The Independent Medical Expert Group (IMEG) 6th Report

Report and recommendations on medical and scientific aspects of the Armed Forces Compensation Scheme

July 2022

Chair's letter to Minister for Defence People and Veterans

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Ministry of Defence

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Minister of State for Defence People and Veterans
Ministry of Defence
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Whitehall
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Dear Minister,

I have pleasure in submitting the Sixth Independent Medical Expert Group (IMEG) report.

Set up in 2010 following the recommendation of Lord Boyce's AFCS review, in 2012 IMEG became a Non-Departmental Public Body. Its role is to provide you with independent evidence-based advice on medical and scientific aspects of AFCS, reflecting contemporary scientific and medical understanding. This advice is published in a report covering several topics and produced about every two years. Topics are suggested by claimants, their supporters, members of the public and the MOD, and endorsed by you.

The period since the Fifth report was published (February 2020) has seen the COVID-19 pandemic, leading to the introduction of remote IMEG meetings and discussion with external experts. Over the years IMEG has been able to visit the Defence Medical Rehabilitation Centre, now at Stanford Hall, as well as a Personnel Recovery Centre, and has held Stakeholder meetings at the Royal Society of Medicine in London. These have provided valuable feedback on the scheme and insights on the priorities and perspectives of service personnel, veterans, and the charities. I very much look forward to resuming both face-to-face meetings and the visits, particularly as recent and new IMEG members have not yet had such opportunity.

IMEG investigates topics by identifying and appraising relevant evidence, reviewing the published peer-reviewed international medical and scientific literature, and discussing topics within the group and with recognised military and civilian experts.

The Sixth report covers a range of topics, including updates on earlier reports on traumatic brain injury (TBI), particularly mild TBI (mTBI) and its diagnosis; and non-freezing cold injury (NFCI). Mental health and well-being in the armed forces and veterans remains high profile and not always the subject of evidence-based comment. Criticisms include that AFCS compensation awards are inadequate, there is lack of parity of esteem with physical injury and disorder, and too many interim awards are made. Suicide, both in the general community and the armed forces and veterans, is also a matter of great concern and we have taken opportunity to review current understanding of risk factors and preventive measures. There is also a paper on COVID-19, including clinical features, compensation aspects and the military experience to date. As understanding of the virus, its variants, and clinical effects is not yet complete, the associated comment represents current best interim advice. Lastly, following on from the 2017 IMEG review of the science and medicine underpinning the Policy Statement on claims for ionising radiation related conditions, and seventy years after the first UK atmospheric nuclear test, we have reviewed the scientific and medical findings of the Fourth Nuclear Test Veteran data linkage follow-up study, published online at the end of February 2022.

New insights into concussive sporting injuries and the recent conflicts with high rates of blast-related head injury from improvised explosive devices (IED) prompted comment on traumatic brain injury, notably mild traumatic brain injury (mTBI), which IMEG reviewed in its 2013 and 2017 IMEG reports, and in a further report in February 2021. mTBI may be accompanied by psychiatric disorder with often overlapping symptoms, causing additional compromise of function, with impact on prognosis and return to work. An evidence base for effective treatment of neuropsychiatric and psychiatric disorders is developing, but distinguishing mTBI and discrete psychiatric disorder is challenging both for clinical management and in relation to compensation. Functional neuroimaging using magnetoencephalography (MEG), and its possible role in diagnosis and differentiation of mTBI and psychiatric disorders is being actively researched, both in military and civilian populations in the UK.

In June 2019 Min DPV tasked IMEG with review of mTBI, with focus on the clinical utility of MEG. An Interim report to Minister followed in September 2019 and was presented at an international meeting in January 2020 at Imperial College London (ICL).

The Sixth report contains further update on new research. Based on the findings of literature scrutiny and discussion with experts active in the field, IMEG concludes that: -

1. The published scientific literature on MEG reveals lack of agreement about optimal methods of analysis of data from MEG, and limited agreement on investigation protocols. As a result, MEG research has not yet reached sufficient sensitivity and specificity for application to the investigation of mTBI or PTSD in routine clinical practice. It remains a promising technique, but one best undertaken in the context of ethics committee-approved research studies, which are now ongoing.

2. The evidence that TBI can cause not only direct cerebral damage in the short term but is associated with longer term susceptibility to increased incidence of neurodegenerative disease, notably Alzheimer's and Parkinson's diseases, is now substantial, especially for moderate and severe TBI. However, much further research is needed to establish the risk following mTBI, and to understand the neuropathology, mechanisms and clinical features developing over periods of many years.

3. mTBI and PTSD remain defined in the UK and internationally, solely on clinical criteria; imaging is not currently a requirement for making the diagnosis of mTBI. For AFCS compensation, no one is disadvantaged by not having had a head scan. The diagnosis of mTBI and its assessment can be confidently made on clinical grounds in the great majority of individuals. Since April 2005 until 31 March 2021 around 400 awards have been made for mTBI. Annual numbers of awards peaked in 2012/13 and 2013/14 and since then have steadily declined.

4. IMEG will continue to monitor research developments in mTBI and related areas, recognising the important contribution MEG is likely to make, not only in understanding the nature and mechanisms of mTBI and PTSD, but also in a wide range of other neurological and psychiatric conditions.

For the Sixth report we have also revisited non-freezing cold injury (NFCI), previously investigated in the 2015 Report. I am pleased to note that both the incidence and severity of NFCI have improved since 2015. The prognosis of NFCI has also improved, and this is likely to be directly related to better prevention strategies and less severely affected individuals. Recent research has clarified the pathophysiological basis of the pain, which is the main persistent and debilitating symptom in NFCI; this pain is neuropathic in type. Diagnostic accuracy of those with NFCI and persistent pain has been improved by skin biopsy, with objective histochemical analysis showing damage to small nerve fibres (small fibre neuropathy, SFN), but this is currently an investigation available only in a few specialist centres. For AFCS, we conclude that no modification of existing descriptors for NFCI, or additional descriptors, is presently required.

In view of the ongoing interest and concerns expressed about AFCS awards for mental health disorders, IMEG undertook a statistical review of Defence Statistics awards from the beginning of the scheme in 2005 and contrasted these against awards for other conditions. We also carried out an audit of a sample of 150 initial mental health disorder claims processed to notification in 2019/20. This included two sub-samples to assess timings of the steps in the care pathway and medical discharges. Results showed that 76% of all mental health claims were awarded, compared to 45% of all other claims categories; 22% of the former attracted guaranteed income payments (GIP), compared to 5% of all other awards. Interim awards were frequently and correctly made, in the context of incomplete treatment programmes.

The results from examining the time intervals in the care pathway steps were limited by missing data, but suggested that delay in seeking help in general, and delays in accessing specialist care for veterans, are common. Issues for further systematic study include the time interval between stressful incidents and seeking help, and the role of comorbid alcohol misuse, in determining response to treatment and prognosis. We found no evidence that mental health claims were assessed inappropriately, or without parity of esteem. We also confirm that as intended, the evidence confirmed award of the level 4 mental health descriptor, introduced in 2019, was appropriate.

There is understandable public concern regarding service personnel or veterans who tragically end their own lives, but often much misunderstanding. The incidence of death by suicide in service personnel is lower than in the general population of similar age and sex. For UK veterans, present evidence is more limited, but rates are in line with that of the general age and sex-matched population. The one exception is a higher risk in young men with short army service who have recently left the armed forces. It is difficult to prevent suicide or predict whether an individual will take their own life. The strongest risks occur generally in men, those with adverse childhood experiences, those with a mental health disorder (particularly mood disorders and/or alcohol misuse) and in those who have previously harmed themselves. Suicide occurs also in those without these risks, and this varies across cultures. One of the most effective ways to prevent suicide is the removal of access to lethal means. Improved access to mental health and social

care may also help, and the NHS Transition and Liaison Service, and devolved equivalents, may have an important role to play in supporting veterans.

Our COVID report is necessarily interim, providing an overview of scientific and medical knowledge on the adverse health effects of COVID-19 infection, protection and prevention and comment on the UK military experience of the pandemic to date. COVID-19 infection can cause severe, sometimes fatal acute illnesses. What is less clear is the range of longer-term complications arising from acute infection, and the prognosis of persistent symptoms. The sequelae of infection generally reflect the severity of the initial disease. Patients with less severe symptoms during acute infection usually recover completely and rapidly, although a proportion report persistent fatigue and shortness of breath, probably at a rate similar to survivors of other forms of community-acquired pneumonia. The diffuse and sometimes disabling cognitive and physical symptoms, termed post-COVID syndrome or long COVID, are not easily explained by organ damage. The pandemic has also brought uncertainty, anxiety, fear, and loss and sometimes, development of mental health problems and discrete psychiatric diagnoses. Studies to date suggest that psychological effects are relatively short-lived in the majority of those affected, and review of the international literature reveals no reports of increased suicide rates.

As a young, selected group with few pre-existing co-morbidities, the UK armed forces personnel were not expected to be generally at high risk of disabling or prolonged illness from COVID-19, and so far, that has been the case. Up to February 2022 around 250, fewer than 1% of the UK armed forces population had reference in medical records to post-COVID syndrome or long COVID. Of these 124 were medically downgraded. Seventeen were medically limited deployability, of whom 14 were temporary and less than five were permanent; and 108 were medically non-deployable, with 99 temporary and 9 permanent. Claims to date divide into: -

- asymptomatic, minimal, or mildly symptomatic PCR-test positive cases - by far the most common claim.
- acute COVID-19, with symptoms and/or signs for up to four weeks.
- ongoing symptomatic COVID-19, with symptoms and/or signs for four to twelve weeks.
- much less common have been COVID-19 complications related to acute COVID-19.
- long COVID or post COVID-19 syndrome with symptoms and/or signs that develop during or after a COVID-19 infection, continue for more than twelve weeks and are not explained by an alternative diagnosis: usually, these are clusters of symptoms which can fluctuate and change over time and affect any system in the body.
- deaths from COVID-19.

The final paper in the Sixth report is a review of scientific and medical aspects of the Fourth Nuclear Test Veteran follow-up data linkage study, published online in February 2022. Between 1952 and final site clean-up in 1967, the UK conducted a series of atmospheric nuclear weapon tests, and a weapons experimental programme in Australia and islands in the Pacific. By the early 1980s, concern was growing about adverse health effects amongst participants, and in 1983 the MOD commissioned a longitudinal follow-up study into their health. Over 20,000 military personnel who took part in the tests and a control group of similar size, age, rank, and date of service entry, with service in tropical and sub-tropical areas around the same time but not present at the tests, were identified from MOD archives. The subsequent data linkage study compared overall mortality, cancer mortality and incidence, regardless of the precise cause, in participants and controls. Given the context, the study also considered whether the available recorded radiation exposures of test participants might be a possible source of any observed health effects. In the early tests, most participants were monitored, when the majority of the film badges recorded zero ionising radiation dose, and Defence policy was changed to focus monitoring personnel most at risk of radiation exposure. 23% of the test veterans had film badges, with 64% of these showing zero dose, and 8% of the total cohort of participants a greater than zero dose, average 9.9 mSv.

