tough on the outside. As soon as they admit there's a mental health issue, even though

39 *Proof Committee Hansard*, 5 November 2018, p. 28.

40 *Committee Hansard*, 30 August 2018, p. 8.

41 *Committee Hansard*, 31 August 2018, p. 13.

42 *Committee Hansard*, 31 August 2018, p. 13.

43 *Proof Committee Hansard*, 5 November 2018, p. 24.

> the system says 'come seek help', the reality is you think that if you put up your hand there's a career detriment to that.[44]

4.44 Mr Rose told the committee that he has only recently started to seek support for PTSD due to the challenges of seeking help:

> It's something you don't like to admit. It's a bit hard, being a man and saying you've got mental problems. It's not the best.[45]

4.45 Mr Kruizinga acknowledged these cultural issues and suggested that there needs to be more assistance when a soldier transitions to civilian life.[46]

Lack of information

4.46 Mr Colin Brock reported that information about the trials has not been shared between Defence and DVA:

> I guarantee DVA doesn't know that we were on mefloquine or tafenoquine. How does DVA know? Defence hasn't told them. We haven't told them.[47]

Mefloquine support line

4.47 As outlined earlier in the chapter, DVA established a dedicated mefloquine support line to assist veterans who were concerned about antimalarials. Veterans and their families told the committee about their difficulties getting advice from this dedicated team.[48]

4.48 Mr Mark Armstrong explained his experience seeking information via the DVA dedicated mefloquine line:

> They [DVA] told me that they didn't have a list of mefloquine users and to contact the Department of Defence. They did give me a number for that, and the Department of Defence told me to contact DVA. So I contacted DVA, and we went back and forth a few times. There was supposed to be some special team that looked after it. Then, after a while, a lady rang me back, and she was in a special team—I think they call it a special team or something along those lines—who don't just look after mefloquine; they look after anything special.[49]

4.49 In a supplementary submission from the Australian Quinoline Veterans and Families Association (AQVFA), Mr McCarthy described his experience contacting the dedicated mefloquine support team in DVA. Mr McCarthy details two phone calls he made to the dedicated number in August and September 2018 seeking information

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44 *Committee Hansard*, 31 August 2018, p. 37.

45 *Committee Hansard*, 31 August 2018, p. 17.

46 *Proof Committee Hansard*, 5 November 2018, p. 5.

47 *Committee Hansard*, 31 August 2018, p. 13.

48 Mrs Raelene King, *Proof Committee Hansard*, 5 November 2018, pp. 30–31; Mr Mark Freer, *Proof Committee Hansard*, 5 November 2018, p. 48.

49 *Committee Hansard*, 30 August 2018, p. 15.

about the ADF use of tafenoquine. On both occasions, officers were unable to provide responses to questions. He reported:

> The 'dedicated mefloquine support team' was announced by DVA in 2016. The DVA Secretary has stated that this dedicated team and toll free number are part of her focus 'on the treatment for veterans who need assistance', however the staff of the 'dedicated mefloquine support team' do not hold contact information for healthcare providers and are unaware of the most basic, factual information regarding the ADF's use of mefloquine and tafenoquine.[50]

4.50 Following feedback from veterans, the committee was told that DVA made additional changes to the support line in October this year. The mefloquine support line is now answered by a team in Canberra that comprises:

> …some higher-level staff that actually understand the detailed nature of our SOPs and who can help any veteran that phones that dedicated line to assist with their claims—particularly to assist them to access treatment. [51]

DVA claims process

4.51 The committee heard about the difficulties experienced by some submitters trying to navigate the DVA claims process, and that some veterans and their families found it daunting or demoralising.[52] Some witnesses explained that they were assisted to submit their claims by an advocate but even with such assistance, veterans provided examples of the claims process taking up to 10 years.[53]

4.52 The committee heard that support is available to assist to navigate the claims process. For example, Ms Cosson, Secretary of DVA, told the committee:

> We're happy to sit down with a veteran and help them put forward what they are claiming. Certainly in the…consultation—that we had in Adelaide and we propose having around the country, where a veteran does present, which happened in Adelaide, we're able to sit down with them and help them through the claiming process.[54]

4.53 Professor Nick Saunders AO, Chairperson of the Repatriation Medical Authority (RMA), emphasised the importance of using an advocate to help navigate the system:

> …there are a lot of veterans who actually could establish a causal link between their service and their health today if they actually went through it in a systematic way with their advocate and looked at a range of statements and principles and a range of conditions that they might have. For example,

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50 *Submission 16.4*, p. 3.

51 Ms Cosson, *Committee Hansard*, 11 October 2018, p. 63.

52 See for example Mr Wayne Karakyriacos, *Committee Hansard*, 31 August 2018, p. 11.

53 Mr Michael Bush, *Proof Committee Hansard*, 5 November 2018, p. 15; Mr Brian Carlon, *Proof Committee Hansard*, 5 November 2018, p. 22.

54 Ms Cosson, *Committee Hansard*, 11 October 2018, p. 62.

> we have a statement of principle for post-traumatic stress disorder. Indeed, the people who are advocating for chronic brain injury being caused by mefloquine say that there is significant overlap in the symptoms and there's confusion in the system. Well, if one does have post-traumatic stress disorder, it almost certainly will be able to be related to the service, and it will be able then to related to access to appropriate treatment and compensation—although…access to treatment is less of an issue now [that the non-liability pathway has been established].[55]

Liability and non-liability pathways

4.54 As previously noted, veterans may access DVA-funded services through two pathways. DVA stressed to the committee that there is help available to veterans in need under the non-liability pathway which does not need to be connected to service-related activities:

> In relation to any treatment for anything that's part of the [Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition] DSM-5, which is anything to do with a mental health condition, which includes brain injury, our veterans are eligible for free treatment. There are two pathways to get treatment with the Department of Veterans' Affairs. The first is through that non-liability line, where you don't need to prove your condition is related to service, and we will get you straight into treatment.[56]

4.55 Mr Kruizinga was positive about the establishment of the non-liability pathway:

> In recent times, DVA have added a new strain of help that they call 'non-liability health care'. I believe this is a great step forward—it means that any soldier can then go and find help for their mental health—but I think that's a DVA umbrella trying to hide the issue that we are talking about today.[57]

4.56 Mrs Kruizinga described how this change made a difference to the circumstances of her husband and family:

> When he was admitted into psychiatric in February for a month, he was only on the white card at that stage. I had to fight tooth and nail to keep him there, and they were wanting us to pay the cost, which was quite exorbitant. I was going to have to pull him out, because there is no way we could afford that. I think a week into his stay, this non-liability kicked in, which was great…otherwise I would have had to pull him out.[58]

4.57 Alternatively, veterans can submit claims through the liability pathway. DVA assesses these claims to establish whether the condition was related to the claimant's service. Claims are also assessed against Statements of Principles (SOPs). These inform decisions regarding claims for compensation or liability for service injuries,

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55 *Committee Hansard*, 15 October 2018, p. 5.

56 Ms Cosson, *Committee Hansard*, 11 October 2018, p. 60.

57 *Proof Committee Hansard*, 5 November 2018, p. 8.

58 *Proof Committee Hansard*, 5 November 2018, p. 8.

diseases and death under the legislation relevant to DVA.[59] SOPs are set out by the RMA, which noted that SOPs 'state the factors which 'must' or 'must as a minimum exist if service is to be accepted as contributing to a particular kind of disease, injury or death'.[60] Professor Saunders emphasised that:

> If an exposure can be causally related to a disease or injury then it can become a factor within a statement of principles, but we do not make statements of principles relating to exposures to drugs, toxins or those sorts of things.[61]

4.58 DVA explained that when a veteran makes a liability claim in relation to the use of antimalarials, it is necessary for DVA to establish that:

- the claimant had a diagnosable condition answering the claim;
- the claimant had taken a relevant antimalarial medication;
- the relevant SOPs (if one has been determined by the RMA) includes a causal factor relating to the use of that medication;
- any other requirements set out in the SOP factor are met; and
- the use of the antimalarial medication was related to the person's service.[62]

Statements of Principles with factors relating to mefloquine or tafenoquine

4.59 DVA advised that the RMA has included mefloquine and tafenoquine, either by name or in more general terms, as a potential causal factor in the SOPs for a total of sixteen conditions: 16 for mefloquine and six for tafenoquine.[63] The RMA told the committee that they:

> …are confident that we have included mefloquine or tafenoquine in statements of principle for all diseases or injuries which could be linked to taking these drugs based upon sound medical scientific evidence that meets standard epidemiological criteria when examining things for causation.[64]

4.60 The RMA noted that 'the wording of the mefloquine- or tafenoquine-related factors in these SOPs requires a close temporal link between the taking of the drug and the onset of the condition…reflecting the well-accepted evidence that these agents can have acute neuropsychiatric effects'.[65] Ms Cosson suggested that if a trial

59 RMA, *Submission 4*, p. 4.

60 RMA, *Submission 4*, p. 4.

61 *Committee Hansard*, 15 October 2018, p. 1.

62 *Submission 2*, p. 7.

63 The list of relevant SOPs was provided in the RMA submission: RMA, *Submission 4*, Attachment 2. DVA, *Submission 2*, p. 7.

64 *Committee Hansard*, 15 October 2018, pp. 12.

65 RMA, *Submission 4*, p. 6.

participant reported an adverse event during the trial, DVA may be able to use Defence's records to assist with establishing this temporal link required by the SOPs.[66]

4.61 As noted in Chapter 2, Professor Saunders emphasised that the RMA takes a very generous view of evidence when they write the SOPs.[67] Therefore in his view the key for many veterans is getting assistance from an advocate for example to establish a causal link between their service and their current health conditions as:

> …when the department has conducted reviews in the past about claims that have been turned down or groups of claims being turned down for a particular injury, when one looks through the list, there are many other factors whereby those people could have legitimately claimed and got access to compensation through the standard route. So there is access to the system. The statements of principles cover 94 per cent of the claims that are made in the department, and there is a higher rate of success for claims based on a statement of principle than for those six or so per cent of claims that are made, really, not based on statements of principle but relying upon medical opinion, and the like. So the system is there for people to be able to gain access to the outcomes of the system and assessment.[68]

4.62 Acknowledging the chronic and complex symptoms being presented to the committee, Professor Saunders also raised the SOP concerning 'chronic multisymptom illness' determined in 2014:

> We have a statement of principle on an illness called chronic multisymptom illness. This arose out of an inquiry that we conducted in relation to Gulf War syndrome. Although this did not satisfy the Gulf War advocate group that was presenting to us, it became quite clear to us that there were a significant number of veterans who had quite debilitating symptoms that fitted into particular patterns of illness, but this wasn't related just to serving in the Gulf War. In fact, it was related more broadly to deployment into hazardous environments. So we wrote a statement of principle called 'Chronic multisymptom illness'. That statement of principle is available today for those people who were deployed to, say, East Timor, took antimalarial drugs and now have debilitating symptoms that are broad-ranging.[69]

Antimalarial-related claims

4.63 DVA 'has maintained a record of specific claims relating to antimalarial medications since September 2016'.[70] As of 30 July 2018, 42 veterans had lodged 53

66 *Committee Hansard*, 11 October 2018, p. 62.

67 *Committee Hansard*, 15 October 2018, p. 8.

68 *Committee Hansard*, 15 October 2018, p. 5.

69 Professor Saunders, *Committee Hansard*, 15 October 2018, p. 5. See Statement of Principles concerning chronic multisymptom illness No. 55 of 2014.