The first analysis presented follow-up to the end of 1988, the second to the end of 1993 and the third to the end of 1998. Each concluded that, increasing with follow-up duration, participation in the Tests had no detectable effect on expectation of life, nor risk of developing most cancers. In late 2018, to increase statistical power, the Fourth follow-up study was commissioned, with the same aims, methods, measured outcomes, and statistical analyses as the first three, extending follow-up to the end of 2017, by when 56% of participants and controls had died.

The Fourth follow-up study showed that differences in risk of disorder incidence and mortality between participants and controls were usually only a few per cent, and risks were not consistent over time, either in risk direction or magnitude. Apparent differences in incidence and mortality values were often driven not by raised rates in test veterans, but by rather low rates in the military controls. In scientific terms, the present conclusion must be cautious, and in the words of the authors of the study: -

"Taken overall, the current analysis indicates that the possibility that test participation has caused a small increased risk of leukaemia other than chronic lymphatic leukaemia (CLL) cannot be ruled out and that, whilst the evidence for any risk appears to have been greatest in the early years after the tests, a small risk might have persisted in more recent years, this long-term risk being particularly evident for chronic myeloid leukaemia (CML)."

The basis of this finding is unknown. For war pensions compensation based on the scientific findings of the Fourth Report, IMEG would recommend no change.

All members of IMEG took part in the discussions and agreed the findings and recommendations in the Sixth Report, which I believe fully reflects the contemporary evidence and AFCS aims and priorities.

Since the last report several members have left IMEG, and others have joined. Those leaving include:

- Professor James Ryan, Emeritus Professor in Conflict Recovery at St George's University of London, and Professor of Military Surgery at the Royal Army Medical College.
- Professor Linda Luxon, Emeritus Professor of Audiovestibular Medicine at University College London, and the National Hospital for Neurology and Neurosurgery.
- Professor David Snashall, Emeritus Professor of Occupational Medicine, King's College London, and Guy's and St Thomas' NHS Foundation Trust.
- Professor Peter White, Emeritus Professor of Psychiatry at Queen Mary University of London, and St Bartholomew's Hospital.

Those joining IMEG include:

- Professor Paul Cullinan, Professor of Occupational and Environmental Lung Disease, Imperial College, London and Honorary Consultant Respiratory Physician, Royal Brompton and Harefield NHS Trust, London.
- Dr Ali Hashtroudi, Clinical Director of Occupational Health and Safety at Guy's and St Thomas' NHS Trust, and Head of the National School of Occupational Health, Health Education England.
- Dr Louisa Murdin, Consultant in Audiovestibular Medicine within the Ear Nose and Throat Service at Guy's and St Thomas' NHS Foundation Trust, London.
- Mr Nick Bunting, Secretary General of RAFA, as the Ex-Services Charities Organisation member.

I am extremely grateful for their unstinting hard work and commitment to IMEG's purpose. I also wish to express my thanks to the ex officio members of the Group, and to the Secretariat for their expert support, guidance, and willingness.

Yours sincerely,

Dr John W Scadding

Independent Medical Expert Group (IMEG) – List of Members

Chair

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Lay Members

Mr Nick Bunting OBE CDir FIOD MCIM, Secretary General of RAFA, as the Ex-Services Charities Organisation member.

JJ Chalmers, an injured person who has claimed under the AFCS

A Service representative who sits on the CAC (Central Advisory Committee for Compensation)

Secretariat

Armed Forces Compensation Policy Team

Observer

Brigadier D R Wilson QHP MBChB MD MSc FRCP, Medical Director to the Surgeon General.

Contents

Mild Traumatic Brain Injury: an Updated Review

SUMMARY AND KEY POINTS

1. This Report follows and updates the extensive review of traumatic brain injury (TBI) published in IMEG's Fourth Report in December 2017, and updates the further report published in March 2021. In the 2017 report we paid particular attention to mild TBI (mTBI). Since then, there have been advances in research in the field of functional neuroimaging using magnetoencephalography (MEG), and in several other areas of clinical science relevant to mTBI. We review these advances in this Report, with special emphasis on MEG.

2. IMEG was tasked by Min DPV in June 2019 to review mTBI, with reference to the clinical utility of MEG. This coincided with a request from the Surgeon General for a report on MEG. An Interim Report was submitted on behalf of IMEG in September 2019, and subsequently endorsed by IMEG. The Report was circulated in military medical circles and presented as one of the papers considered at an international meeting convened by the Surgeon General in January 2020 at Imperial College London (ICL), chaired by Professor Anthony Bull, Director of the Centre for Blast Injury Studies at ICL. In the interests of clarity and transparency, both the IMEG Interim Report and the Consensus Statement arising from the ICL meeting are annexed to this Report.

3. The purpose of this Report is to review research advances and interpret these in the context of mTBI in the military. mTBI and post-traumatic stress disorder (PTSD) are frequently comorbid conditions. This Report re-examines the relationship between the two conditions in the light of MEG research.

4. There are currently 13 MEG scanners in the UK, all based in research facilities. Each scanner costs in the region of £2m, with high annual maintenance costs. MEG scan results need to be co-registered with high-field magnetic resonance scans (MRI). Thus, total investigation costs are large. MEG scanning is not, at the time of publication of this Report, routinely available in the NHS.

5. The currently established clinical applications of MEG include the pre-surgical assessment of highly selected patients with epilepsy, and the determination of cerebral dominance prior to neurosurgery in some patients with cerebral tumours.

6. The published scientific literature on MEG reveals a lack of agreement about optimal methods of analysis of the data acquired by MEG scanners, and limited agreement concerning research investigation protocols. The Consensus statement from the ICL meeting, referred to above, includes a call for greater collaboration between the MEG research groups in the UK which are active in mTBI research. IMEG supports this.

7. We conclude that MEG research has not yet reached sufficient sensitivity and specificity for application to the investigation of mTBI or PTSD in routine clinical practice. MEG remains a research investigation which should be offered only in the context of research ethics committee-approved studies. This conclusion is in line with the Consensus Statement from the ICL meeting.

8. The evidence that TBI can cause not only direct cerebral damage in the short term but is also associated with longer term susceptibility to increased incidence of neurodegenerative disease, notably Alzheimer's and Parkinson's diseases, is now substantial, especially for moderate and severe TBI. However, much further research is needed to establish the risk following mTBI, and to understand the evolving neuropathology, mechanisms and clinical features developing over time. Cognitive symptoms, including problems in attention and executive function, are common after mTBI and are usually transient. However, in some individuals, cognitive problems may first present long after the index injury. Recent advances in neuroimaging and neuropathology are now shedding light on possible mechanisms, including the occurrence and clinical effects of diffuse axonal injury, and resulting chemical changes in the brain.

9. Chronic traumatic encephalopathy (CTE), due to repetitive concussive and sub-concussive blows to the head, may take many years to develop, and although this diagnosis may be suspected in life, it is reliably diagnosed only with post-mortem examination of the brain.

10. Given that TBI, and particularly mTBI, is very common worldwide, trauma to the head could prove to be an important contributory factor in the causation of a proportion of all degenerative dementias. Current evidence does not permit definite conclusions to be reached concerning the magnitude of this in relation to mTBI. Emerging neuroimaging techniques, and discovery of other potential biomarkers, including brain atrophy rates and neurofilament light protein levels in cerebrospinal fluid (CSF) and blood, show promise for assisting in differentiating the underlying neurobiology of psychiatric and neurological conditions, in understanding mechanisms and the pathogenesis of neurodegeneration, and in time, having a role in evaluating treatments that may slow or prevent progression.

11. We emphasise that both mTBI and PTSD remain defined in the UK and internationally solely based on clinical criteria. There may be strong clinical indications for neuroimaging with CT or MRI scans in the management of some patients with mTBI, but imaging is not currently a requirement for making the diagnosis of mTBI.

12. In relation to compensation under AFCS, no affected individual should feel disadvantaged by not having had a head scan. The diagnosis of mTBI can be confidently made on clinical grounds in the great majority of individuals, with an assessment for compensation being made accordingly. However, it is important to note that traumatic vestibular syndromes (due to damage to the inner ear) may result in identical symptoms to mTBI and may be overlooked. Clinical awareness of this, and appropriate objective vestibular investigation are necessary.

13. IMEG has reviewed the current Descriptors and Tariffs for mTBI and finds no indication to change these now.

14. It is important to reiterate here that the level of AFCS compensation is based on the severity of loss of functional capacity, particularly for future civilian employment, resulting from attributable physical injury or other disease, irrespective of specific diagnosis.

15. IMEG will continue to monitor research developments in mTBI and related areas, recognising the important contribution MEG is likely to make, not only in understanding the nature and mechanisms of mTBI and PTSD, but also in a wide range of other neurological and psychiatric conditions.

16. IMEG's examination of MEG and mTBI presented here builds on the Interim Report (Annex 1). A Summary and Key Points of this current report were presented to Min DPV and the Central Advisory Committee on Compensation in January 2021. The full Report, approved by IMEG in February 2021, was made available publicly in electronic format in March 2021. This further updated Report is now included in IMEG's Sixth Report.

17. Although this review pays particular attention to the place of advances in neuroimaging in the assessment of mTBI, an understanding of related recent scientific evidence is also essential, to set this in a comprehensible and practical broader clinical context. This review therefore re-examines a wide range of clinical, investigative, neuroimaging and pathological aspects related to both acute and possible long-term sequelae of mTBI. This field of scientific study is evolving rapidly and is complex. This complexity is reflected in the text of this report. IMEG recognises that until the full clinical implications of this new evidence become clearer, some of the content of this report is inevitably challenging for a non-medical readership. Wherever possible, we have attempted to provide explanations that are accessible to our intended wider readership.

Introduction

18. Traumatic Brain Injury (TBI) is a common problem in both military and civilian populations worldwide. In the UK there are approximately 1.3 million attendances at Accident and Emergency departments annually. Severe TBI accounts for about 3% of all TBI, moderate for about 20% and mild TBI (mTBI) for 70-90%. The latter wide estimate reflects the fact that mTBI does not always come to medical attention (1). Severe TBI is a leading cause of death in young adults. mTBI is not fatal, and although recovery overall is good, a minority of those affected experience persistent symptoms and functional disability (2). Head injury of all severities, and in similar proportions, is an issue in the UK armed forces. The previous IMEG reports focused on mTBI, with the in-depth 2017 report recording many gaps in our understanding of mTBI (3). Attention was drawn to variations in definitions, classification, and nomenclature of severity within the clinical range currently embraced by the diagnosis of mTBI. Current definitions agree that the diagnosis is made entirely based on history and clinical features, which distinguish mTBI from moderate and severe TBI, in which standard brain imaging is

usually abnormal. However, clinical examination will not identify the presence of a primary vestibular disorder, as distinct from mTBI (see paragraph 94). Conventional brain imaging with CT scanning is normal in mTBI, though may be helpful in identifying unsuspected cerebral abnormalities, such as small intracerebral haemorrhages, indicating clinically unsuspected more severe forms of injury. However, as discussed in the 2017 Report, research studies with advanced non-routine methods of MRI scanning can sometimes demonstrate subtle changes in mTBI. Furthermore, a new type of functional brain imaging, magnetoencephalography (MEG), frequently demonstrates abnormalities in subjects with mTBI. MEG has attracted a great deal of interest in recent years in the investigation of brain function resulting from trauma, and from a wide range of other neurological and psychiatric conditions, including PTSD. Other issues considered in the extensive 2017 IMEG Report included epidemiological aspects, pathophysiology, the relationship of mTBI and concussion, investigation and management, the distinction between, and overlap of, primary traumatic labyrinthine pathology and audio-vestibular features of mTBI, mental health and TBI, and the comorbidity of mTBI and PTSD. It is worth emphasising here that patients with mTBI frequently experience a wide range of symptoms, including physical, audiovestibular, cognitive, emotional, and behavioural, occurring in different proportions, with all these symptoms contributing to overall morbidity in mTBI. Many persistent symptoms are not specific to mTBI but may also occur following traumatic injury to other body structures, in relation to mental health disorders, such as PTSD and depressive disorder, and indeed, in otherwise apparently healthy individuals (4)(5)(6). Trauma to the inner ear, resulting in labyrinthine concussion, decompensation from an earlier vestibular disturbance, post-traumatic vestibular migraine presenting with vestibular, auditory, or neurological symptoms (including headache, visual blurring, or double vision), psychological symptoms (anxiety, panic attacks and depression) (7)(8), or cognitive symptoms (9), and in the absence of any brain injury and normal brain imaging, may exactly mimic the symptoms of mTBI. In addition, persistent postural-perceptual dizziness (PPPD) is a newly defined functional neurological syndrome, characterised by chronic dysfunction of the vestibular system and brain with persistent dizziness, non-spinning vertigo and/or unsteadiness, with significant disability, reflecting long-term maladaptation to a labyrinthine, medical, or psychological event (10). Specialist vestibular assessment should be available in individuals with mTBI and prominent vestibular symptoms, to diagnose balance disorders and institute appropriate treatment.

19. mTBI and mental health disorders may co-exist, with overlap of symptoms and difficulty in clinical differentiation. We recommend reading the 2017 IMEG Report, which discusses these issues in depth, alongside the present Report. The present Report again examines mTBI and related psychiatric morbidity, notably post-traumatic stress disorder (PTSD).

20. Since the 2017 IMEG report, in addition to developments in neuroimaging, there have been research advances in mTBI in the fields of genomics, computational biology, neuropathology, and serum biomarkers, with many publications in the mainstream peer-reviewed scientific literature. In time they promise improved disease characterisation, understanding of mechanisms and the relation between mTBI and later development of neurodegenerative disorders, and will hopefully also inform best practice treatments.

21. This review considers key recent research on mTBI including diagnosis, early predictors of persistent post-concussion symptoms, prognosis and long-term risk of neurodegenerative disorders, putative biomarkers, differentiation of mTBI from comorbid mental health disorders, and mTBI treatment evaluation and current best practice. An objective, sensitive and specific biomarker for mTBI would be helpful, and in this context the role of functional neuroimaging, particularly magnetoencephalography (MEG) is discussed. The Interim IMEG Report from September 2019 is at Annex 1 (11).

mTBI in military populations

22. More than seven years from the end of the conflict in Afghanistan, it is appropriate to summarise mTBI findings so far. In the same theatres and at the same dates, the reported rates of mTBI in US and UK military personnel in Iraq and Afghanistan were markedly different. Studies of clinician-confirmed injury in deployed US military personnel found that about 23% sustained mTBI, with higher rates amongst combat personnel, and substantially higher rates (59%) in those with combat injury (12)(13)(14). For UK troops on return from deployment, equivalent prevalence rates were 4.4% among those deployed, with 9.5% in combat personnel. Pre-deployment alcohol misuse and PTSD symptoms were associated with subsequent mTBI in UK servicemen (15). The difference between US and UK data may be either a real effect, resulting from longer deployment, for example, or be artefactual, due to either different mTBI definition or different approaches to screening. In a later UK study that was conducted in theatre in the fifth month of a six-month deployment in Afghanistan, looking at self-reported undocumented mTBI in 1363 deployed personnel (96% response rate), 6% reported one or more potential mTBI exposures ('…any injuries as a consequence of the following: fragmentation, round (bullet), fall, blast, direct head injury and motor vehicle accident') during the deployment, and 1.6% reported injury followed by one or more mTBI symptoms (2). Only six individuals reported loss of consciousness, all for less than five minutes. Higher PTSD symptom scores were significantly associated with reporting blast exposures and symptomatic mTBI. Data collected during deployment for this study revealed a substantially lower incidence of mTBI than that recalled post deployment. Similar inflation is seen in history taking of remote events in US studies (16).

23. The most recent UK study of mTBI and post-concussion symptoms (PCS) was longitudinal, conducted by asking Iraq and Afghanistan veterans whether mTBI reported in 2007-2009 was associated with PCS 7 or 8 years later (17). The symptoms were headache, dizziness, fatigue, sleeping difficulties, irritability, double or blurred vision, forgetfulness, ringing in the ears and loss of concentration. The study was by questionnaire, with about half those surveyed responding (2,318 out of 4,601). Females, higher rank and education, reserve service, being older and serving in the RAF were linked with completing the follow-up questionnaire. Those who at baseline in 2007-9 met the criteria for mTBI or had alcohol misuse problems were less likely to respond in 2014-16, while those who reported PCS in 2007-9 were more likely to respond at follow-up. When adjusted for baseline social, military, and demographic factors, in those responding at follow-up, there was no longer an association of likelihood of response with baseline alcohol misuse, reporting 1 or 2 post-concussion symptoms, or mTBI. Of

the symptoms followed up, continuing dizziness and loss of concentration were again reported more frequently 7 to 9 years later in those originally reporting mTBI, compared with the two control groups, "no injury“ and “other injury” individuals. This was regardless of adjustments, including for social and demographic factors, PTSD and further mTBI occurring between 2009 and 2014. With adjustment, the risk of long-term loss of concentration became borderline significant (prevalence ratio 1.29; 95% CI 0.98-1.71). The study also found that in 2014-16, in the fully adjusted models in both the mTBI and control groups, the prevalence of 7 of the 9 post-concussion symptoms, but not headache or irritability, increased over time, suggesting they were not directly related to the original mTBI. There were some limitations to the study. The response rate was only 50%, absolute numbers reporting the various symptoms were small and the effect of some unknown confounders may have been overlooked. The symptoms of the index mTBI event in these studies were not exclusively due to blast or bullet injury, but included fragmentation injury, falls, motor vehicle accidents and some events described only as "other exposures”. It is also true that the same symptoms could be associated with vestibular dysfunction which were not defined initially in the study, as present or absent.

Early predictors of persistent post-concussion symptoms

24. Prognosis in mTBI and predictors of long-term disabling symptoms were considered in the 2017 IMEG report, when it was concluded that findings across different studies were inconsistent, mainly owing to different definitions of mTBI, variations in patient age groups and comorbidities, the presence of other traumatic injuries from the incident and in some studies, inclusion of different levels of TBI severity without clinical stratification. Other differences included variations in treatment interventions and study outcomes, and assessment at different intervals from the index injury. Since the UPFRONT prognosis study (18), discussed in the 2017 IMEG Report, the focus has been on development of prognostic models where patient characteristics are combined in a mathematical formula and can be used to provide information on expected outcome in individual patients, adjust for differences in case-mix in studies, and standardise outcome measures and rates to improve design of clinical trials and benchmark care quality (19). Although not yet routinely used clinically, robust models have been developed for moderate and severe TBI, but are not yet available for mTBI (20) (21) (22) (23).

Biomarkers

25. Biomarkers are biological markers that can be measured and evaluated and serve as specific and sensitive indicators of normal or pathological processes or responses to therapeutic interventions. Biomarkers will aid understanding of prediction of disease onset, causation, diagnosis, progression, prognosis, and outcome of disease treatment. Potentially relevant to our understanding of neurological damage caused by

mTBI are measurements of certain blood or cerebrospinal fluid (CSF) constituents, and the emerging imaging techniques which provide insights into both structural alterations and brain function.

Neuroimaging

Magnetic Resonance Diffusion Tensor Imaging in mTBI

26. The role of conventional imaging with CT and MRI scanning in the investigation of individuals with mTBI was discussed in the 2017 IMEG Report, and reference was also made to research concerning newer neuroimaging techniques not yet widely available in routine clinical practice. These included more sophisticated approaches to magnetic resonance imaging (MRI) and specifically diffusion tensor imaging (DTI), and MEG.

27. The molecular pathology of mTBI was also considered in the 2017 IMEG Report. Molecular changes are recognised to occur in the absence of recognisable cellular pathology. These changes include abnormalities in chemical neurotransmission, ionic changes, increased energy demands, changes in cellular metabolism, and excitotoxicity, which are all acute and potentially reversible changes, and which possibly explain transient cognitive and mood changes in the majority of individuals with mTBI who make a rapid and complete recovery; see Iverson for a full review (24).

28. Research has demonstrated that mTBI can cause axonal (nerve fibre) stretching, inflammatory changes, disruption, and separation of nerve fibres, together comprising diffuse axonal injury (DAI), although complete severance of nerve fibres (axotomy) is apparently unusual (25). Nerve fibre damage which is less severe than axotomy may prevent electrical nerve impulse transmission (conduction block), leading to functional disconnection, often referred to in this context as deafferentation. This is potentially reversible.