70 DVA, Response to questions on notice from 11 October 2018 public hearing (received 1 November 2018), [p. 1].

claims since reporting commenced.[71] As at 15 October 2018, DVA had received claims from 44 veterans from a total of 71 conditions 'that have been contended as relating the use of antimalarial medications'.[72] DVA detailed the outcome of the 71 conditions considered:

- 29 have been accepted either consistent with the original claim or as relating to a different SOP;
- 24 have been rejected as either not meeting the requirement of the SOP or there being no diagnosed condition as claimed;
- six have been withdrawn by the veteran; and
- 12 are in progress.[73]

4.64 The veterans who made these claims were deployed to a range of locations as follows: East Timor (30 veterans), South East Asia (four veterans), Australia-Pacific region (five veterans), Middle East (two veterans), Africa (one veteran) and two veterans from an unspecified location.[74] The following table shows which antimalarial medications were being attributed by the veteran as the cause of the condition being claimed, and the outcome of the claim.[75]

Table 2: Outcome of claimed condition by antimalarial medication

Condition	Chloroquine	Doxycycline	Mefloquine	Tafenoquine	Mefloquine/ Tafenoquine	Mefloquine/ Doxycycline/ Tafenoquine	Chloroquine/ Primaquine	Unspecified	Total
Accepted as claimed	0	3	0	0	0	0	0	0	**3**
Accepted under another SOP	1	1	18	5	1	0	0	0	**26**
Rejected	0	3	9	1	1	0	1	1	**16**
No diagnosable condition	0	1	5	0	2	0	0	0	**8**
Withdrawn by veteran	0	0	6	0	0	0	0	0	**6**
In progress	0	3	4	1	0	4	0	0	**12**
Total	1	11	42	7	4	4	1	1	**71**

Source: DVA, Response to questions on notice from 11 October 2018 public hearing (received 1 November 2018), [p. 6].

71 DVA noted that a single claim may represent one or more conditions per veteran, and a veteran may have more than one claim for the same condition to reflect they may have entitlements to test the same claim under multiple Acts. Response to questions on notice from 11 October 2018 public hearing (received 1 November 2018), [p. 1].

72 Response to questions on notice from 11 October 2018 public hearing (received 1 November 2018), [p. 1].

73 Response to questions on notice from 11 October 2018 public hearing (received 1 November 2018), [p. 3]. Note: the six withdrawn conditions relate to one veteran.

74 Response to questions on notice from 11 October 2018 public hearing (received 1 November 2018), [p. 2].

75 Response to questions on notice from 11 October 2018 public hearing (received 1 November 2018), [p. 6].

Further investigation of claims by DVA

4.65 At the hearing on 11 October 2018, Ms Cosson noted that DVA are 'looking at each individual client claim to understand what the claim was that they were seeking and to try and understand a little bit further about why they were not accepted'.[76]

Claims team

4.66 On notice, DVA provided information about the composition of the claims team:

> The dedicated Complex Case Team in the Melbourne office consists of seven delegates (three APS6 and four APS5) supported by an EL1 Assistant Director, a contracted medical advisor and two social workers. The team previously consisted of four delegates and was increased to seven delegates when combined with the Mefloquine Claims Team. The delegates in the team are experienced and have expertise across the *Veterans' Entitlements Act 1986*, the *Safety, Rehabilitation and Compensation (Defence-related Claims) Act 1988* and the *Military Rehabilitation and Compensation Act 2004*. Mefloquine or other anti-malarial drugs claims receive a higher level of priority and all calls relating to these claims are handled by the Complex Case Team.[77]

4.67 DVA further advised that of the seven delegates processing claims, five have been in the team for greater than 12 months. The team also processes claims relating to physical and sexual abuse in the ADF and 'given the nature of these claims delegates are rotated after about 12 months'.[78]

What assistance and support are veterans seeking?

4.68 Given the range of challenges highlighted by veterans and their families, the committee explored what other assistance and support is being sought in relation to their health. A range of suggestions were put forward throughout the inquiry including: acceptance that use of mefloquine and tafenoquine are the primary cause of the veterans' health issues, improved response times by Defence and DVA, information and support for families, a proactive outreach program and tailored treatment programs.

Acceptance of antimalarials as the cause of health issues

4.69 A number of witnesses called for the use of mefloquine and tafenoquine to be recognised as the sole or primary cause of the veterans' ill health. Mr Kruizinga distinguished this from the current situation:

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76 *Committee Hansard*, 11 October 2018, p. 61.

77 DVA, Response to questions on notice from 11 October 2018 public hearing (received 1 November 2018), [p. 7]. See also Ms Cosson, *Committee Hansard*, 11 October 2018, p. 62.

78 DVA, responses to questions taken on notice at a public hearing on 11 October 2018 (received 1 November 2018), p. 7.

> …although DVA have added mefloquine and tafenoquine as the basis for several SOPs, as a contributing factor, I do not believe yet that DVA have acknowledged that mefloquine can be a sole factor.[79]

4.70 The AQFVA submission similarly advocated:

> That an SOP be established for chemically acquired brain [injury], quinolone poisoning or similar, to facilitate claims and compensation for veterans and their families exposed to these drugs during ADF clinical trials or general military service.[80]

4.71 Lieutenant General John Caligari AO DSC (Rtd), a commanding officer during the tafenoquine prevention trial, also stated:

> In my view, there is sufficient evidence to acknowledge that mefloquine and tafenoquine are the cause of significant suffering among them. I believe much more can be done, and needs to be done, to help them…I would like to see four outcomes from this inquiry: acknowledgement that it is possible that mefloquine and tafenoquine have an adverse effect on the mental health of some service personnel and that the treatment may be different to the common treatments for PTSD; commencement of suitable research to understand how best to treat those who have experienced adverse effects from the use of mefloquine and tafenoquine; initiation of a program to identify every service person who has been prescribed mefloquine and/or tafenoquine and has been adversely affected by those drugs; and alerting the treating GPs and mental health practitioners of these individuals that these people need to be dealt with under a common protocol as directed by DVA and not automatically treated with PTSD.[81]

4.72 Dr Remington Nevin told the committee:

> [A] veteran can derive a significant amount of relief simply from learning that it's not all in their head; that they're actually sick from a disease with a name that doctors recognise. I don't think the amount of relief that comes from simply having their lifelong concerns finally validated can be understated. Many veterans have suffered with this problem for 25 years. To be finally told that what they suspected all along is true, that their government unintentionally or unwittingly poisoned them, can itself be deeply therapeutic.[82]

4.73 Associate Professor Jane Quinn provided her view

> …until that acknowledgement is there, it doesn't really matter what we put in place—that system is still going to ignore that it exists, and that's always going to be a problem.[83]

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79 *Proof Committee Hansard*, 5 November 2018, p. 8.

80 *Submission 16*, p. 6.

81 *Proof Committee Hansard*, 31 August 2018, p. 20. The tafenoquine prevention trial compared tafenoquine and mefloquine use in 1 RAR in Timor-Leste from October 2000 to April 2001.

82 *Committee Hansard*, 11 October 2018, p. 7.

83 *Proof Committee Hansard*, 5 November 2018, p. 46.

4.74 Some of the family members of veterans participating in the inquiry also highlighted their desire to see the antimalarials publicly recognised as the primary or sole cause of the ill health experienced by veterans. Mrs Susan Armstrong, the wife of veteran Mr Mark Armstrong, explained to the committee that while they were not interested in assigning blame or looking for financial compensation, they hoped the inquiry could provide:

> …acknowledgement and acceptance of the existence of the permanent adverse health effects of mefloquine; education of medical doctors and specialists so they understand the permanent adverse health effects that can arise; funding for long-term studies and research into methods or tests for detection of toxicity and how to treat to mitigate the adverse health effects; real and practical support for the veterans and their families; and legislation prohibiting the testing of drugs on ADF personnel.[84]

4.75 At the public hearing in Melbourne, Mrs Raelene King cautioned:

> I find that if this isn't acknowledged—that tafenoquine and mefloquine have caused this problem—this is not going to move forward. It needs to be acknowledged that this is the cause of our problem. Without acknowledgement, it's not going to move forward.[85]

Improving response times

4.76 The committee also heard the view that Defence and DVA should respond more quickly when contacted by concerned veterans. Mr Benjamin Whiley explained that he waited two months to receive information from ADFMIDI about the medication he had taken and then several months to get an appointment with a doctor and then another four months for the recommended brain injury rehabilitation program to be approved and commence. Mr Whiley was concerned about the impact this sort of timeframe can have on veterans' health.[86]

4.77 The need for a timely response to assist veterans was noted by Mr Kel Ryan, National President, Defence Force Welfare Association:

> I have quite a deal to do with DVA in another capacity, and I would agree that DVA is becoming a lot more responsive than it was 10 or 15 years ago. But the fact that we're only now addressing this very issue, 15 or 30 years after the event, means, to me, we have to become a lot more agile with the way we deal with these issues. I know enough about soldiers and soldiering to say that people present with issues, often, many years after they've left the service, and they present because of triggers that might not have occurred 20 or 30 years ago that have suddenly occurred. So somehow or other we need to get a more agile process to deal with these issues.[87]

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84 *Committee Hansard*, 30 August 2018, p. 15.

85 *Proof Committee Hansard*, 5 November 2018, p. 31.

86 *Committee Hansard*, 30 August 2018, pp. 32–33.

87 *Proof Committee Hansard*, 30 August 2018, p. 27.

4.78 As noted above, some claims, even with the assistance of an advocate, have taken up to 10 years to be finalised. Some individuals the committee spoke to were clearly in need of more immediate assistance.

Information and support for families

4.79 As has been raised in other inquiries undertaken by this committee, support from the partners and family members of veterans is very important. Several veterans who provided evidence to this inquiry did so alongside partners, parents and other support people. Similar to the experiences of the veterans themselves, family members reported difficulties accessing information about the ADF trials, veterans' health records and any support that may be available.

4.80 Mrs Naomi Kruizinga, wife of a veteran, outlined some challenges her family experienced when in crisis.

> I was completely overwhelmed. I had three children trying to make sense of what had happened and unable to give their dad a hug at night. I had to keep going, and I was the only bread winner. There was no assistance from DVA. They couldn't do anything. Except offer a one-time payment of 900 [dollars] to tide us through. We have had to get food vouchers from RSL and bravery trust to get us [by]. Hock personal belongings to help us through. Why is there no help from your government for this? I am not the only family who is going through this right now.[88]

4.81 In addition to providing counselling services, Mrs Kruizinga asked that more coordinated support be available for families:

> Especially for the children as well—they do give us counselling, but there needs to be sort of a team involved that will come out and help assess each family individually and try and find out what supports they need, whether it's financial assistance, other things as well. There's no-one out there like that. We have to make the calls. When you're so busy dealing with him in hospital—I don't have the time and I have three children whose needs I have to look after as well. Having that team come in and help me would be highly beneficial, just to take that load off.[89]

4.82 The role of ex-service organisations was also discussed. Mr and Mrs Kruizinga explained that their children had attended 'highly beneficial' support programs with Legacy and also accessed some services from the RSL. Mrs Kruzininga explained that because there is no coordination between ex-service organisations, as well as with DVA, family members must approach each service individually to find out what assistance is available.[90]

4.83 When describing her experience, Mrs Raelene King also advocated for more support for children to be available:

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88 *Submission 90,* p. 2.

89 *Proof Committee Hansard,* 5 November 2018, p. 4.

90 *Proof Committee Hansard,* 5 November 2018, p. 4.

> I would also perhaps like to see a quinoline support group for all children of affected trial participants to establish what the impact these psychological effects have had on them. My children are adolescents and adults now. Personally, seeing my husband go through this has affected me deeply in so many ways. So try to imagine seeing this through the eyes of my children.[91]

Proactive outreach program

4.84 Several submissions and witnesses advocated for a proactive outreach program to be initiated whereby all trial participants are contacted individually to inquire about their health and to check whether support or assistance is required.[92] For example, Mr Benjamin Fleming, a veteran who participated in the mefloquine prevention trial, was supportive of a broad outreach program because:

> …there are a lot of people out there who don't know they have got the issue….Defence and DVA, et cetera, have in their means the ability to contact every individual who has consumed these drugs. The first step is very much to reach out to them and help educate.[93]

4.85 He called for a program 'funded to speak with every Defence Force member who consumed these drugs—not just one that focuses on sufferers in Townsville'.[94] Also appearing at the public hearing in Brisbane, Mr Whiley agreed that an 'outreach program is vital' and that such a program 'needs to occur at a faster priority'.[95]

4.86 The AQFVA called for the establishment of a working group:

> …encompassing veterans advocates experienced in the effects of quinoline toxicity with appropriate, independent advisers sourced from the military mental health community, family services, occupational health practitioners, brain injury rehabilitation specialists, neurologists, psychologists, cognitive and behavioural experts and psychiatrists, to establish a recommended assessment and treatment program for those affected by mefloquine and tafenoquine during their military service.[96]

4.87 It further suggested that such a group 'be appropriately resourced to deliver a national outreach and rehabilitation program for quinoline veterans and families in Australia'.[97] The AQVFA submitted a proposal to then Minister for Veterans' Affairs, the Hon Dan Tehan and DVA in December 2016 to direct a pilot outreach, rehabilitation and research program for quinolone veterans and families.[98] The

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91 *Proof Committee Hansard*, 5 November 2018, p. 28.

92 See for example, Name withheld, *Submission 48*, p. 2; Mr Karakyriacos, *Committee Hansard*, 31 August 2018, p. 14.

93 *Committee Hansard*, 30 August 2018, p. 33.

94 *Committee Hansard*, 30 August 2018, p. 32.

95 *Committee Hansard*, 30 August 2018, p. 32.

96 *Submission 16*, pp. 54–55.

97 *Submission 16*, pp. 54–55.

98 See Mr Stuart McCarthy, *Submission 94*, pp. 6–7.

AQVFA's outreach program proposal was supported by other participants in the inquiry.[99] Mrs Kruizinga emphasised that a broad ranging outreach program would also be able to provide assistance for families and advise about other support services:

> This is where having this outreach program that can do the advocacy and the support and all that for the families is really beneficial, because it's just too overwhelming. I'm just so focused on the children and my husband that I just don't get the time to do that.[100]

4.88 Associate Professor Quinn told the committee that when responding to the proposal from the AQVFA, Minister Tehan did not support the proposal and noted that there are existing services available through DVA, or through Defence for serving members.[101]

4.89 Dr Remington Nevin noted that the American Quinism Foundation has recommended that all recent American veterans be screened for a history of symptomatic mefloquine exposure.[102]

Tailored treatment programs

4.90 The committee heard views from veterans that current treatment options are not sufficient to meet their health needs. Veterans reported that the difficulty in obtaining a definitive diagnosis covering the complexity of their health issues also makes it more difficult to access treatment.

4.91 Mr Kruizinga explained that the DVA process is one of exclusion or elimination to reach a diagnosis, which in his case, after numerous tests, has not been reached.[103]

4.92 The Defence Force Welfare Association also expressed concern about the effect of an incorrect diagnosis:

> The absence of effective diagnostic routines, referral protocols and dedicated rehabilitation programs is leading to very poor health care. Affected individuals are commonly wrongly diagnosed with posttraumatic stress disorder (PTSD) or other mental health disorders and subsequently subjected to treatments which fail to improve their condition and may inadvertently make it worse. The patient's neurological and psychological difficulties arise not from a functional brain problem as current treatment follows but from a structural change problem, drug mediated, that will require a different treatment approach. Here in lies the reason for these individual patient's failure to thrive. And for their on-going treatment.[104]

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99 Mrs Raelene King, *Proof Committee Hansard*, 5 November 2018, p. 28.

100 *Proof Committee Hansard*, 5 November 2018, p. 4.

101 *Proof Committee Hansard*, 5 November 2018, p. 42.

102 Quinism Foundation, *Submission 17*, p. 11.

103 *Proof Committee Hansard*, 5 November 2018, p. 8.

104 *Submission 95*, p. 2.

4.93 Associate Professor Quinn noted she has received reports from veterans that address a 'common theme':

> That certainly seems to be the common theme that runs through the experience of the people that I talk to. They have ease of access to psychiatry and they have ease of access to counselling, but if they ask for something that sits outside any of those particular domains then all of a sudden [their] SOP and their claim doesn't fit, and accessing that treatment becomes almost impossible.[105]

Treatment for neurocognitive issues

4.94 As outlined in Chapter 2, the AQVFA has argued that mefloquine has caused 'lasting or permanent brain damage, with chronic symptoms typically misdiagnosed as PTSD or other psychiatric disorders'.[106]

4.95 Dr Nevin indicated that in his view that treatment 'is a little premature to discuss'.[107] However, veterans who provided evidence to the inquiry supported the view that additional treatments needed to be available that address potential brain injury and other neurocognitive issues.[108]

4.96 Associate Professor Quinn explained that treatments for brain injuries acquired from taking antimalarials are not currently available:

> I think the treatments that are lacking at the moment are those that are applied to an actual brain injury as opposed to those that are applied to a psychiatric condition. In the vast majority of cases of people who have suffered long-term side effects from these drugs, what we see is the profile of, essentially, a brain injury.[109]

4.97 Furthermore, Associate Professor Quinn explained that in her view, should someone be incorrectly diagnosed with PTSD, they will be unresponsive to that treatment:

> What we see is that people who are treated for post-traumatic stress disorder without having that as an absolute formal diagnosis that is 100 per cent correct—when that post-traumatic stress disorder is present as an accumulation of symptoms caused by that underlying brain disorder, they're actually non-responsive to the treatments for PTSD, and that's extremely common in this group.[110]

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105 *Proof Committee Hansard*, 5 November 2018, p. 43.

106 *Submission 94*, p. 1. See also *Submission 16*, p. 42. *Submission 16.1*, p. 6; The Quinism Foundation, *Submission 17*, p. 5; Defence Force Welfare Association, *Submission 95*, p. 2.

107 *Committee Hansard*, 11 October 2018, p. 6.

108 See for example, Ms Anne-Maree Baker, *Proof Committee Hansard*, 5 November 2018, p. 31.

109 *Proof Committee Hansard*, 5 November 2018, p. 42.

110 *Proof Committee Hansard*, 5 November 2018, p. 42.

How can the concerns raised by veterans be addressed?

4.98 While acknowledging the actions already undertaken by Defence and DVA to date, the challenges and barriers reported by veterans demonstrate that these actions are not meeting the needs of all veterans. The committee heard a number of suggestions from veterans about the assistance and support they would like. Noting the challenges of coming to an agreed position on the cause/s of their symptoms between the veterans and their advocates and the medical community, the committee discussed how best to address their health concerns.

Improving connections with the veteran community

4.99 The committee heard various suggestions for how to improve the connections between veterans and service providers, to ensure that veterans are accessing the support to which they are entitled. It appeared that while submitters agreed on this general point, views varied on how this could be achieved. While many in the veteran community were calling for a proactive outreach program, other evidence to the inquiry highlighted concerns with that approach.

Ethical and practical concerns regarding proactive outreach

4.100 The committee was told that this kind of 'active outreach program' could cause additional and unnecessary suffering to veterans and 'could also undermine measures being applied more broadly to address the mental health of veterans'.[111] Associate Professor Harin Karunajeewa cautioned that it is:

> …hard to see how such a program could be implemented without implicitly suggesting to recipients of the outreach that their symptoms are indeed related to previous drug exposure. This approach is therefore highly susceptible to an important and very well characterised phenomenon known as 'recall bias'. It effectively becomes a 'self-fulfilling prophecy' and one which I believe would contribute significantly to anxiety and other psychological morbidity in these veterans.[112]

4.101 Defence has on a number of occasions indicated it does not support undertaking a proactive outreach program as it is concerned that this approach could potentially cause veterans undue harm. VADM David Johnston AO, Vice Chief of the Defence Force explained:

> Defence has considered whether individual follow-up of all those who were involved in the antimalarial studies in the late nineties and early 2000s is warranted. The vast majority of individuals who have taken these medications are unlikely to have ongoing health problems. Our view has been that contacting this majority might cause more harm than good. It may cause unnecessary worry to individuals who have no reason to be concerned. The significant profile of this issue now and the confusion that

111 Associate Professor Harin Karunajeewa, *Submission 15*, [pp. 10–11].

112 *Submission 15*, [pp. 10–11].

> may now exist amongst study participants mean that we need to keep this approach under review.[113]

4.102 Defence suggested that there may be benefit in future outreach activities being:

> …focused more broadly on encouraging all veterans with any health concerns to seek help, rather than specifically focussing on this group. It remains pivotal that veterans and their families understand the services available to them regardless of their diagnosis, many of which can be accessed through DVA or through their GP, who are best placed to investigate, manage and if necessary refer patients for specialist advice.[114]

New consultation program

4.103 An important issue is enhancing trust with this group of veterans as the committee heard some have lost trust in the system, such as Ms Anne-Maree Baker, who told the committee 'I have a real distrust in the government, the military and any institutions because of my experiences since 2001 when my health started to decline'.[115] Mr Stuart McCarthy similarly said 'I have zero trust and zero faith in any democratic institution in this country, because the culture of those institutions is denial, at best'.[116]

4.104 As outlined above, DVA will be holding a series of consultation forums. The consultation forum mechanisms may present an opportunity to enhance trust by facilitating greater collaboration and fostering connections between veterans, families, advocates and service providers, particularly DVA.

Improving cooperation

4.105 Ms Cosson, Secretary of DVA, acknowledged that there has been differing views on what should be regarded as 'outreach' and, as a result, DVA is undertaking what they are referring to as 'consultation'.[117] Ms Cosson observed that, among the attendees at the recent Adelaide consultation forum, there was not a strong level of awareness about what services are available generally to veterans:

> Recently we had a consultation session in Adelaide and we talked with our veteran community. Forty of our veterans and families participated in that consultation. What seemed to be a gap in understanding is that when we introduced non-liability health care in the budget last year we extended that free treatment for any condition that's listed in the DSM-5.[118]

113 *Committee Hansard*, 11 October 2018, p. 46.

114 *Submission 1*, pp. 31–32.

115 *Proof Committee Hansard*, 5 November 2018, p. 28.

116 *Committee Hansard*, 30 August 2018, p. 8.

117 *Committee Hansard*, 11 October 2018, p. 64.

118 *Committee Hansard*, 11 October 2018, p. 60.

4.106 Following the 11 October 2018 public hearing, DVA provided more detail about the Adelaide forum including a summary of areas discussed which included: health experiences related to ADF service (including experience with antimalarial medicines), a lack of awareness of what supports are available through DVA or Defence and concerns about how to access the mental health workforce eg. psychiatrists and psychologists in Adelaide and South Australia.[119]

4.107 A number of suggestions came out of the public forum held in Adelaide. DVA advised that attendees were invited to provide feedback via a short survey and that overall, attendees reported that the 'forum provided helpful information and a good opportunity to openly discuss their concerns'. However:

> …some felt that the discussion became too emotional and that a smaller group might help facilitate a more focused and comfortable discussion for attendees. Attendees also identified that additional information on available supports and services, including non-liability health care arrangements, would be helpful.[120]

4.108 Regarding the forum in Adelaide, Associate Professor Quinn noted the need to build on the information provided:

> The other thing that did seem to be a deficit in the way the first one [session in Adelaide] was carried out was that there really wasn't any provision of information about what the next step for those people needed to be other than 'put in your claims'. So we always give effect to this circular—whatever you want to do, put in your claims.[121]

4.109 Associate Professor Quinn also suggested that DVA could proactively contact groups such as the AQVFA to inform them of upcoming consultation or information-sharing activities. She noted that in relation to the DVA sessions held in Adelaide:

> …what was interesting was that we [the AQVFA] weren't informed of any of them directly. We found about the dates of all of them through ex-service organisation members who have been on the mailing lists for them, which is odd because I have Liz Cossin's personal email address and Tracy Smart's mobile number and either of them could have given me a call and told me when they were.[122]

Ensuring GPs have access to relevant information

4.110 One of the key messages from Defence has been for those concerned to seek assistance from medical practitioners. GPs are therefore central to ensuring veterans have access to a range of health services and ongoing support. Dr Penny Burns,

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119 DVA, responses to questions taken on notice at a public hearing on 11 October 2018 (received 1 November 2018), [p. 9].