29. Standard MRI scanning in mTBI is usually normal. Magnetic resonance DTI quantifies the diffusion characteristics of water, which are altered by changes in tissue microstructure, acting as a sensitive marker of white matter damage. MR DTI findings in a series of 63 military personnel with a clinical diagnosis of mTBI have been reported from the USA (26). All had suffered primary blast exposure, but also another, non-blast-related mechanism of injury including a fall, motor vehicle crash or other blunt head injury. They were compared with 21 military personnel who had experienced blast exposure and other injuries, but who did not have a clinical diagnosis of mTBI. All were scanned within 90 days of the mTBI event. As a group, compared to the controls, 18 of 63 (29%) with blast-related mTBI showed marked changes in several brain sites, a significantly greater number of abnormalities than expected by chance ($p<0.001$). Re-scanning in 47 subjects with mTBI, 6-12 months later, revealed persistent abnormalities, judged to be consistent with evolving injuries. However, the majority of the mTBI subjects in this series did not have abnormalities on DTI, questioning the sensitivity of DTI in mTBI. This led the authors to conclude that mTBI remains a clinical diagnosis,

not dependent on the results of brain imaging. They further concluded that the observed DTI abnormalities were evidence of axonal injury. However, because all those with blast injury had also suffered additional blunt head injury, the authors cautioned against assuming that the blast injury event was responsible for all the abnormalities shown on DTI. Finally, attention was drawn to the high rate of post-traumatic stress disorder (PTSD) in those with blast-related mTBI (further discussed in the 2011 systematic review of Carlson et al (12).

30. Standard brain imaging, including CT and MRI scanning using routine signal analysis, does not detect the subtle changes that may occur in mTBI. However, MR DTI demonstrates white matter damage, as discussed above, due to diffusion characteristics of water indicative of axonal damage, in a proportion of patients, variable in different series and possibly partly related to severity (within the current broad clinical definition of mTBI) and interval after head injury (26, 27). This limited evidence was discussed in the 2017 IMEG Report. The fact that, although more sensitive than positron emission tomography (PET) and standard MRI, changes have been reported in widely variable proportions (29-70%) of those with mTBI (26) (27) (28) indicates that DTI sensitivity is insufficient to regard it as a gold standard diagnostic test in mTBI. However, the degree of white matter damage in mTBI demonstrated by DTI is associated with the severity of cognitive impairment (29)(30)(31)(32). DTI has thus proved to be a valuable research tool in mTBI, providing insights into the structural damage and neurological consequences. In addition, another means of magnetic signal analysis, Susceptibility Weighted Imaging (SWI), has a role in identifying the presence of very small haemorrhages (microbleeds).

31. A systematic review of DTI findings in 86 civilian, military and sport-related mTBI in adults took account of mTBI category, (based on time interval between injury and assessment, acute, subacute, chronic, remote, and whether single or repetitive), as well as injury mechanism (33). It was anticipated that the stratified mTBI study groups might provide different white matter diffusivity metrics, but the variations recorded were inconsistent. Since the effects of mTBI can be modified by comorbid medical and socioeconomic factors, studies were also reviewed which considered socioeconomic status (SES), major depressive disorder (MDD) and attention deficit hyperactivity disorder (ADHD). The authors concluded that DTI is sensitive to a wide range of mTBI group differences in diffusion metrics and in patients affected by MDD, ADHD and socioeconomic factors, and was therefore not specific enough for routine clinical use (33). Difficulties in data comparisons include control group variability and different analytic and reporting techniques. To be useful clinically, studies must include appropriate controls, be longitudinal in design and use standard functional outcomes. Additional MRI research studies are cited in Annex 1, paragraph 5.

Positron Emission Tomography

32. Positron emission tomography (PET) is used to study proteinopathies (disorders resulting from accumulation of abnormal proteins) including neurodegenerative disorders, by detecting markers such as tau protein in neurofibrillary tangles, and beta amyloid aggregates (34). Short half-life radioactive tracers are injected intravenously, and the gamma radiation emitted is detected by gamma camera arrays arranged to

produce a three-dimensional image. PET is providing insights into the mechanisms of TBI, such as inflammation and metabolic disturbances, and changes relating to neurodegeneration (35), and the function of cellular organelles such as mitochondria and activated microglial cells (36). These remain research investigations, and PET does not currently have an established role in routine assessment of these disorders.

MEG: basic considerations

33. Magnetoencephalography (MEG) is a brain imaging method for recording magnetic fields produced by electrical activity in the brain, using sensitive magnetometers. It records brain function with high temporal and spatial resolution. The results of MEG always need to be co-registered with detailed images obtained by MRI to produce a detailed 'map' of the different regions of the brain active both at rest and in the performance of cognitive tasks. The recording of the very small magnetic fields generated by electrical activity in the outermost part of the brain, the cerebral cortex, presents major technological problems. Environmental magnetic fields, including the earth's magnetic field, need to be excluded, by making recordings in a magnetically shielded room. The cost of a MEG scanner is currently in the region of £2m. There are currently 13 MEG scanners in the UK, though it is likely that more will be established in the next few years.

34. The physics of recording and the accurate localisation of magnetic fields generated from the cerebral cortex is complex (37)(38). MEG does not record magnetic fields from deeper structures in the brain, but, as with electroencephalography (EEG), such abnormalities may be reflected in the recorded cortical magnetic fields. In addition, removal of confounding magnetic signals from blinking, eye, and facial movements, and from the heart is an important issue (39).

35. The unique properties of MEG, with its high spatial and temporal resolution, explain why it is proving to be a useful research tool in neurological and psychiatric conditions, in combination with existing functional imaging techniques including functional MRI (fMRI) and single photon emission computed tomography (SPECT). MEG has a sub-millisecond temporal resolution and is far superior in this respect to fMRI which is dependent upon changes in blood flow and has a temporal resolution of hundreds of milliseconds; and to SPECT which has a temporal resolution of minutes. EEG also has a high temporal resolution, but the advantage of MEG over EEG is that magnetic fields are not distorted by the skull and scalp in the way that EEG electrical signals are. This results in a spatial resolution of millimetres for MEG, in contrast to centimetres for EEG (40). Thus, MEG can provide sensitive real-time information about the functioning of the brain.

36. The analysis of MEG data presents another major technological challenge, evident from the range and complexity of the methods described in the research literature (41)(42)(43). The variety of analytical methods used in different published studies to date indicates the need to adopt a cautious interpretation of MEG in research papers. It also demonstrates that MEG is a rapidly developing research technique for investigating brain function, but with limited consensus concerning routine clinical utility.

Current Clinical Applications of MEG

37. The most advanced clinical application of MEG is as part of the pre-surgical assessment of highly selected patients with epilepsy, with its ability to localise epileptic activity to within a few millimetres (44)(45)(46). MEG is also establishing a role in determining cerebral dominance for language function in other conditions, including cerebral tumours. MEG is a functional imaging technique, allowing recordings to be made during the performance of cognitive tasks and in response to visual and auditory stimulation. MEG is revealing exciting insights into the relationship between brain activity, cognition and behaviour, and there are research reports of its application to a wide range of conditions including schizophrenia, stroke, Alzheimer's disease, chronic alcoholism, facial pain, multiple sclerosis, and autism (47) (48)(49)(50).

MEG in mTBI

38. MEG identifies abnormalities of the electrical activity in nerve cells in the cerebral cortex and their injured nerve fibres. As with EEG, damaged cerebral tissue gives rise to ongoing electrical activity of lower frequency, detectable by MEG. Recordings from normal cerebral cortex show activity predominantly with frequencies above 8Hz, while injured neurons generate delta (1-4Hz) or theta (5-7Hz) activity. Localisation of such abnormal activity using MEG was demonstrated more than 20 years ago (51).

39. The sensitivity of MEG has been demonstrated in two further studies. In the first (52), MEG was compared with EEG and standard MRI in subjects who were symptomatic following concussion (mTBI). MEG detected slow wave abnormalities in 65%, whereas EEG was abnormal in 20-25%, and MRI in 20%. In a later study (53), a series of 30 mTBI patients with persistent symptoms of more than one year's duration were compared using investigation with MEG, SPECT, and MRI. MEG proved to be more sensitive than MRI or SPECT and correlated with cognitive deficits; temporal lobe abnormalities were associated with memory problems, frontal lobe with executive deficits, and parietal lobe with attention deficits.

40. In recent studies, the most consistent MEG findings in mTBI patients, while awake and resting, are increased delta and theta slow wave activity at the site of injury and in the contra-coup area of the brain. This was seen in a multi-modal study in 87% of 45 patients with mTBI and persistent post-concussion symptoms (PCS) at 1-46 months post-injury (54). This high detection rate for MEG in mTBI should be compared with EEG, MRI, SPECT, and DTI, which detected only 20%, 2-25%, 40% and 29-70% of cases respectively (26)(27)(28). MEG can also locate areas of brain affected when other symptoms are present, for example memory impairment (temporal lobe) and attention deficit (parietal lobe). Slow wave activity, demonstrated by either EEG or MEG, is not unique to mTBI but is also seen in many other conditions including, for example, Alzheimer's disease, brain tumour, PTSD, epilepsy, and stroke. Unlike normal resting state MEG data, where neuronal activity is typically recorded at frequencies over 8Hz, neuronal tissues in these conditions generate abnormal signals at low frequency, in the delta (1-4 Hz) or theta (5-7 Hz) range (55)(56)(57)(53)(58)(59)(60)(61). However, activity within the beta range (13-30 Hz), and particularly bursting beta activity, which is important in mediating connectivity and thus networking between different brain regions,

and particularly between the cerebral hemispheres, has very recently been shown to be reduced in mTBI, the degree of this impairment correlating with symptom severity (62). This demonstrates an additional feature of interest in MEG-recorded brain activity, and the potential of future MEG research to elucidate pathophysiological mechanisms in mTBI and other brain conditions, with the prospect of more precise clinico-pathological correlation, prognosis, and evaluation of treatments. MEG is also affected by therapeutic and recreational drugs (63)(64). Thus, the type of abnormal MEG activity found in mTBI is not specific to this condition. Furthermore, in the absence of longitudinal studies involving sufficient numbers of patients with symptomatic mTBI, it is not possible to date the MEG findings and be certain that they relate to a recent rather than a past event, nor to what extent evidence of previous injury is detectable by MEG in asymptomatic subjects. Without MEG recordings in appropriate control subjects with mTBI but without symptoms, it is not possible to know whether similar changes occur also in asymptomatic subjects following mTBI. A recent review concluded that MEG offers the most sensitive marker available for detection of disturbed function resulting from mTBI. However, further investigation within the range of clinical severity of mTBI and over time from injury (longitudinal study) is needed before MEG can be applied and reliably interpreted in routine clinical practice (28).