120 DVA, responses to questions taken on notice at a public hearing on 11 October 2018 (received 1 November 2018), [p. 10].

121 *Proof Committee Hansard*, 5 November 2018, p. 44.

122 *Proof Committee Hansard*, 5 November 2018, p. 44.

representing the Royal Australian College of General Practitioners (RACGP) explained the organisation's role:

> The role of the RACGP in this discussion is around ensuring general practitioners are available to provide ongoing support to veterans affected by mental health symptoms and/or physical symptoms, whatever the cause. Their aim is to continue to update GPs so they can provide the best evidence based treatment on an ongoing basis. The aim is to decrease the level of dysfunction experienced with symptoms and get people back to more normal lives. In practice, when people present with symptoms—mental health issues, for example—it's sometimes not possible to definitely define a cause, but, in most cases, we're still able to look at managing symptoms to improve the conditions.[123]

4.111 Furthermore, Dr Burns emphasised:

> In summary: the RACGP is keen to ensure easy access by veterans to GPs for any support needed—be it for mental health symptoms and/or physical symptoms, or just general distress; whatever the cause—and to ensure that GPs are educated to provide the best possible evidence based support, diagnosis and treatment for veterans.[124]

4.112 Evidence to the inquiry has reported varying levels of awareness among GPs of the mefloquine and tafenoquine antimalarial drugs and it was suggested that more needs to be done to better educate GPs about the issues being reported by veterans.[125]

4.113 Officials from DVA recognised the important role of GPs to provide assistance to veterans as well as the role that DVA has to support and educate GPs:

> …What we are very aware of, as I've looked into this and I've worked with my colleagues and I've worked across the last year, is that we need to find ways to educate our GPs better so that, when veterans present with this type of disorder, there is a very clear, signposted way for people to get to these specialists—because it is a specialist area.[126]

4.114 Dr Burns said most GPs would have a reasonable understanding of mefloquine due to the fact that mefloquine 'has been used for quite some time'. She spoke about the resources that have been made available to increase awareness about mefloquine:

> My understanding of most of the GPs who I know is that they would have a reasonable understanding of that. There have also been clinical guidelines brought out by the Joint Health Command. Recently, I think that the Gallipoli Medical Research Foundation and the Returned Services League of Australia put out a comprehensive brief on some PTSD stuff. And there

123 *Committee Hansard*, 11 October 2018, p. 15.

124 *Committee Hansard*, 11 October 2018, p. 15.

125 See for example, Mr Benjamin Fleming, *Committee Hansard*, 30 August 2018, p. 33.

126 Dr Hodson, *Committee Hansard*, 11 October 2018, p. 65.

> has also been some stuff coming out recently about mefloquine as well. So there's a lot of education that comes out continually to GPs around that.[127]

4.115 Dr Burns noted that as tafenoquine is new, GPs would not typically have received information about that yet:

> Tafenoquine, no. I hadn't actually heard of it before or seen it before the invitation to this inquiry. So, if I'm an example of the average GP, I would presume that they don't have much information around that.[128]

4.116 Mr Karl Herz, Biocelect, informed the committee about the information they will be providing to GPs leading up to the official release of tafenoquine. As well as the information that is already provided on the TGA website, Biolcelect is finalising a 'Dear Doctor' letter which will provide information about the medication with a focus on explaining the contraindications.[129]

Ensuring information sharing between health professionals and DVA

4.117 As noted earlier in the chapter, DVA has undertaken activities to increase GPs' awareness of the use of antimalarials in the context of the veterans' community. Dr Burns noted that the clinical guidelines for GPs produced by DVA and Defence 'are fantastic' and the importance of ongoing information sharing and promotion across GP groups:

> I think that one of the things that need to happen is that it needs to be promoted through all the GP groups continually, and workshops and webinars are the ways that GPs are now accessing information. I think having the GP groups involved—so the AMA [Australian Medical Association], the college, ACRRM [Australia College of Rural and Remote Medicine], the various groups, promoting it. I think webinars, workshops, guidelines particularly—GPs love guidelines and workshops. At the moment, there's a big conference, the annual GP conference, GP18. That's another way of getting information out to GPs.[130]

4.118 Dr Burns suggested that the provision and promotion of this sort of information was particularly relevant around major bases as well as in other locations where there is high volume of 'travel back and forth between malarial areas'.[131]

4.119 On notice, the RACGP explained that a RACGP representative attends the DVA Health Providers Partnership Forum[132] meetings three or four times a year to provide advice to DVA about developing information resources for veterans. Attendance at these meetings also facilitates information sharing back to the RACGP about DVA programs. Furthermore, the RACGP 'helps to distribute DVA information

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127 *Committee Hansard*, 11 October 2018, p. 16.

128 *Committee Hansard*, 11 October 2018, p. 16.

129 *Proof Committee Hansard*, 8 November 2018, p. 22.

130 *Committee Hansard*, 11 October 2018, p. 16.

131 *Committee Hansard*, 11 October 2018, p. 16.

132 See DVA, *Health Providers Partnership Forum, Terms of Reference*, p. 1.

and resources through RACGP publications' and has endorsed a number of resources that provide information and support for veterans.[133]

Additional research underway

4.120 Professor Sandy McFarlane AO, Director of the Centre for Traumatic Stress Studies, stressed the need for research which is independent in order to provide reassurance to veterans about the findings.[134] The committee is aware that Defence and DVA have jointly commissioned the University of Queensland to undertake a research study on 'Self-reported health of ADF personnel after use of antimalarial drugs on deployment'[135] using 'de-identified data extracts from the Bougainville, Timor-Leste, and Solomon Islands deployment health studies'.[136]

4.121 In its submission, DVA explained the new research will:

> …focus specifically on the health outcomes of deployed veterans who took anti-malarial medications. It is anticipated that this research will be completed in the second half of 2018.[137]

4.122 Defence added that this research will examine the following research questions:

> a. Did deployed veterans who reported taking mefloquine have different rates of mental and general health outcomes compared to veterans who reported taking doxycycline or other antimalarials?
>
> b. Did deployed veterans who reported taking primaquine on return to Australia have different rates of mental and general health outcomes compared to veterans who did not?
>
> c. Did deployed veterans report a significant reaction to specific medications received during their deployment or raise use of antimalarial drugs as an area of concern in response to open ended questions?[138]

4.123 At the time of the hearing in October 2018, there was no further information available about the ongoing research. It was confirmed that the research will be finalised later in 2018 and that the report will be published.[139]

The need for a multi-disciplinary approach

4.124 The health issues identified by veterans in this inquiry are complex with several individuals submitting long lists of symptoms and documenting a range of

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133 RACGP, responses to questions taken on notice from a public hearing on 11 October 2018 (received 31 October 2018).

134 *Submission 58,* p. 4.

135 Department of Defence, *Submission 1*, p. 42.

136 Department of Defence, *Submission 1*, p. 42; DVA, *Submission 2*, p. 6.

137 *Submission 2*, p. 7.

138 Department of Defence, *Submission 1*, p. 42.

139 Ms Veronica Hancock, Acting First Assistant Secretary, Veterans' Services Design, *Committee Hansard,* 11 October 2018, p. 68.

conditions. Some had been diagnosed with particular conditions by a health professional while others were still undergoing various tests and consults to determine a diagnosis.

4.125 It was noted that responding to such varied and complex health needs requires a multi-disciplinary approach. One veteran described the range of supports he needs as follows:

> One of my recommendations moving forward is that sitting in front of a psychiatrist and being prescribed medication is not going to help or do anything for my brain injury. What I need is psychosocial support…I've got to the point where I need to start re-learning how to do things. I've managed to get access to a social worker and I'm basically learning how to schedule a day and tasks—things like that—and that's the support that we need.[140]

4.126 The RACGP has defined 'multidisciplinary care' as occurring:

> …when professionals from a range of disciplines with different but complementary skills, knowledge and experience work together to deliver comprehensive healthcare aimed at providing the best possible outcome for the physical and psychosocial needs of a patient and their carers'.[141]

4.127 Health professionals may include community health professionals, general practitioners, and medical specialists. This approach is often used to treat and support people with conditions such as cancer, and systematic approaches to team based care are also emerging in 'primary care clinical areas such as diabetes, aged care, mental health and disability'.[142]

4.128 Associate Professor Quinn emphasised the importance of including a broad support network when providing treatment:

> Managing those [people with brain injuries] isn't just a matter of giving somebody a script with an antipsychotic or a sedative drug and expecting them to go away and get better. There is also a whole family support network that needs to be drawn up around somebody with a long-term brain injury. If we were looking at somebody who had been brain injured in a car accident and was going to be anticipated to have long-term neurological and cognitive deficits, there's no way that we would be suggesting that that person was going to manage their environment, manage their work-life balance or manage their employment prospects without having a network of support around them and their family. This is the thing that is missing when we have a situation with a system that doesn't recognise this as a brain injury.[143]

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140 Mr Whiley, *Committee Hansard,* 30 August 2018, p. 35.

141 RACGP, *The RACGP Curriculum for Australian General Practice 2011*, p. 453. See also GK Mitchell, JJ Tieman and TM Shelby-James, 'Multidisciplinary care planning and teamwork in primary care', *Medical Journal of Australia*, 2008, vol. 188, no. 8, S61–4.

142 RACGP, *The RACGP Curriculum for Australian General Practice 2011*, p. 454.

143 *Proof Committee Hansard,* 5 November 2018, p. 42.

4.129 Dr Stephanie Hodson CSC, National Manager, VVCS, DVA, acknowledged that it can be challenging to confirm a diagnosis when individuals present with a range of complex symptoms. The symptoms reported by veterans are wide ranging: concerns about the 'neurocognitive element', anxiety, PTSD as well as other 'somatic symptoms' including digestive issues and skins problems. She acknowledged that the complexity of these issues requires a holistic response:

> All of this means that we've got to get to person-centred care. We've got to have a way that we assess comprehensively the individual for all those domains and then assist them to get to pathways. Just saying, 'Go to your local GP,' doesn't necessarily mean that you're going to get the sort of wraparound assessment you need. We need to help GPs actually identify the more complex individuals who we need to put into a signposted pathway where we can link them to the right professionals.[144]

4.130 Dr Hodson spoke further about the recognition by DVA that some individuals need tailored, wrap around assistance which needs to include neurocognitive aspects:

> Across this journey, we've reached back into the department. We hadn't, when we first started, thought a lot about rehab. With the pathways to care that [Mr Stuart McCarthy] talked about, we are now figuring out how someone gets there from maybe turning up in a VVCS office. We do the right assessment and say, 'We do think there are some problems here that are not down the anxiety end of the spectrum, or PTSD; they're actually in the neurocognitive end,' and we now need to get those people to rehab specialists, to speech pathology, and we are working for the first time ever with rehab occupational therapists. There's a whole specialty here.[145]

Neurocognitive Health Program

4.131 In addition to offering existing treatments and support through DVA's non-liability pathway, DVA advised that they are developing a new Neurocognitive Health Program to assist veterans who may indicate symptoms of a neurocognitive disorder (NCD). This program has been developed following feedback from veterans that they have been unable to access appropriate support to address some of the concerns they have attributed to mefloquine use.