41. As noted above, with refinement of data processing and analysis, the sensitivity of MEG can be increased to 87% in subjects with mTBI and persistent symptoms (54). Of those included in this study, half had mTBI due to blast injury and half due to other causes. In mTBI, multiple cortical areas may be affected in an unpredictable pattern, in contrast to studies of MEG findings in patients with some other neurological conditions (50). This finding raises as yet unanswered questions about specificity and the nature of the injury. Finally in relation to current clinical practice, to date, there has been only one systematic review of published MEG studies in mTBI (65). This concluded that while MEG reveals several promising biomarkers in mTBI, in the absence of structural abnormalities demonstrable by either CT or MRI, there is insufficient evidence to support routine clinical use of MEG in mTBI.

42. Importantly, it should be emphasised that MEG is a functional brain imaging technique, but to date there have been few studies of altered function in response to the performance of cognitive tasks (cognitive loading). In one study (66), MEG recordings were made in civilian subjects with mTBI from a variety of causes, during performance of a comprehensive battery of cognitive tests. Half of the mTBI subjects were studied at 6 days to 2 months following the mTBI event, and half at 6 months after the mTBI event. MEG abnormalities were found in the left parieto-temporal cortex, left superior frontal gyrus and right parietal regions. The authors concluded that the observed alterations in cortical activity during cognitive loading may provide measurable neurophysiological correlates of cognitive difficulties in subjects with mTBI, even at the individual level. This could potentially have important practical application for individual patients, but the research finding requires confirmation.

MEG in PTSD

43. MEG studies in PTSD are limited in number, and interpretation is challenging, largely due to the differing methods of computational analysis which, as with mTBI studies, are complex. This subject is further elaborated in the Interim IMEG Report (11). Clinically, matters are complicated by the fact that mTBI with persistent symptoms and PTSD are frequently comorbid. Functional MRI (fMRI) has played a pivotal role in revealing aspects of disturbances of cerebral processing in psychiatric illness (66), including the model of PTSD which proposes that behaviour and cognitive phenotypes of PTSD arise from abnormal interactions involving the amygdala, prefrontal cortex and hippocampus (67). The 2019 Interim Report discussed the evidence on MEG and PTSD, citing particularly a study which included an overview of the complex advanced computer principles and approaches used to detect and map MEG signals, needed to investigate neural circuit function via neural oscillations and their connections across different brain regions (42). Unsurprisingly, given the different study conditions, results from the various research studies reviewed were mixed, but the overall conclusion was that compared with normal subjects, there is a reduction in network efficiency and increased randomness in PTSD, while in mTBI there is an increased degree of structure and high levels of clustering co-efficients. These abnormalities were shown in brain regions relevant to core behavioural PTSD phenotypes including disturbances of memory, attention, and impulsivity. It was proposed that these MEG changes might prove to be useful markers for PTSD in support of a clinical diagnosis (42). We have reached the conclusion that further research is needed to clarify understanding of brain function in PTSD, and that it is premature to regard MEG as having utility in routine clinical practice in PTSD.

Recent EEG Studies on brain connectivity

44. A recent research report raises the possibility that refined analysis of EEG data may provide another means of looking at brain connectivity in health and disease (68). As mentioned already, EEG has high temporal resolution, but relatively poor spatial resolution, and importantly, much lower than MEG. This is due to electrical properties within the brain and the transmission through the skull and scalp which lead to distortion of the electrical signal and the potential for identifying functional connectivity within the brain where it does not in fact exist.

45. A new method addressing this volume effect is orthogonalized power envelope correlation, which is a method of assessing apparent connectivity from different brain regions. It does this by detecting the signal from two separate brain areas and looking for synchrony in their different signal envelopes. The orthogonalization process means that only true connectivity remains. This finding was validated in a recent paper on EEG profiling in PTSD (69). When network patterns, using a theta carrier frequency and ‘eyes open while resting’ method, were established in a group of demographically homogeneous US combat veterans with PTSD, or sub-threshold PTSD, and compared with civilians without PTSD or any other psychiatric diagnosis, hypoconnectivity was detected between 74 areas of the brain in the PTSD group (particularly those of the anterior middle frontal and orbital cortices), similar in location to that seen with fMRI. The researchers went on to seek correlations of these changes with cognitive functions and symptoms. The hypoconnectivity related to digit span impairment but not to other cognitive deficits, symptoms, comorbid depression or taking psychotropic therapeutic

drug medication. Importantly, these differences were a group, not individual, effect and were not seen when orthogonalized power envelope correlation was not used.

46. An issue raised by the authors was how far possible interference known to occur with MEG and EEG from eye movements and blinking was taken into account as an explanation for the findings. Frontal lobe connectivity in the theta frequency, as observed in this study, is a potential issue with blinking and eye movements. This will require further study. Further research on band connectivity in PTSD is a promising approach, perhaps particularly in relation to treatment effects and evaluation. The refined EEG analysis described in this study represents yet another means of assessing cognition and brain connectivity and has the advantage of being relatively inexpensive. We mention it here for the sake of completeness, but for the moment, the technique does not have clinical utility at the level of the individual patient. Sophisticated EEG analysis of this sort, if shown to have clinical utility, would be much less expensive than MEG, but the likelihood is that the techniques will become complementary in clinical practice.

Meeting at Imperial College London (ICL) to set a National Consensus for managing mTBI

47. Reference has already been made to the meeting at ICL, held on 15 January 2020, and the Meeting Consensus report is at Annex 2 (70). The first part of this meeting focused on research and the clinical utility of neuroimaging in mTBI, and in particular the use of MEG. The second part considered the neuroendocrine consequences of TBI, their investigation and treatment. From this emerged a consensus statement, which we summarise below: -

- mTBI due to blunt head injury and blast related mTBI may co-exist in armed forces personnel. Separate work, notably in animals suggests that blast and blunt mTBI may not be pathologically identical, but MEG studies of the issue are scarce (only two to date) and, while suggesting the two are different pathologically, research studies did not always include appropriate controls
- There is overlap in symptoms between mTBI and mental health disorders, including PTSD
- There is currently no diagnostic test for mTBI based on "signature" imaging or other abnormality
- Present treatment of suspected co-existing mTBI and PTSD in armed forces personnel and veterans is not informed by imaging, but rather based on symptoms and disability
- More research on military blast induced mTBI is needed to include: i) those exposed to blast but with no reported long-term effects, ii) those exposed to blast and reporting persistent symptoms /long-term sequelae, and iii) those at risk of future blast exposure. Such research should satisfy several criteria, including adequate study size, randomised controlled trials of treatment, longitudinal research, including, in some instances, neuropsychological and neuroendocrine testing according to

standard protocols over time; and there should be suitable controls including personnel with traumatic injuries other than TBI
- Since one possible influence on the varied incidence of blast-related TBI (bTBI), reported in different countries and militaries, is the time interval of reporting symptoms after the blast incident, care should be taken to assess index injury severity and numbers of exposures as objectively as possible
- Multimodal imaging including standard MRI, DTI and SWI, as well as MEG, offer opportunities to investigate and clinically manage patients with mTBI and blast mTBI, but ahead of findings becoming more robust, and adoption of MEG for clinical use, research based on agreed standard technologies, protocols and data analysis will be needed
- For the future, neuroendocrine testing with standard protocols should also be further explored

48. The meeting also made a clinical recommendation for implementation of TBI screening in various circumstances and following further research:

- Since a high percentage of military personnel at recruitment have had at least one blunt mTBI or concussion episode (not necessarily reported), as blast and blunt injury mTBI may arise from the same combat related blast event, and since blunt sport related injury mTBI may occur in service, introduction of screening at recruitment, pre-deployment and for those likely to have been exposed in service to blast or a blunt mTBI is recommended
- Neuroendocrine testing for diagnosis should also be further investigated by expert groups including members from universities and practising NHS clinicians

IMEG 2020/21 scrutiny of mTBI and MEG

49. There are three important caveats to bear in mind in the interpretation of the currently published research on MEG studies in subjects with mTBI. First, that MEG has not yet been sufficiently studied in either neurological or psychiatric disorders to be able to conclude that the reported findings are reliably specific to mTBI. Second, that in the absence of MEG recording prior to the incident mTBI event, it is not possible to be certain that the mTBI event in question is the cause of the recorded abnormality. Third, that no prospective longitudinal study has yet been reported, and it is possible that there are subjects exposed to blast injury and other causes of mTBI who show similar MEG abnormalities but who are asymptomatic.

50. In preparing this Report, IMEG has carried out further scrutiny of the literature, mainly from 2015 onwards, and had discussion with experts on MEG and TBI. Professor Matthew Brookes, of Nottingham University, is one of a handful of UK scientists at the cutting edge of computational biology and MEG in mTBI and mental health disorders. In October 2020 IMEG was fortunate to discuss these issues with him. Professor Brookes gave a presentation entitled: "Magnetoencephalography: principles, applications and use in mTBI". Key points included: -

- As yet there is neither MEG evidence nor other valid objective method to detect mTBI in the acute phase, nor in those who have had a single mTBI injury but recover completely without persistent PCS
- Most MEG recordings have been resting state examinations and at a single time point following mTBI. Longitudinal studies, with cognitive loading, are a priority
- Whether blast and blunt injury mTBI are the same pathologically is of great interest in military populations but the issue is not yet resolved. It is hoped MEG will provide insight
- Given that MEG seems able to identify changes in those with psychiatric diagnoses, a particular interest in the military context is the objective diagnosis of PTSD and its differentiation from mTBI
- Symptoms of PTSD and mTBI overlap. The research work of Dunkley and Zhang in Toronto, classifying PTSD and differentiating it from mTBI, using MEG neural synchrony, is promising (71)(67). Other planned topics of investigation include functional connectivity in mTBI, results to date having yielded inconsistent findings. More work is needed on cognitive task-based MEG in mTBI. To date, both hypoactivation and hyperactivation have been reported
- Longitudinal assessment of mTBI with MEG in acute, subacute and chronic phases will throw light on recovery from mTBI and help to predict development of PCS and cognitive deficits

51. Professor Brookes then confirmed that most MEG studies to date have been conducted on small numbers of subjects, with often inconsistent results. There are many challenges and limits to consistent findings in such studies. A major issue is the diversity of computational analytical techniques used. As well as study design, matters such as use of different scanner types and the timing of investigation relative to the injury are important and incompletely studied. Some research groups are now investigating patients in the immediate aftermath of the injury (within 2 weeks), while others investigate at longer intervals (2 months or longer). The presence or absence of PCS needs to be identified. Finally, the recognition that age has a marked effect on MEG recorded activity means that those with mTBI and controls should be carefully age matched. It has been observed that delta (low frequency) oscillations characteristic of mTBI decline with age (72).

52. In relation to the suggestion that MEG can be regarded as a diagnostic test for mTBI, we conclude that:

- MEG is providing important insights into functional alterations in the brain in mTBI and PTSD but has not reached levels of sensitivity and specificity to be regarded or used as an investigation in routine clinical practice
- Differences in published MEG research findings indicate that there are important methodological differences between research groups that need to be resolved
- As recommended in the Consensus Statement arising from the ICL meeting held in January 2020, IMEG supports the need for collaborative research on MEG in mTBI
- The diagnosis of mTBI and PTSD remain clinical, dependent upon the history of the event(s) and clinical examination, in the case of mTBI, supported by CT or MRI scans in a minority of individuals, according to specialist opinion

- IMEG recognises that these conclusions will need to be reviewed regularly in the light of research advances

Other Putative Biomarkers of mTBI - Neuroendocrine and Metabolic

53. As stated, the agreed diagnostic criteria for mTBI are exclusively clinical, both in the UK and elsewhere, but there is increasing interest in the possibility that, in addition to neuroimaging techniques, specific and sensitive biomarkers of mTBI in body fluids might prove to have clinical utility in routine practice. There are now research reports of putative biomarkers of brain damage, including blood, cerebrospinal fluid (CSF) and salivary markers of axonal injury, which might inform underlying pathology, prognosis, potential therapeutic targets, and treatment evaluation.

54. For many years, moderate and severe TBI have been recognised as causes of hypopituitarism (deficiency of pituitary gland function). The underlying mechanisms are not yet established, but genetic predisposition, autoimmunity and neuroinflammatory changes may all be involved (73). There is evidence that hormone replacement, most commonly with growth hormone (GH) can at least partially reverse the clinical manifestations, including psychological and cognitive deficits (74). The 2013 UK Biosap study (75) investigated the prevalence and consequence of pituitary dysfunction in 19 military personnel who survived a moderate to severe blast-induced TBI (bTBI) due to improvised explosive devices (IED) in Afghanistan between December 2009 and March 2012. The controls were 39 age and gender-matched civilians with moderate to severe non-blast induced TBI (nbTBI). Some of the bTBI individuals had also had previous TBI due to RTAs, falls, assault, or sporting injury. Cases and controls all had full dynamic endocrine assessment 2-48 months after injury, MRI and DTI, and cognitive assessment by neuropsychological testing. Exclusion criteria for both groups included the presence of PTSD diagnosed by psychologist interview, diabetes, previous craniotomy (neurosurgery), current drug or alcohol use and reverse sleep cycle. nbTBI injuries were RTAs (43%), assaults (32%), falls (23%) and sporting injuries (2%). The military personnel also had routine MRI, DTI and susceptibility-weighted imaging, to detect structural changes which might be associated with pituitary gland deficiencies. Six of the 19 soldiers had anterior pituitary dysfunction, compared to only one of 39 nbTBI controls. Two soldiers had GH deficiency, two had hyperprolactinaemia, one had adrenocorticotrophic hormone (ACTH) deficiency, and one had GH/ACTH/gonadotrophin deficiency.

55. Amongst the nbTBI controls only one had pituitary dysfunction, manifested by isolated GH deficiency. Neuroimaging results showed more cerebral contusions and skull or facial fractures in the soldiers with pituitary dysfunction, and DTI showed greater white matter damage in the blast injured soldiers. No structure-specific hypothalamic-pituitary hormone abnormalities were seen in soldiers with pituitary dysfunction. Soldiers with pituitary dysfunction after blast damage had worse cognitive functioning.

56. This may relate to GH deficiency, but the basis for this is presently unclear. The findings led to the recommendation that all patients with moderate or severe bTBI should have detailed endocrine function assessment including dynamic stimulation

testing. This was an initial research study and unanswered questions remain. The position with mTBI is still less clear. Repeated mTBI may exacerbate pre-existing neurological deficits (76) and a single study suggests that repeated mTBI can produce endocrine disturbance (77). In the aftermath of TBI, endocrine abnormalities are common but often resolve spontaneously. The frequency and severity of neuroendocrine abnormalities following mTBI remain under investigation. While there are, as yet, no clear clinical guidelines, current UK best practice indicates that investigations, including dynamic function tests, should be carried out at an interval after the acute event, preferably in a specialist unit, in patients with mTBI who have persistent and unexplained PCS, refractory to treatment (see Annex 2).

57. Total tau protein and neurofilament light protein (NFL), present in cerebrospinal fluid (CSF) (78), are markers of neuronal damage, with levels being elevated acutely in CSF after mTBI (79)(80). For mTBI, practical and ethical considerations exclude routine CSF examination, which requires lumbar puncture. A recent prospective study of acute blood-based biomarkers in sports related concussion followed up 106 concussed American football players, controls comprising 84 uninjured football players and 50 non-contact sports athletes (81). Blood was collected at pre-injury baseline, within 6 and then 48 hours post-concussion. Levels of glial fibrillary acidic protein, ubiquitin, S100 calcium binding protein, interleukin 6 and 1 receptor antagonists and C-reactive protein were measured in blood. All proteins, except glial fibrillary acidic protein and C-reactive protein, were elevated at 6 hours compared with baseline and the control groups. While individually the proteins showed varied ability to differentiate concussed and uninjured controls, when combined they showed good to excellent discrimination. The study had several limitations. The best discriminator of "concussed" versus the two "normal control "groups was symptom severity score. The study was not adjusted for multiple comparisons, and nothing was known about possible previous concussions in any of the groups. Inclusion of additional control groups, for example people with acute non-neurological medical disorders, would have enhanced the study.

58. An issue with chemical biomarkers is that they may be present in multiple tissues and so, in polytrauma, raised levels may not be specific to brain injury. Neurofilament light protein (NFL) is a neurone-specific protein shown in multiple studies to be elevated in blood and CSF in the first 15 days after acute mTBI (82). Further longitudinal studies on timing of investigations relative to injury, correlation with clinical progress and neuroimaging are required (83).

Differentiating blunt and blast TBI

59. The question as to whether blunt and blast induced mTBI are different in relation to pathological changes in the brain remains unresolved. Much investigation has been done in animal models. Human studies are few and observations and conclusions have been inconsistent, influenced by different protocols, including enquiry into previous TBI, baseline timing, and lack of verifiable clinical details. Blunt and blast mTBI types may co-exist in military populations, with a high percentage of personnel having sustained concussion pre-service, mainly due to sport, often unrecorded at the time and unreported at recruitment, while military service carries the risk of blunt TBI from sports injury, road traffic accidents (RTAs), assault, falls and other accidents.

60. Primary blast injuries are due to a sudden increase in air pressure following an explosion. If casualties are close to detonations, primary blast injury has high mortality, with severe damage to air-containing organs and structures, including the chest, abdomen, middle ear, and nasal sinuses with rupture into the cranial cavity in severe cases. Secondary blast damage occurs when bomb fragments or debris cause penetrating injury. Tertiary blast damage causes rapid displacement of the person within the blast environment, who is then injured by collision with objects and structures in their path. This results in blast and blunt brain injury often being sustained at the same time, making it difficult to identify those with 'pure' blast injury. Quaternary blast injury is due to thermal injury and inhalational effects (84). These mechanisms and effects occur to greater or lesser extent in military blast-related TBI, dependent on factors such as blast energy, distance from the blast, body position, use of body armour and helmets, whether blast was sustained in a closed environment or an open space, and number of exposures. Primary blast injury may cause TBI of any severity while secondary, tertiary, and quaternary blast injuries are associated with moderate or severe TBI.

Neuropathological changes over time in mTBI

61. A post-mortem human study has added to understanding of TBI pathology (85). Brain specimens from five military male cases of chronic blast exposure, and three who had died shortly after acute severe blast exposure, were compared with five male civilian cases with no history of blast exposure but with multiple impact TBI, five civilian cases with chronic exposure to opiates and three uninjured civilians with no known neurological problems. Limited case histories including for psychological symptoms were available for all participants. The military chronic blast cases had astroglial scarring involving the sub-glial plate, cortical blood vessels, grey-white matter junctions and structures lining the ventricles, while the acute blast cases showed early astroglial scarring in the same distribution. All five chronic blast cases had a diagnosis in life of PTSD. None of the civilian cases had astroglial scarring. The researchers concluded that interface astroglial scarring could indicate specific areas of blast damage occurring at brain tissues of different density or adjacent to vascular or cerebrospinal fluids, such a pattern being consistent with the understanding of blast wave biophysics. An important limitation of the study, related to the limited case histories available, was the absence of a record of lifetime TBI event exposures experienced by the military subjects, including sports-related concussion. It is also impossible to be sure that the pathological and clinical changes were due to blast primary pressure and not the secondary or tertiary blunt injury elements, and since mTBI itself is not fatal, it is more likely that the military TBIs were moderate or severe in nature, rather than being mild, though there may have been inclusion of individuals with mTBI who died from their other injuries. A further consideration in relation to this neuropathological study is that in mTBI associated with multiple injuries, a mild brain injury may be exacerbated by systemic factors resulting from the other injuries, including lack of oxygen supply to
62. the brain and metabolic disturbances (86). These additional factors might affect later post-mortem changes observed in the brain. This work needs to be confirmed.

Long-term cognitive impairment in mTBI

63. A major issue of medical and public concern is the possibility that mTBI might predispose to later degenerative change, only becoming evident many years later, manifested by the development of dementia.

64. Worldwide, the numbers of older people, including those living with dementia, is rising. At the same time, in many countries the age-specific incidence of dementia has fallen, probably related to better education, healthcare, nutrition and healthier lifestyles. Nine potentially modifiable risk factors for dementia have been identified. These include limited education, high blood pressure, smoking, obesity, deafness, physical inactivity, depression, diabetes, and social isolation. Recently, three additional factors have emerged, which comprise alcohol consumption, air pollution and TBI (87, 88). All twelve factors are thought to account for about 40% of the variance in who develops dementia.

65. Memory disturbance, slow mental processing and executive dysfunction are common acutely after TBI of all severities and usually improve, but there is increasing evidence of long-term cognitive decline, and, following moderate and severe TBI in the presence of certain genotypes, an increased risk of neurodegenerative disorders, including APOE-epsilon, Alzheimer's disease (89), and Alpha-synuclein Rep 1 and Parkinson's disease (90). The case is much less convincing for mTBI. Many published studies do not differentiate TBI severity or whether there has been single or repetitive injury, and for mTBI are reliant on self or family report, recognised only at an interval after the index incident. The studies are often cross-sectional, small, and so underpowered.