4.132 Dr Hodson advised that:

> The DSM-5 [Diagnostic and Statistical Manual of Mental Disorders] made quite a big step forward around the fact that we all do tend to forget the brain and psychology. Mental health is all interconnected, and it starts with the brain. There is an area in the whole diagnostic continuum which is about neurocognitive disorders, which can be caused from a range of issues. It can be exposures, it can be playing sport, it can be mild traumatic brain injury and it can be long-term life alcohol use. All of these can result in

144 *Committee Hansard*, 11 October 2018, p. 66.

145 *Committee Hansard*, 11 October 2018, p. 65.

> impacts that are about a loss in memory, speech, neurocognitive functioning.[146]

4.133 Dr Hodson explained that a number of veterans from the 'mefloquine cohort' had raised concerns that when they have tried to access DVA services to discuss a possible brain injury, the response was to discuss PTSD.[147] This experience reported by Dr Hodson is consistent with the evidence to the committee's inquiry.

4.134 Dr Hodson explained that DVA had reflected on those representations and acknowledged that the response to veterans' concerns may need to change:

> We acknowledged, about a year ago, that we were not well equipped to be able to do those assessments. It's actually a very specialised area within the community. Over the last 12 months, we've been working really hard to look at whether this is an area we can measure. The good news is that we've we talked to Westmead Hospital and we've talked to people like Professor Richard Bryant and Dr Ian Baguley, who do specialist work in this area, and they've said that the science has really moved forward. A lot of it has come out of the US to do with mild traumatic brain injuries. In fact, we've now got much better neurocognitive screening that we can do. Importantly, there is remediation we can do to bring about better outcomes.
>
> What we're trying to do at the moment is develop a pathway so that, if you come in, we can baseline where your functioning is. For anyone who has served in the military, that's super important. If you've had a 20-year career, you may have been around exploding ordnance, you may have played a lot of rugby, you have potentially had toxic exposures, you may have drunk a bit of alcohol—there are a whole range of reasons why your cognitive functioning would be putting you at risk for early onset Alzheimer's down the track. We want to be able to assess functioning baseline for anyone who is worried about functioning. Where we find there is a problem, we have to have pathways to care.[148]

4.135 It is envisaged that the program will be accessible to veterans assessed as requiring treatment from anywhere in Australia. The assessment of current functioning and provision of treatment will not be linked to any possible cause.[149]

4.136 Dr Hodson further reported to the committee advice she has received from a neuroscientist:

> …it doesn't really matter whether the inflammation in the brain was caused by PTSD or it came from a toxic exposure; at the end of the day we've got to work with the inflammation of the brain.'[150]

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146 *Committee Hansard*, 11 October 2018, p. 65.

147 *Committee Hansard*, 11 October 2018, p. 65.

148 *Committee Hansard*, 11 October 2018, p. 65.

149 *Submission 2*, p. 6.

150 *Committee Hansard*, 11 October 2018, p. 65.

4.137 This program is being developed 'initially through a Discovery Phase of consultation and co-design to establish what the service would need to provide'.[151] In his submission, Professor McFarlane, noted that he has been asked by DVA to advise on the development of the Neurocognitive Health Program. Mr Stuart McCarthy also advised the committee that the AQVFA was invited to 'co-design this program with them, in consultation with ABI rehabilitation specialists already experienced in providing health care to affected veterans…'.[152]

4.138 Associate Professor Quinn also discussed the development of the Neurocognitive Heath Program and in particular focused on the benefits of the co-design model being used for its development as an example of different groups working together in a cooperative manner:

> I think we're beginning to work on that with the neurocognitive health program that's being extended through VVCS, now Open Arms, with DVA presumably sitting in the background of that. So that program encompasses us, as QVFA, and senior leaders from Open Arms/VVCS. In that process, we have engaged a number of healthcare experts who sit outside the normal VVCS psychological counselling banner. Those include people who are specialist in brain rehabilitation, people who are specialist in trauma psychiatry, people who are specialist in providing family support, particularly around rehabilitation. That's the kind of team that you start to need to build together. It doesn't exist currently under the DVA/VVCS banner. So these are specialists and agencies that are not routinely employed by either of those organisations. But they are the types of agencies, and we'll find out who those people are, and that group will extend the more that we go through that process.[153]

4.139 The committee notes that DVA has discussed the development of the Neurocognitive Health Program at the recent consultation forums and will continue to inform veterans about the program.

151 *Submission 2*, p. 6.

152 Mr Stuart McCarthy, *Committee Hansard*, 30 August 2018, p. 2.

153 *Proof Committee Hansard*, 5 November 2018, p. 46.

Chapter 5

Conclusions and Recommendations

Medical concerns

5.1 The inquiry focused on three issues raised which will be addressed in turn. First, the claims that the current symptoms experienced by individuals are due to taking mefloquine and/or tafenoquine over 18 years ago. The committee spoke with the individuals and groups making these claims and then with the medical community in Australia, particularly those organisations responsible for assessing these claims.

5.2 As in the executive summary, the committee again states that it is not comprised of medical experts and so can make no medical findings or rulings on this matter but it facilitated the case from each side to be presented. It is clear to the committee that in the view of the medical professionals, the weight of medical evidence does not support the claim that their current symptoms are caused by antimalarial use 18 years ago. More specifically, in summary, the committee was told that long term problems as a result of taking mefloquine are rare and there is no compelling evidence that tafenoquine causes long term effects.

5.3 It is important to note that although individuals presenting evidence to the committee often did not clearly distinguish between them, mefloquine and tafenoquine are different drugs that act differently in the body.

5.4 In relation to mefloquine, the committee notes that there has always been recognition by Defence that mefloquine, like any drug, has side effects and this has been taken into consideration in the development of health policy. The committee accepts that Defence, when deploying ADF personnel to malarious areas, takes it duty of care seriously[1] and needs to provide the best protection for them for field conditions and to have more than one option available in case the first line antimalarial, doxycycline, is not tolerated or the deployment is to an area with antimalarial resistance.

5.5 The medical evidence provided to the committee shows that the incidence of long term or persistent neuropsychiatric adverse reactions to mefloquine is very rare. The committee heard there have been an estimated 40 million doses of mefloquine worldwide, with safety data on at least 1 million people in a recent published Cochrane review. The committee was provided with no evidence that the same symptoms reported by some veterans are manifesting in the Australian population or across the world in the civilian population.[2] The committee heard that there is no evidence of an emerging global public health issue.

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1 Vice Admiral David Johnston AO, Vice Chief of the Defence Force, Department of Defence, *Committee Hansard*, 11 October 2018, p. 45.

2 For example, primaquine has been used for more than 60 years in the USA and Australia. See 60P, *Submission 9*, p. 2.

5.6 While sympathising with the veterans who spoke with the committee and hoping for them to get the help they need, the medical experts have been very clear with the committee that the medical evidence does not support their contention that their current health conditions are caused by the drugs they took over 18 years ago.

5.7 Mefloquine was an approved drug at the time of the trials, tafenoquine was not. The committee notes that the newer drug tafenoquine has undergone rigorous safety evaluation by the US FDA and the Australian TGA. TGA's Advisory Committee on Medicines and the US FDA's Antimicrobial Drug Advisory Committee (AMDAC) have all had input for both indications, prevention and radical cure, and the findings are consistent. The processes of the US FDA and TGA included an audit of the relevant Defence studies which would have affected registration if anomalies or concerns about clinical practice had been found. On the contrary, the committee was told that the auditor found that the level of oversight of the studies was of a very high standard. The committee also notes that for the independent regulators, commercial concerns of pharmaceutical companies are not part of their considerations.

5.8 The committee is reassured that every effort has been made by the systems and regulators in place to ensure the safety of patients who have access to mefloquine and who will have access to tafenoquine. The committee was also reassured by the efforts of the pharmaceutical companies to address the concerns being raised by investigation and transparency of data. The committee wishes to note that it received full cooperation during the inquiry by the pharmaceutical companies who provided submissions, supplementary submissions to address specific evidence and appeared at a hearing, with some witnesses travelling from overseas to provide evidence in person.

5.9 The committee has confidence that Australia's independent medical bodies have looked specifically at the issue of acquired brain injury (ABI) from the use of mefloquine or tafenoquine. The committee was informed that the claim that taking mefloquine and tafenoquine results in ABI is not backed by definitive evidence. In August 2017, the Repatriation Medical Authority (RMA) found there was insufficient sound medical evidence to support this claim. This decision was reviewed by the Specialist Medication Review Council which in September 2018 supported the decision of the RMA.

5.10 The committee was reassured that, should any sound medical-scientific evidence pertinent to this inquiry arise in the future, it would be identified through existing channels and responded to by Defence and DVA. Existing monitoring mechanisms include the regular reviews of the evidence undertaken by the RMA and the work undertaken by Defence Joint Health Command (JHC).

5.11 It was suggested to the committee that it was hearing mostly from malariologists.[3] This is not the case as can be seen by the range of evidence detailed in Chapter 2. The wide range of specialists contributing to accumulating and analysing medical data was evident to the committee. The committee notes that the US FDA engaged specialists including not only malariologists but psychiatrists,

3 Dr Nevin, *Committee Hansard*, 11 October 2018, p. 7.

epidemiologists, postmarketing surveillance professionals and others. The TGA has toxicologists, pharmaceutical chemists, inspectors for the manufacturing facilities as well as the ability to call on external advice from an advisory committee of doctors, community representatives, epidemiologists and statisticians. The committee notes the range of professionals who reviewed the information in the RMA and SMRC with specialists drawn from pharmacology, neurology, mental health, neuropsychology as well as medical academics and epidemiological academics.

5.12 In conclusion, on this aspect, the committee respects the medical findings of the various regulators and their experts as well as the vast amount of evidence from international and domestic studies and clinical experience. Also, this issue seems to be manifested in military populations where it appears to the committee that trying to assign a single cause to veterans' illnesses does not reflect the many potential contributors to their physical and mental health at the time and in the many years since the medications were taken.

5.13 The committee notes that the concerns of veterans have not been ignored by pharmaceutical companies or regulators. Adverse events reported more recently for tafenoquine were followed up, scrutinised and this work included in the information provided to the US FDA and TGA. Dr Nevin presented to the US FDA. The committee notes that he was the only person who submitted evidence critical of the proposal to approve tafenoquine. The committee is reassured that the medical concerns raised with the committee have been taken into consideration by the independent regulators which have recently approved tafenoquine and whose job it is to focus on safety and efficacy of medications.

5.14 However, the committee does not doubt that the symptoms being experienced by individuals are real and regardless of the cause or causes, these veterans are unwell and should receive the assistance to which they are entitled. It has therefore been the focus of the committee to ensure that any current and past ADF members receive appropriate treatment and the support they need. The committee notes that this is not a different view to that stressed by Defence and DVA, ie. that regardless of the cause of the symptoms, help is available.

5.15 The committee understands that the individuals and families who spoke with the committee are searching for answers to their poor health and acknowledges the comfort and support felt by most veterans and family members who are part of the group organised by the AQVFA. The committee is, however, concerned that this support does not come at the expense of them reaching out to receive available assistance because it does not come under the label they would prefer it to have. The committee is also concerned that the efforts of such advocates may unnecessarily cause public concern and negatively affect the global effort to eradicate malaria.

5.16 The committee was concerned at the personal nature of some submissions and evidence from advocates questioning the honesty and motives of witnesses with whom they disagree. The committee accepts that officials and other witnesses have provided evidence to the committee in their professional capacities in good faith. In these cases the committee facilitated an exchange of views and the individuals mentioned were given the opportunity to respond to the submissions and evidence.

ADF participation in medical research

5.17 The second issue raised with the committee was the conduct of the trials. The issue of ADF members participating in medical research is complex. The committee is concerned that some members may not fully engage with the information provided by researchers if they perceive participation in the research to be a mandatory or routine part of their role. The committee also believes that members are potentially vulnerable to feeling pressured to participate by their superior officers due to the hierarchical culture of the military.

5.18 However, the committee does not believe that all medical research with members of the ADF should be prohibited, provided it does not disrupt the work of the ADF and has been approved in accordance with the National Statement on Ethical Conduct in Human Research (National Statement). This is because research is essential for advancing medical care and force protection measures, and the ADF has a duty of care to protect and maintain the health of its personnel.

Informed consent during the trials

5.19 As noted above, the processes of the US FDA and TGA included an audit of the trials involving tafenoquine, which Defence characterised as representing 'a thorough, independent validation of all aspects of the conduct of the studies'.[4] Moreover, allegations of misconduct in some of the trials involving the use of mefloquine and tafenoquine have been investigated by the Inspector-General of the Australian Defence Force (IGADF), a statutory role that is independent of the ordinary chain of command. The IGADF found that the trials undertaken by the Australian Malaria Institute from 2000 to 2002 in East Timor involving mefloquine and tafenoquine 'were conducted ethically and lawfully' in accordance with the guidelines issued by the National Health and Medical Research Council (NHMRC) and the Therapeutic Goods Administration.[5] It also concluded that members voluntarily consented to participate in the trials involving mefloquine and tafenoquine, and were informed of the potential side effects known at the time.

5.20 Some submitters have not accepted the findings of the audit and investigation and have called for a Royal Commission. However, the committee has not received evidence that undermines the existing independent findings, and so does not support a further investigation. The committee was concerned to hear that some ADF members who agreed to participate in the trials felt that they were not provided sufficient information, or were pressured into participating. The committee recognises that this perception is distressing for some veterans and their families. Therefore, the committee makes some recommendations for improving the consent process.

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4 Defence, *Supplementary submission 1.1*, p. 5.

5 IGADF, *Inquiry report into issues concerning anti-malarial trials of the drug mefloquine between 2000 and 2002 involving Australian Defence members deploying to East Timor*, 2016, pp. ii–iii.

Improving the process of providing informed consent

5.21 The committee believes that issues of informed consent should be carefully considered when study protocols are developed by researchers, and when the current Departments of Defence and Veterans' Affairs Human Research Ethics Committee (DDVA HREC) reviews and decides whether or not to approve the research. This is in accordance with the NHMRC National Statement and the recent recommendations made by the IGADF.

5.22 The committee notes that the DDVA HREC is comprised of a range of members, including a veteran, lawyer, lay people, a pastoral care member, a civilian clinical care provider and others with relevant experience in research.[6] The DDVA HREC terms of reference also establish that 'at least one third of the members are to be external to Defence and DVA'.[7] The committee views these requirements to sufficiently ensure a range of perspectives are represented during the consideration of new study protocols.

5.23 The committee was pleased to note Air Vice-Marshal Smart's letter requesting DDVA HREC also consider new methods of ensuring the military chain of command does not influence the voluntary choice of members of the ADF to participate or not in research.[8] The committee encourages DDVA HREC, Defence and the Department of Veterans' Affairs to implement measures to achieve this aim. It is supportive of initiatives including providing a standard script to Command and standard briefing materials to prospective participants, and engaging an external agency observer to monitor, evaluate and report on the consent process.

5.24 Defence informed the committee that DDVA HREC already considers the issue of informed consent in military populations each time it considers a research proposal 'to ensure that there is no coercion, real or perceived, in the recruitment of participants from the ADF'.[9] This responsibility is implicitly contained in the DDVA HREC terms of reference as it reviews research protocols in accordance with the National Statement, which covers issues of informed consent.[10] However, the committee view is that there is an opportunity to develop the DDVA HREC terms of reference to explicitly note its responsibility to consider the vulnerability of prospective participants to coercion.

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6 Defence, *Submission 1.1*, p. 15.

7 Defence and Department of Veterans' Affairs, *The DDVA HREC Terms of Reference*, pp. 2–4, http://www.defence.gov.au/health/hrec/ (accessed 11 October 2018).

8 Defence, *Letter form AVM Tracy Smart Am to Mr Ian Tindall*, Chair DDVA HREC, 4 October 2018, [p. 1] (tabled 11 October 2018).

9 Defence, *Submission 1*, p. 33.

10 *The DDVA HREC Terms of Reference*, p. 1; NHMRC, Australian Research Council and Universities Australia, *National Statement on Ethical Conduct in Human Research*, p. 68.

Recommendation 1

5.25 The committee recommends that the terms of reference of the Departments of Defence and Veterans' Affairs Human Research Ethics Committee be updated to explicitly include consideration that prospective research participants may be vulnerable to perceived coercion to participate.

5.26 Once DDVA HREC has approved a study protocol, the committee believes that individual members should have access to independent advice regarding their potential participation in medical research. The NHMRC National Statement suggests:

> In the consent process, researchers should wherever possible invite potential participants to discuss their participation with someone who is able to support them in making their decision. Where potential participants are especially vulnerable or powerless, consideration should be given to the appointment of a participant advocate.[11]

5.27 The committee did not hear evidence of participant advocates being appointed elsewhere, however believes that this model may provide an opportunity to improve the consent process for ADF members considering whether to participate in research. The committee recommends that each prospective participant should have access to a private conversation with an independent participant advocate before providing their consent to participate. This person should be informed of the study protocol and have knowledge of the medical field, but should not be employed as part of the research team.

Recommendation 2

5.28 The committee recommends that all members of the Australian Defence Force who are invited to participate in medical research have access to a confidential conversation with an independent participant advocate prior to consenting to participate.

Screening and post-trial communication processes

5.29 The committee was concerned that a very small number of members participated in a trial even though their previous experiences of mental illness should have excluded them. The committee notes the development of the Defence eHealth System, and supports the IGADF recommendation that future trial investigators should be given access to the system to enable any relevant medical history of contraindicators to be identified at the time of obtaining a Defence member's consent to participate in a trial.[12]

5.30 The committee was also concerned to hear that some participants who withdrew from the trial early may have missed out on some of the follow up provided to other participants. However, the committee was reassured that these members would have still received the healthcare provided to all ADF members, including a

11 *National Statement*, p. 68.

12 IGADF, *Inquiry report*, 2016, p. iii.

medical examination at the end of deployment, two post deployment psychological screenings and annual health assessments while with the ADF.[13]

5.31 The committee heard some veterans faced distressing delays while waiting to receive information on their participation or otherwise in the trials. The committee supports efforts to improve this process. It notes the Defence eHealth System is likely to prevent future delays, as information on trial participation can be incorporated into the ADF members' medical records once the trial process has been concluded.

Assistance and support for veterans

Overarching need for assistance

5.32 While the committee acknowledges the actions taken by Defence and DVA to address the concerns of veterans raised with the committee, the evidence to the committee indicated that either more needs to be done to assist veterans or done differently. Several witnesses who provided evidence were clearly in need of immediate assistance.[14] While there were some different views about the best and most appropriate ways to provide assistance and support, there was unanimous agreement that these veterans and their families need help. Therefore the focus of the committee was to look for new and different approaches to facilitate better support for this cohort and the wider veteran community.

5.33 The committee notes the commitments made and actions taken by the government in this area in response to the recommendations in the committee's report on veterans' mental health. However, the committee noted that despite these efforts, this cohort of veterans, at which the actions were directed, were mostly unaware of them. It was evident to the committee that additional support is necessary to address the issues faced by these veterans.

Veterans' experiences with seeking assistance

5.34 The clear message from Defence and DVA was that regardless of the cause of their symptoms, assistance is available. While this may be true it was not the experience for most individuals who spoke with the committee. The committee explored with individuals their experiences of accessing assistance; whether they had tried to access assistance, and if so, the details of that experience. The committee also spoke to veterans who had not accessed assistance and explored the reasons why not.

5.35 Some individuals appeared to be accessing helpful assistance but unfortunately this was not a common experience for those who participated in the inquiry. The committee heard of a number of practical barriers that are inhibiting veterans accessing support, including cultural issues, unavailability of information and challenges accessing and navigating the DVA claims process as outlined below.

13 Defence, *Submission 1*, p. 28.

14 DVA was in attendance at public hearings to provide assistance to veterans if required.

Barriers to assistance

ADF cultural issues

5.36 The committee heard from veterans who either did not wish to engage with DVA as they had lost trust in the system or they found it difficult to ask for assistance as the culture of the ADF means there are barriers to self-reporting issues and vulnerability.

5.37 Acknowledging these cultural issues, it was suggested to the committee by a veteran that there needs to be more assistance and support when a soldier transitions to civilian life. To this end the committee notes the inquiry into transition from the ADF being undertaken by the Joint Standing Committee on Foreign Affairs, Defence and Trade which is examining support provided to members of ADF as they transition from active service to civilian life. The committee is not aware of the timeline for concluding the transition inquiry but recognises the importance of the issues and that this is a critical time for many veterans.

5.38 While the committee is concerned that some veterans do not wish to engage with DVA, the committee encourages those veterans to seek assistance. Although previous experience accessing assistance may not have been optimal, there have been a number of actions taken to improve services in recent years.

5.39 The committee was also reassured that when a veteran is ready to seek assistance, organisations such as the RSL and the Defence Force Welfare Association as well as a community of advocates and DVA officials are ready to help.

Provision of information

5.40 Some suggestions for assistance focused on addressing some of the barriers reported by veterans to access information.

5.41 Veterans consistently told the committee that there is an ongoing need for information about a range of issues: details about their participation on the trials, information about the antimalarial medication they took and advice about what support and assistance is available. The committee recognises that both Defence and DVA have taken steps to make information available to veterans, by providing information about their trial participation, publishing information on websites and establishing a dedicated support team. It is important that these actions continue and are built upon.

Dedicated support line

5.42 The dedicated mefloquine support line was a commitment by government as detailed earlier in this report. The committee received a number of accounts from witnesses which showed the support line has not been operating as effectively as it could. The committee was pleased to note that DVA has recognised this and taken action to make additional changes to ensure that veterans calling this line receive appropriate assistance. Given the consultation forums recently undertaken by DVA, there may be an increase in the number of calls made to the dedicated support line. Therefore, it is important that DVA ensures that staff working in that area receive

ongoing training and information about these matters and are ready to provide details about available assistance.

DVA claims process

5.43 The committee recognises that the DVA claims process can be difficult to navigate. Veterans reported that the process is particularly challenging when dealing with complex health conditions that cannot be linked to a single Statement of Principles. To this end the committee notes the evidence from the RMA that with assistance from an advocate to navigate the system there is often the ability to link some of their symptoms to service; however the committee notes the extraordinary length of time this can take for some.

5.44 The committee was pleased to note that DVA is conducting further investigation into the claims lodged relating to antimalarial medications since September 2016. The committee urges DVA to expedite this process and continue to offer these individuals either assistance from DVA or facilitate access to an advocate.

Recommendation 3

5.45 The committee recommends that the Department of Veterans' Affairs expedite their investigation on antimalarial claims lodged since September 2016 and continue to offer individuals assistance to lodge their claims and facilitate access to an advocate if required.

Claims team

5.46 Evidence from DVA detailed the composition of the Complex Case Team, noting that the seven delegates are supported by an EL1 Assistant Director, a contracted medical advisor and two social workers. The committee notes that delegates in this Complex Case Team also process claims relating to physical and sexual abuse in the ADF and are rotated after approximately 12 months.

5.47 The committee recognises that the Complex Case Team are dealing with challenging issues and that staff rotations are important to enable staff to take a break. However, the regular rotation of staff may result in loss of corporate memory. To ensure that all staff in the Complex Case Team consistently have an understanding of the issues identified by veterans in this inquiry, DVA needs to remain focused on providing ongoing training to staff.