66. Another complication is the definition of dementia, which differs amongst clinicians, and in the current and proposed international disease classifications, the WHO International Classification of Diseases (ICD, 11th edition) (91), and the American Psychiatric Association (APA) Diagnostic and Statistical Manual (DSM 5) (92). Most clinicians understand dementia to describe a global cognitive decline due to an underlying progressive neurodegenerative or neurometabolic process. However, in the different classifications, dementia covers both acute post-injury, often static non-progressive cognitive impairment, as well as progressive cognitive decline due to an underlying continuing neuropathological process.

67. There are at least five possible interpretations of these definitions of dementia in relation to TBI. The first refers to a deficit presenting shortly after the injury, due to a primary TBI, which may remit or remain stable over time. Second, after the primary injury there may be a slow further decline over many years. Third, there may be individuals in whom there is initial good recovery, followed by the development of a dementing illness, unrelated to the previous mTBI, many years later. Fourth, there may be confounding by lifestyle factors such as alcohol use. And fifth, there may be reverse causality, in that those with early dementia may be prone to falls leading to TBI and later confirmation of dementia, rather than the causal association being in the opposite direction.

68. A 2018 Swedish nationwide cohort study considered three factors. First, whether risk of dementia decreased over time from acute injury; second, whether risk differed with injury type; and third, whether risk was influenced by familial factors (93). The

potential study population was all 3,329,360 individuals in Sweden aged 50 years or over in 2005. Diagnoses of TBI and dementia, taken from a national database of hospital records, were tracked from 1964 until 2012 and three cohorts were assembled. In the first, 164,334 individuals with TBI but no dementia at baseline were each matched with up to two controls. The second comprised 46,970 full sibling pairs with discordant TBI status. The third comprised all subjects diagnosed with dementia during follow-up, and again, each subject matched with up to two controls. The follow-up period ranged from 0-49 years with a mean of 15.3 years. The risk of dementia was analysed using multivariable conditional logistic regression. Odds ratios (OR; the odds of dementia occurring in those exposed to TBI divided by the odds of it occurring in controls) were adjusted for age, civil status, education, early retirement pension, and baseline diagnosis.

69. 21,963 individuals were diagnosed as having dementia during follow-up. Of these 6.3% had had TBI and 3.6% no TBI, giving an adjusted OR of 1.81 (1.75-1.86), the association being strongest in the first year after TBI with OR 3.52 (3.23 -3.84). Single mTBI showed a weaker association, OR 1.63 (1.57-1.70) than more severe TBI, OR 2.06 (1.95-2.19) and multiple TBIs, OR 2.81 (2.51-3.15). In the sibling pairs, TBI was also associated with increased dementia, OR 1.89 (1.62-2.21) and followed a similar time course with risk highest soon after the TBI and then declining, but still significantly raised more than ten years after TBI. It may be that in this study the early peak represented a direct acute post-injury effect or reverse causality, while the later "tail" was due to progressive underlying neurodegeneration.

70. The study is unusual in having a long follow-up time (mean 15 years for those with TBI and up to 50 years follow-up overall). Short follow-up studies can be at risk of reverse causality, meaning that an elderly person with the early stages of dementia is liable to TBI due to falls (94). With significant risk observed more than 30 years after TBI, reverse causality is unlikely to be the full explanation here, although it may account for some cases diagnosed soon after the TBI. The study also showed the influence of familial factors and a clear dose response between TBI severity and the development of dementia. Diagnoses were made by hospital doctors, although register-based, and so the researchers were unable to confirm the basis of diagnosis. Another possible bias is that in the aftermath of a TBI, subsequent healthcare and follow-up may be especially rigorous, thus more cases are diagnosed. Finally, despite the strong suggestion of an association between TBI and subsequent dementia, as an observational study it cannot prove causation, due to potential confounding factors, so that having a TBI may be more common in those with other risk factors for the development of dementia.

71. A recent US retrospective cohort study involved 325,870 nationwide US military veterans enrolled in the Veterans' Health Administration (VHA) healthcare service, average (SD) age 46.9 +/- 17.4 years, of whom half had TBI (defined as mild or moderate to severe) and the remainder no recorded TBI diagnoses. The primary outcome was a diagnosis of Parkinson's disease (PD) a year or more after the first TBI diagnosis, or selection for the study for those without TBI. The veterans were followed for an average of 4.6 years, by which time 1462 had been diagnosed with PD. PD and TBI exposure and severity were determined via physician assessment. Among those diagnosed with PD, those with prior TBI did not differ significantly on education, income,

incidence, or time to death, but were diagnosed at a younger age, had higher prevalence of both PD and of nearly all medical and psychiatric co-morbidities compared with those without recorded TBI, suggesting this might be due to ascertainment bias. Of those with prior documented TBI of any severity, 0.58% developed PD compared with 0.31% of those without recorded TBI, while for mTBI the comparable figure was 0.47%. The increased risk of PD in TBI of all severities was still statistically significant after adjustment. There were some limitations, particularly the fact that some TBIs may have gone unrecorded and the short follow-up time, but advantages included physician diagnosis of TBI and PD, the large nation-wide sample size, and the longitudinal design. Most of the TBIs occurred during civilian life either before or after military service so the findings may have wider societal implications (89).

72. A second study of US veterans looked at the association of mTBI, with and without loss of consciousness (LOC), and subsequent diagnosis of dementia (90). It was a large cohort study of all veterans diagnosed with TBI in the VHA healthcare system between October 2001 and September 2014 and a suitably matched comparison group. Diagnoses were part of a comprehensive TBI evaluation by a neurologist or allied health professional. For study purposes severity was based on the most severe injury recorded on the databases. 178,779 veterans were diagnosed with a TBI in the VHA database and there were a similar number of controls selected from the database without TBI. TBI severity varied. Differences in age and gender between those with and without TBI were small. Incident dementia was diagnosed by a neurologist using the VA Steering Committee ICD 9 codes. Following adjustment for demographics and medical and psychiatric diagnoses 4,698 (2.6%) veterans without TBI developed dementia compared with 10,835 (6.1%) with TBI.

73. The risk of dementia rose with the severity of TBI; the adjusted hazard ratio (HR) for mTBI was 2.36 (95% CI, 2.10-2.66), (adjusted for demographic characteristics, medical conditions, and psychiatric disorders), for mild TBI without LOC, going up to 3.77 (3.63-3.91) in those with moderate or severe TBI. This apparent dose response relationship with severity of TBI supports the association between TBI and later dementia. While results of prior studies of the association between mTBI and dementia have been mixed, the Barnes study (90), which was large, longitudinal in design and adjusted for a range of confounders, adds to the weight of evidence suggesting that mild TBI is also associated with increased dementia diagnosis risk. Its limitations are the propensity matching design and the uncertainty regarding unmeasured confounders.

74. As discussed in the 2017 IMEG report, since the 1920s and the first description of dementia pugilistica, there have been suggestions that sports such as boxing, leading to repeated blunt brain injury, may be associated with a distinctive progressive neuropathological change, usually called chronic traumatic encephalopathy (CTE). A study of former soccer players, playing on average for 26 years, all skilled headers of the ball and dying in their seventies, and with progressive cognitive impairment of average duration 10 years, included 6 individuals with previous identifiable concussion (mTBI) (95). Six had post-mortem brain examination, which showed cavum septum pellucidum (CSP). The septum pellucidum is a thin triangular membrane lying between the cerebral hemispheres, immediately below the corpus callosum, the large band of nerve fibres connecting the right and left hemispheres. CSP occurs during foetal life,

closure occurring in 85 percent, but persisting into post-natal life in 15 percent of normal infants (96). It is thus a normal variant, but also shows an association with traumatic brain injury (97). Four brains examined post-mortem showed CTE, and other pathological changes were apparent in six cases, including Alzheimer's disease, cerebral amyloid, hippocampal sclerosis, and Lewy body disease. The authors concluded that further work, particularly longitudinal study, was needed (95).

75. Since then, interest in a causal link between contact sport, mTBI and development of neurodegenerative disease has remained high. A 2019 data-matching retrospective cohort mortality study of former Scottish professional football players, with 7,376 former players and 23,028 controls from the general population matched on age, gender, and social deprivation, found that, during 18 years' follow-up, all-cause mortality up to age 70 was lower in the footballers (15.4%) than the matched general community (16.5%); deaths from ischaemic heart disease were 20% lower in players and 50% lower from lung cancer (98). Mortality from neurodegenerative disease, listed as a primary or contributory cause on the death certificate occurred in 1.6% of former players compared to 0.5% of population controls. When adjusted for competing risk of death from heart disease or any cancer, it was still higher amongst players than controls. Mortality was highest for Alzheimer's disease (AD) with hazard ratio of 5.07 (CI 2.92-8.82) compared with controls, while deaths from Parkinson's disease (PD), had a hazard ratio of 2.15 (CI 1.17-3.96). Dementia-related medications were prescribed more frequently to footballers (but not goalkeepers) compared with controls. However, in this study death from neurodegenerative disease was not related to field position played, comparing goalkeepers with outfield players (98). This finding casts doubt on whether heading the ball is indeed a factor in the development of later dementia. Again, prospective matched cohort studies are needed, bearing in mind that leather footballs, which become heavier in wet conditions, were replaced by non-absorbent material balls some years ago. In addition to the direct head trauma in sports such as soccer and rugby, where frequent sub-concussive and sometimes concussive blows directly to the head are well-recognised, there is increasing concern that indirect head trauma, caused by repetitive deceleration injury, as for example in the winter sports of luge and skeleton, might lead to the development of cognitive impairment at an interval. Published studies in the medical literature have yet to appear.

76. A 2020 systematic review of evidence on concussion and long-term cognitive impairment among professional or elite sports persons was carried out on 14 studies across a range of sports (99). Three comparisons were made: i) athletes within the same sport - concussed and non-concussed; ii) between sport comparison (contact vs non-contact sport); and iii) athletes compared with the general population. From a total of 3,783 studies screened, 14 were selected as meeting the inclusion criteria. The evidence overall suggested an association between a sport-related concussion and poorer cognitive function later in life in rugby, American football and boxing. However, the authors concluded that overall, the quality of the evidence was poor. Limitations in the selected studies included selection bias, with many subjects being volunteers. Controls met varied definitions, concussion had different definitions across the studies and was almost always diagnosed by self-report. Cognitive decline used different assessment methods and there was poor adjustment for potential confounders. The

authors recommended urgent high quality well-designed, appropriately powered epidemiological studies.