5.48 In its report, *The Constant Battle: Suicide by Veterans*, the committee recommended that DVA conduct a review of its training programs for delegates and other staff dealing with veterans making claims for compensation and rehabilitation. While the committee recognises that this recommendation was accepted and progress against it has been reported as part of the estimates process, the committee again emphasises the importance of DVA officers working in the claims area undergoing ongoing training and support about issues facing veterans. The feedback from veterans following the recently held consultation forums may be instructive for the practices adopted by the Complex Case Team.

Recommendation 4

5.49 The committee recommends that the Department of Veterans' Affairs continue to provide ongoing training, information and support for the officers working in the Complex Case Team.

Ensuring access to additional support and assistance

5.50 Many of the identified barriers are familiar to the committee from its previous inquiries into similar issues, including its inquiry into veteran suicide. The committee has continued to monitor the implementation of the recommendations of that report through the estimates process. While the committee recognises that DVA is taking steps to streamline its systems and processes in order to provide better support for veterans and their families, it notes that results for veterans can take some time to flow through the system.

5.51 The committee notes that underlying some of these practical barriers is the stated need from some veterans and their families to have their symptoms recognised as being primarily caused by mefloquine and tafenoquine, a view not supported by the medical professionals (outlined in Chapter 2). As a committee of non-medical experts, the committee can only respect the view of the medical community. However, the committee notes the clear message from Defence and DVA that regardless of the cause, assistance is available.

5.52 Building on the initiatives already in place or underway, the committee has identified a number of areas for further improvement as outlined below. Due to the fact that these issues are affecting the veteran community, the committee's recommendations will necessarily be focused towards DVA.

Information for and consultation with veterans and families

5.53 A clear concern identified to the committee was the need to provide more information and support to families. If a veteran is unwell the burden of seeking assistance often falls to family members which, the committee heard, can sometimes mean seeking assistance from multiple agencies at the same time as providing direct care for a veteran. As with its previous inquiries, family members asked for support and information to be more readily available.

5.54 Family members identified that more tailored and coordinated support is needed particularly during times of crisis, when family members are primarily focused on addressing the immediate health needs of veterans and do not have the time and ability to seek advice about various support options. The committee heard that family members have received beneficial support from ex-service organisations but these services have not been provided in a coordinated manner. The committee sees the consultation forums being undertaken by DVA at various locations as a way to increase family members' awareness of short and long term assistance and how it can be accessed.

Consultation

5.55 It was clear to the committee that the previous commitment to an outreach program was interpreted differently in the veteran community. Most interpreted it as

Defence or DVA contacting people individually who were involved in the trials. Defence was clear to the committee that it did not view this approach as beneficial as it does not wish to cause concern among veterans who are well. Defence emphasised that they will continue to provide information to trial participants upon request and provide support should there be concerns.

5.56 The committee understands the concerns raised by Defence about proactive outreach, but also understands that this veteran community will continue to call for what it considers to be an outreach program where soldiers involved in the trials are contacted. Noting this stalemate in positions, the committee supports the current round of consultation forums which is seeking to provide information to veterans about available assistance at the same time as receiving feedback from the veteran community.

DVA consultation

5.57 The recent consultation forums hosted by DVA in Adelaide, Melbourne and Townsville, as well as other locations nationally, provide a further opportunity for veterans and their families to access information and support from DVA. DVA advised that attendees at the first forum in Adelaide reported that it provided helpful information and was a good opportunity to openly discuss their concerns.

5.58 Given that Defence is continuing to provide information to veterans concerned about the use of antimalarials on its dedicated website, it would be beneficial for Defence officials to attend the consultation forums to maintain their knowledge of the issues raised by the veteran community and to update their website accordingly.

5.59 The committee is pleased that DVA remains open to expanding their consultation schedule and hosting additional events should there be sufficient interest. DVA is also seeking formal feedback from participants about their experience at the forum which will provide valuable insight about any changes that could be made to future forums. Given the complexity of some of the issues considered, it would be beneficial for consideration to be given to establish mechanisms to follow up matters raised by attendees, such as running a series of follow up events or a more individualised approach. As noted earlier, seeking assistance at a time of crisis is particularly challenging for families and the committee suggests that the consultation forums need to take account of the best ways to assist families at this time.

5.60 The committee recognises that some veterans may be unable, unavailable or currently unwilling to attend a consultation forum in the current schedule. The committee is of the view that information should be made available in a variety of ways to ensure that as many veterans as possible are able to access the information.

Non-liability pathway

5.61 Evidence from DVA highlighted that some veterans are unaware that access to mental health services is available under the non-liability pathway, with no requirement to link the condition to their service. In light of this, it would be beneficial for DVA to undertake an awareness raising campaign, targeted to the veteran community, to increase veterans' understanding of the non-liability pathway.

This campaign could be developed in consultation with advocates and ex-service organisations.

Recommendation 5

5.62 The committee recommends that the Department of Veterans' Affairs, in addition to the existing program of consultation forums, ensure matters raised by attendees and families are followed up. The forums should continue to be promoted widely and in consultation with ex-service organisations and advocate groups.

Recommendation 6

5.63 The committee recommends that the Department of Veterans' Affairs make the material provided at the consultation sessions available online.

Recommendation 7

5.64 The committee recommends that the Department of Defence attend the Department of Veterans' Affairs' consultation forums to maintain their knowledge of the issues raised by the veteran community. This will assist Defence to ensure their dedicated website is updated appropriately.

Recommendation 8

5.65 The committee recommends that the Department of Veterans' Affairs undertake a targeted awareness raising campaign, in consultation with ex-service organisations and veterans' advocates, to increase veterans' awareness of the non-liability pathway.

Assistance from General Practitioners

5.66 One of the key messages from Defence and DVA is that veterans who are concerned about their health should contact their GP. The Royal Australian College of General Practitioners (RACGP) and veterans also recognised the central role of GPs.

5.67 Some veterans were concerned that their GP was not aware of mefloquine and tafenoquine and therefore was unable to provide the required assistance. Other witnesses described experiences when their GP had been helpful in terms of referrals and making connections with specialist services. The provision and regular review of information resources for GPs is important to ensuring that GPs are able to provide appropriate assistance to veterans and their families.

Information resources for GPs

5.68 The committee notes that DVA and Defence developed information resources for GPs about antimalarials and this material was distributed in 2016. The committee also notes that an information briefing for GPs was held in Townsville in 2016. The committee recognises that the actions taken to provide information to GPs are positive however some evidence provided to the committee suggested that veterans had experienced difficulties obtaining information from their GP. It would be beneficial for the information resources previously developed to be reviewed with particular advice for GPs to recognise the complex conditions with which some veterans may present.

5.69 Furthermore, given the recent TGA approval of tafenoquine, it may be beneficial for additional follow up information to be provided to GPs. This could build on information that will be sent to doctors from the pharmaceutical companies which will be producing tafenoquine.

5.70 The RACGP recognised that the provision of information about antimalarials is particularly relevant around major bases as well as in locations where there is a high volume of travel to and from malarial areas. In this context, it would be advantageous for DVA and the RACGP to take this into consideration when providing information.

5.71 The committee is pleased to note that a representative from the RACGP attends the DVA Health Providers Partnership Forum to provide advice about developing information resources for veterans. In addition, the committee is aware that the RACGP includes DVA information and resources in its publications distributed to the GP community. The continuation of this flow of information is important. Furthermore, the terms of reference of the Health Providers Partnership Forum indicate that the Forum can continue to provide a mechanism to update resources and facilitate information sharing.

Recommendation 9

5.72 The committee recommends that the Department of Veterans' Affairs and Department of Defence, in collaboration with the Royal Australian College of General Practitioners and other health professionals, review and update the clinical guidelines developed in 2016 to recognise the complex conditions with which some veterans may present.

Recommendation 10

5.73 The committee recommends that the Department of Veterans' Affairs consult with the Royal Australian College of General Practitioners to assess whether General Practitioner briefings, like the one that occurred in Townsville in 2016 would be beneficial in other areas, including around major bases.

The need for multidisciplinary care

5.74 The other need which was evident to the committee is that these veterans are dealing with complex and sometimes chronic health needs which require more than a visit to a GP or one specialist to receive a diagnosis. In this context, the committee supports the need for multidisciplinary care. The committee is pleased to note that DVA has recognised that some individuals need tailored, wrap around assistance and that this may need to include supports from a range of specialists to address their complex needs.

Additional research

5.75 The committee is aware that Defence and DVA have jointly commissioned the University of Queensland to undertake a research study looking at the self-reported health of ADF personnel using antimalarials on deployment. This research will use de-identified data from a number of the trials. DVA advised that this new research will focus on the health outcomes of deployed veterans who took antimalarial medications.

5.76 It is expected that this research study will be completed later in 2018. The committee anticipates that the findings from this research may be instructive for DVA in the context of developing services and support that address the challenges reported by this cohort of the veteran community.

Recommendation 11

5.77 The committee recommends that the Department of Veterans' Affairs review the University of Queensland research findings due in late 2018 with a view to further inform the development of any new initiatives and the ongoing review of existing programs.

Neurocognitive Health Program

5.78 As outlined in Chapter 2, veterans suffering from chronic and complex conditions have attributed their symptoms to taking mefloquine or tafenoquine some time ago. The committee heard from individuals that, as many of these reported symptoms are similar to symptoms of PTSD, this has led to veterans being misdiagnosed with PTSD, receiving treatment for PTSD which ultimately has not been successful. While many witnesses including Dr Nevin could not name a specific treatment that veterans attributing poor health to taking antimalarials should be receiving, the committee heard that they are particularly concerned about possible neurocognitive effects.

5.79 Recognising that this is an area which DVA does not have much expertise, DVA has committed to the development of a program to deal with neurocognitive issues, regardless of the cause. This new Neurocognitive Health Program will be accessible to all veterans who have been assessed as requiring treatment for neurocognitive issues.

5.80 The committee is pleased to note that Professor McFarlane and the AQVFA are involved in the design of this program which will add to the range of assistance available from DVA. The committee supports the development of this program, recognising the value of developing treatment and services through a model of co-design.

5.81 Given the potential positive impact of the program, the committee is of the view that its development should be given a high priority. As a first step, the committee encourages DVA to consider early rollout to a targeted population as a pilot program. The pilot program could then be formally evaluated to inform further development of the program prior to broader rollout.

Recommendation 12

5.82 The committee recommends that the Department of Veterans' Affairs prioritise the development of the Neurocognitive Health Program. To enable veterans to access this program as soon as possible, consideration should be given to the rollout of a pilot program to a targeted population.

Recommendation 13

5.83 The committee recommends that the pilot program undertaken as part of the Neurocognitive Health Program be formally evaluated and that the evaluation report be made publicly available.

Collaborative working group

5.84 The committee recognises the importance of fostering cooperation and collaboration between DVA and the veteran community and supports the development of the Neurocognitive Health Program. As stated above, the committee has recommended that a pilot program be considered which would subsequently be evaluated. The post evaluation stage provides another opportunity for DVA to further engage with the veteran community.

5.85 In this context, the committee suggests that a collaborative working group be established to consider the outcomes of the pilot as well as how best to roll out the program more broadly to the veteran community, should it be supported. The establishment of this group could provide another means of facilitating an ongoing dialogue between DVA and veterans. Given the concerns raised by some veterans in the inquiry about the challenges they have experienced when accessing assistance and support, the committee considers that the collaborative working group model could provide a means of further improving relationships and enhancing trust between veterans and the organisations supporting them.

Recommendation 14

5.86 The committee recommends that, following the evaluation of the Neurocognitive Health Program pilot, a collaborative working group be established, including those who contributed to the development of the program, veterans and advocates, medical professionals and the Department of Veterans' Affairs. This group would consider the outcomes of the pilot and, if supported by the evaluation, how best to roll out and promote the program to all veterans it could assist.

Senator Alex Gallacher

Chair

Appendix 1

Submissions

1 Department of Defence

1.1 Supplementary to submission 1

1.2 Supplementary to submission 1

2 Department of Veterans' Affairs

3 Department of Health

4 Repatriation Medical Authority

5 Asia Pacific Leaders Malaria Alliance

6 Australasian Society for Infectious Diseases (ASID) Inc.

7 Australasian College of Tropical Medicine

8 GlaxoSmithKline Australia Pty Ltd

8.1 Supplementary to submission 8

9 60 Degrees Pharmaceuticals LLC

9.1 Supplementary to submission 9

9.2 Supplementary to submission 9

9.3 Supplementary to submission 9

10 Medicines for Malaria Venture

11 Biocelect Pty Ltd

12 Roche Products Pty Ltd

13 Professor G Dennis Shanks

14 Professor James McCarthy

15 Associate Professor Harin Karunajeewa

16 Australian Quinoline Veterans and Families Association

16.1 Supplementary to submission 16

16.2 Supplementary to submission 16

16.3 Supplementary to submission 16

16.4 Supplementary to submission 16

16.5 Supplementary to submission 16

16.6 Supplementary to submission 16

16.7 Supplementary to submission 16

16.8 Supplementary to submission 16

16.9 Supplementary to submission 16

Response by Mr Mark Reid to Supplementary submission 16.7

Response by Dr Geoff Dow to Supplementary submission 16.7

Response by Dr Bryan Smith to Supplementary submission 16.9

Response by Mr Mark Reid to Supplementary submission 16.8

Response by Professor Brown and Professor Quail to Supplementary submission 16.9

17 The Quinism Foundation

17.1 Supplementary to submission 17

18 LTGEN John Caligari (Rtd)

19 Confidential

20 Mr Luke Kain

21 Confidential

22 Confidential

23 Confidential

24 Confidential

25 Confidential

25.1 Name Withheld, Supplementary to submission 25

26 Confidential

27 Confidential

28 Confidential

29 Confidential

30 Confidential

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42 Confidential

43 Confidential

44 Confidential

45 Name Withheld

46 Name Withheld

47 Name Withheld

48 Name Withheld

49 Name Withheld

50 Name Withheld

51 Name Withheld

51.1 Supplementary to submission 51

52 Mr Greg Jose

52.1 Supplementary to submission 52

53 Name Withheld

54 Name Withheld

55 Name Withheld

56 Name Withheld

57 Indo-Pacific Centre for Health Security, Department of Foreign Affairs and Trade

58 Professor Sandy McFarlane AO

59 Name Withheld

59.1 Supplementary to submission 59

60 Name Withheld

61 Name Withheld

62 Name Withheld

63 Name Withheld

64 Name Withheld

65 Name Withheld

66 Name Withheld

67 Name Withheld

67.1 Supplementary to submission 67

68 Name Withheld

69 Mr Colin Brock

69.1 Supplementary to submission 69

70 Mr Desmond Rose

71 Mr Mark Reid

71.1 Supplementary to submission 71

71.2 Supplementary to submission 71

71.3 Supplementary to submission 71

72 Mr Benjamin Fleming

73 Mr Brian McCarthy

73.1 Supplementary to submission 73

73.2 Supplementary to submission 73

73.3 Supplementary to submission 73

Response by Dr Ian Gardner to Supplementary submission 73.3

74 Name Withheld

75 Name Withheld

76 Name Withheld

77 Name Withheld

78 Name Withheld

79 Mr Paul Gleeson

80 Mr Glen Norton

81 Mr Colin McIntosh

81.1 Supplementary to submission 81

82 Mrs Julie Anderson

83 Ms Stella Salter

84 Mr Jaroslaw Michalski

85 Mr Ian Corr

86 Mrs Raelene King

87 MAJ Phillip Chapman (Rtd)

88 Mrs Valerie Marshall

89 Mr Michael Kruizinga

89.1 Supplementary to submission 89

89.2 Supplementary to submission 89

90 Mrs Naomi Kruizinga

91 Mr David Madsen

91.1 Supplementary to submission 91

92 COL Ray Martin (Rtd)

93 Name Withheld

93.1 Supplementary to submission 93

94 Mr Stuart McCarthy

95 Defence Force Welfare Association

96 Royal Australian Regiment Corporation

97 Name Withheld

98 Confidential

99 Mr Todd Connors

100 Ms Toni McMahon

101 Name Withheld

102 Name Withheld

103 Confidential

104 Ms Angela King

105 Mr Chris Ellicott

106 Mr Anthony Fox

107 Name Withheld

108 Mr Syd Carter

109 Mr Sean Rowe

110 Confidential

111 Confidential

112 Dr Ian Gardner

113 Confidential

114 Confidential

115 Confidential

116 Name Withheld

117 Mr Ross Woodfield

118 Confidential

119 Name Withheld

120 Name Withheld

121 Name Withheld

122 Mr Alexander Hering

123 Confidential

124 Name Withheld

125 Confidential

126 Confidential

127 Name Withheld

128 Mr Brian Carlon

129 Name Withheld

130 Dr Phoebe Donaldson

131 Confidential

132 Confidential

133 Confidential

134 Confidential

135 Confidential

136 SGT Jonathan Duncan

137 Mr Jeb Roberts

Appendix 2

Tabled documents, Additional information, Answers to questions on notice

Tabled documents

1 Opening statement tabled by VADM David Johnston, AO, RAN, Vice Chief of the Defence at a public hearing in Canberra on 11 October 2018.

2 Letter from AVM Tracy Smart to AVM Tindall tabled by AVM Tracy Smart at a public hearing in Canberra on 11 October 2018.

3 Opening statement tabled by Mrs Naomi Kruizinga at a public hearing in Melbourne on 5 November 2018.

4 Opening statement tabled by Mr Michael Kruizinga at a public hearing in Melbourne on 5 November 2018.

Additional information

1 Correspondence from Minister for Veterans' Affairs, The Hon Darren Chester MP, response to Committee Chair, received 18 September 2018.

2 Clarification of evidence provided on 8 November 2018 from Biocelect Pty Ltd, received 19 November 2018.

3 Additional information provided by Roche Products, received 19 November 2018.

Answers to questions on notice

1 Department of Veterans' Affairs, Answers to questions on notice following the Brisbane and Townsville public hearings on 30 and 31 August 2018, received 9 October 2018.

2 Royal Australian College of General Practitioners, Answers to questions taken on notice at 11 October 2018 hearing in Canberra, received 31 October 2018.

3 Department of Veterans' Affairs, Answers to questions taken on notice at 11 October 2018 hearing in Canberra, received 1 November 2018.

4 Department of Defence, Answers to written questions on notice, received 6 November 2018.

5 Roche Products Pty Ltd, Answers to questions taken on notice at 8 November 2018 hearing in Canberra, received 19 November 2018.

6 Department of Health, Answers to questions taken on notice at 11 October 2018 hearing in Canberra, received on 16 November 2018.

7 GlaxoSmithKline Australia Pty Ltd, Answers to questions taken on notice at 8 November 2018 hearing in Canberra, received 21 November 2018

Appendix 3

Public hearings and witnesses

Thursday 30 August 2018, Brisbane Queensland

Australian Quinoline Veterans and Families Association

Mr Stuart McCarthy, President

Mr Mark Armstrong, private capacity

Mrs Susan Armstrong, private capacity

Mr Mark Reid, private capacity

Defence Force Welfare Association

Mr Kel Ryan, National President

Mr Benjamin Fleming, private capacity

Mr Ben Whiley, private capacity

Mr Brian McCarthy, private capacity

Australasian College of Tropical Medicine

Professor Geoff Quail OAM, President

Professor Graham Brown AM

Friday 31 August 2018, Townsville Queensland

Mr Greg Jose, private capacity

Ms Robyn Davies, private capacity

Mr Kevin Davies, private capacity

Mr Colin Brock, private capacity

Mr Desmond Rose, private capacity

Mr Wayne Karakyriacos, private capacity

Mrs Lavina Salter, private capacity

Mr Chris Salter, private capacity

Mr Wayne Preedy, private capacity

LTGEN John Caligari (Rtd), private capacity

Ms Kim Davis, private capacity

Mr Walter Davis, private capacity

Ms Cherie Bayly, private capacity

Mr Warren Goodchild, private capacity

COL Ray Martin (Rtd), private capacity

Thursday 11 October 2018, Canberra Australian Capital Territory

The Quinism Foundation

Dr Remington Nevin, Executive Director

National Health and Medical Research Council

Dr Tony Willis, Executive Director, Research Quality and Priorities Branch

Ms Jillian Barr, Director, Ethics and Integrity, Research Quality and Priorities Branch

Royal Australian College of General Practitioners

Dr Penny Burns, GP Representative

RSL National

Mr Peter Eveille, Chairman, National Veterans' Affairs Committee

Professor James McCarthy, Professor of tropical Medicine and Infectious Diseases, Royal Brisbane Hospital and QMIR Bighofer Medical institute

Associate Professor Harin Karunajeewa, private capacity

Department of Health (incl. Therapeutic Goods Administration)

Adjunct Professor John Skerritt, Deputy Secretary, Health Products Regulation Group

Professor Brendan Murphy, Chief Medical Officer, Australian Government

Adjunct Professor Tim Greenaway, Chief Medical Officer, TGA

Department of Defence

VADM David Johnston, AM RAN, Vice Chief of the Defence Force

AVM Warren McDonald AM, CSC, Chief of Joint Capabilities

AVM Tracy Smart AM, Commander Joint Health

BRIG Craig Schramm CSC, Director General Health Capability

BRIG Leonard Brennan, Director General Garrison Health

COL Peter Nasveld, Director Health J07 HQJOC

ADFMIDI

Professor Dennis Shanks, Director of the ADF Malaria and Infectious Disease

Institute

Department of Veterans' Affairs

Ms Liz Cosson AM CSC, Secretary

Dr Ian Gardner, Chief Health Officer

Mr Craig Orme DSC AM CSC, Deputy President

Ms Veronica Hancock, Acting First Assistant Secretary, Veterans' Services Design Division

Dr Stephanie Hudson, National Manager, Veterans and Veterans Families Counselling Service

Monday 15 October 2018, Canberra Australian Capital Territory

Repatriation Medical Authority

Professor Nicholas Saunders AO, Chairperson

Dr Justine Ward, Principal Medical Officer

Mr Paul Murdoch, Registrar

Monday 5 November 2018, Melbourne Victoria

Mrs Naomi Kruizinga, private capacity

Mr Michael Kruizinga, private capacity

Professor Sandy McFarlane AO, Director, Centre for Traumatic Stress Studies, University of Adelaide

Mrs Mary Bush, private capacity

Mr Michael Bush, private capacity

Mr Todd Connors, private capacity

Mr Aaron King, private capacity

Mr Brian Carlon, private capacity

MAJ Phillip Chapman (Rtd), private capacity

Ms Anne-Maree Baker, private capacity

Mrs Raelene King, private capacity

Australian Quinoline Veterans and Families Association

Associate Professor Jane Quinn, Charles Sturt University

Mr Chris Ellicott, private capacity

Mr Mark Freer, private capacity

Thursday 8 November 2018, Canberra Australian Capital Territory

Roche Products Pty Ltd

Mr Svend Petersen, Managing Director

Dr Peter Stewart, Medical Director

Ms Natalie Touzell, Director, Regulatory Affairs Australia-New Zealand

GlaxoSmithKline Australia Pty Ltd

Mr David Herd, Director, Market Access and Communications and Government Affairs

Dr Alison Webster, Head, Global Health Clinical R&D (Global representative, UK)

Dr Carolyn Tucek-Szabo, Head, Regulatory Affairs, Australasia

60 Degrees Pharmaceuticals LLC

Dr Geoff Dow, Chief Executive Officer and Chief Scientific Officer

Biocelect Pty Ltd

Mr Karl Herz, Managing Director