77. Neuropathological research, from post-mortem human examination and from experimental animal studies, is throwing light on the mechanism of the evolution of changes in the brain resulting from TBI over time, including diffuse axonal injury (DAI). Very rapid axonal stretching, as in TBI, leads to the axon becoming stiffer, probably due to micro-tubule stabilising protein, tau protein accumulation and breakage of the microtubules (100). This then interrupts axonal transport leading to amyloid precursor protein accumulation at sites of injury, and beta amyloid deposition. The majority of injured axons appear normal after TBI but quite likely with impaired conduction of action potentials due to these changes, and ultimately, some axonal degeneration and loss.

78. A single moderate to severe TBI can cause marked cerebral atrophy at 6 months post-injury. This may progress over many years; measured by serial MRI (serial T1 volumetric MRI), cerebral atrophy can track TBI or neurodegenerative disorder progression. Volumetric MRI can identify damaged areas of brain and has an association with cognitive and functional outcomes. Variations in brain volume can provide normative data on expected brain appearance at different chronological ages, allowing comparisons with observed brain age. After moderate or severe TBI, brains appear older than chronological age, an effect that increases over time, with older patients at the time of injury being more at risk (101).

79. A 2015 neuro-imaging study applied an established model of normal brain ageing to 99 TBI patients and 113 healthy controls. The mean (+/-standard deviation) age of cerebral grey matter in TBI patients was 4.66 (+/-10.8) years older than chronological age, while for cerebral white matter it was 5.97 (+/-11.22) years older. This correlated with time since injury, suggesting a progressive process through the post-injury period and not a one-off effect at the time of injury. The effect was seen only in severe and moderate injuries, not in mTBI. Outcome did not depend on the mechanism of injury but did predict cognitive impairment (102).

80. By contrast, a 2016 examination of the association of TBI and late-life neurodegenerative conditions and neuropathological findings considered three prospective cohort studies with 7,130 participants divided into two groups (103). In one, TBI was associated with loss of consciousness (LOC) of less than an hour, while in the other LOC was more than an hour. All were free of dementia at the outset. Followed up for 45,190 person years, no association was found between TBI and LOC of any duration and dementia or Alzheimer's disease, but an association was found with incidence and progression of Parkinson's disease and the development of Lewy bodies, but not neuritic plaques or neurofibrillary tangles. Conflicting outcomes reflect study limitations including study size, absence of matched controls, TBI heterogeneity and diagnostic criteria, as well as reliance on self-report or relatives' reports.

81. In summary, as recorded in the 2017 IMEG report, a relationship has been documented between moderate and severe TBI in the presence of certain genotypes and increased risk of neurodegenerative disorders, Alzheimer's disease (89), and Parkinson's disease (90). The position with mTBI is less clear. Studies have yielded

conflicting results and while neuroimaging has led to better understanding of neuropathology over time from the initial TBI, the associated clinical phenotype at the various stages remains undefined. Understanding of this issue is critical for prevention, early treatment and compensation. IMEG will continue to be guided by the evolving published evidence on the issue.

TBI and suicide

82. This sixth IMEG report includes a comprehensive report on suicide and relevant risk factors, looking both at the military and wider society. There is a substantial international literature on suicidal ideation, self-harm, and suicide in people with TBI. Overall, studies, while heterogeneous in quality, suggest that those with TBI in military and civilian populations are at increased risk of death by suicide, but there remain conflicting results, with some studies finding an association (104), but others no relation between TBI and suicide (105). Data issues include biases related to either retrospective or case-control studies. Often the military population of interest, is compared with general population data which are not age and gender matched. A further limitation is that so many mTBI events are never recorded or, when they are, the means of diagnosis - whether by self-report or objectively verified - is unknown. Suicide is a rare event in both military and civilian populations, and so results from small studies must be viewed with caution.

83. In a 2013 systematic review of 16 relevant studies, on suicidal ideation and behaviours after TBI suggested that there probably was an increased risk of suicide in those who had suffered a previous TBI, in both civilian and military populations (106). The study rated as having the highest quality supported the finding that those with TBI of all severities are at raised risk of death by suicide (104). This was an investigation of US military veterans receiving healthcare through the US Veterans' Health Administration (VHA) health care services between 2001 and 2006. It identified those with TBI who died by suicide. A total of 49,626 patients had a history of TBI and of those, 105 died by suicide. Models were adjusted for demographic and psychiatric co-variates. Those with a TBI history were 1.55 (CI 1.24-1.92) times more likely to die by suicide than those without.

84. Analysis by TBI severity suggested that compared with no TBI, those with concussion, with or without cranial fracture, were 1.98 (CI 1.39-2.82) times more likely to die by suicide, while for cerebral contusion or intracranial haemorrhage the figure was 1.34 (CI 1.09-1.64).

85. An important study used nationwide registers in a retrospective cohort study of 7,418,391 people living in Denmark for ten or more years between 1980 and 2014 and with study follow-up of 164,265,624 person years (107). This found that 567,823 (8%) people had had a medical contact for TBI. Data were analysed against the general Danish population who did not have TBI, using Poisson regression adjusted for co-variates including fractures other than skull, psychiatric diagnoses, and self-harm, compared to the general Danish population who did not have a record of TBI. TBIs were divided into mTBI, skull fracture without documented TBI, and severe TBI, defined as having evidence of structural brain damage. The study outcome was suicide recorded in

the Danish Cause of Death register to 31 December 2014. Altogether, 34,259 had died by suicide, with an absolute rate of 21 per 100,000 person years. 3,536 (10%) had had a medical contact for TBI; 2,701 with mild TBI, 174 with skull fracture without documented TBI, and 661 with severe TBI. The absolute suicide rate in those with TBI of all severities was 40.6 (CI 39.2-41.9) per 100,000 compared with 19.9 (CI 19.7-20.1) per 100,000 for those with no diagnosis of TBI. Adjusting for age, sex and calendar period provided an incidence rate ratio (IRR) of 2.64 (CI 2.55-2.74). When fully adjusted for age, sex, marital and cohabitation status, education, socioeconomic status, other injuries, epilepsy, the Charlson comorbidity index for other chronic disorders, pre-TBI psychiatric diagnosis and self-harm, the incidence rate ratio (IRR) fell to 1.90 (CI 1.83-1.97).

86. Those diagnosed with psychiatric disorder after their TBI had a much higher risk of suicide (IRR 4.90 (CI 4.55-5.29) as did those with a psychiatric diagnosis before their TBI (IRR 2.32 CI 2.10-2.55). It seems that both premorbid and postmorbid psychiatric diagnoses and self-harm significantly mediate the association between TBI and suicide. Suicide risk was associated with the number of medical contacts for distinct TBI events and inversely with time since last medical contact for TBI. Compared with the general population, IRR was 3.67 (CI 3.33-4.04) within the first six months of last contact for TBI and 1.76 (CI 1.67-1.86) for contact after seven years of last medical contact.

87. This study had strengths in its size and long follow-up (35 years), its adjustment for many risk factors for suicide and that it included only suicide, and not ‘uncertain’ deaths as outcome. It also had some limitations. Not all mTBI events would come to medical attention; prior to 1995, mTBI out-patient contacts and self-harm episodes were not recorded and similarly some people in the cohort might have had a TBI incident prior to 1977, the date when the national register was set up. The importance of this study is related to its size and nationwide sample, which shows the important role of psychiatric comorbidity in mediating the risk of suicide in those with TBI. With the growing evidence of a positive association between TBI of all severities and suicide rates overall, further studies on suicide risk factors, screening, prevention strategies and effective support interventions are awaited.

Comorbid mTBI and mental health disorders

88. The prevalence of mental health disorders is increased in mTBI (3). These disorders may pre-date and predispose to TBI, (such as alcohol misuse), be caused by the TBI, or occur independently. Traumatic injury of any type including due to combat occurs in psychologically stressful circumstances, which may cause a transient symptomatic stress reaction or develop into discrete diagnosable disorders.

Distinguishing mild TBI and PTSD

89. Having a psychiatric disorder preceding TBI or occurring simultaneously or in its aftermath is common with mTBI, and if untreated may impact not only functional outcomes but possibly also the effectiveness of mTBI treatment. PTSD is seen in civilian and military patients with mTBI, and symptoms and signs associated with both

disorders such as executive dysfunction, memory impairment, word-finding difficulty and processing speed deficits show substantial overlap (28). Another study suggested that the increased risk of post-concussion symptoms in soldiers with mTBI almost disappeared when studies were adjusted for the effects of comorbid depression and PTSD (4). The 2018 Kulas study investigated mTBI and PTSD separately and together in US veterans of Iraq and Afghanistan, who were treated in the US DVA Veterans' Health Services (VHS), considering socio-demographic factors, psychiatric and medical comorbidities (108). 164,884 veterans took part, diagnosed with both mTBI and PTSD, mTBI or PTSD alone. 23,063 (14%) had both PTSD and mTBI, 9,253 (6%) had mTBI and 132,568 (80%) had PTSD. The PTSD group were at high risk of comorbid psychiatric conditions, regardless of the co-existence of mTBI. The psychiatric disorders included substance misuse, major depression, bipolar disorder and personality disorders. Conversely, although uncommon, those with mTBI were more likely than those with PTSD to have a diagnosed physical disorder. mTBI on its own or together with PTSD did not increase risk of other psychiatric conditions, with the one exception of organic brain syndrome, which although rare, was more common after mTBI than PTSD. Unfortunately, organic brain syndrome was not further defined in the paper.

90. Interpretation of these findings is difficult. On the one hand, we could conclude that PTSD, not mTBI is the most common "signature" injury of Iraq and Afghanistan and a greater driver of health care demand. On the other, we might simply be looking at overdiagnosis of both PTSD and mTBI, given that they are clinical diagnoses based mainly on patient self-report. The major limitation of this study is that those in the sample were all seeking treatment. While the study throws light on VHA practice, and so patterns of care, more work with other patient groups is needed. PTSD was common in relation to reported mTBI in the recent conflicts with a high prevalence of PTSD in some US mTBI series affecting, along with depression, a third of cases (108). Separation of symptoms due to mTBI from those due to PTSD is a challenge. Where there is a documented mTBI and a preponderance of physical and neurological symptoms, such as visual problems, headache, balance problems, or confirmed cognitive impairment, the conclusion would favour mTBI as the primary disorder. However, if nightmares, flashbacks, hyperarousal, and avoidance are the primary symptoms, PTSD is likely to be considered the main diagnosis (3). In these contexts, objectively verifiable biomarkers to differentiate the diagnoses would be useful.

Treatment of psychiatric disorders associated with TBI

91. In terms of treatment, certain symptoms such as anxiety and sleep disturbance may be treated without regard to aetiology, but evidence-based interventions for comorbid psychiatric disorders such as PTSD depend on the role played by the exposure to trauma. Eye movement desensitisation reprocessing (EMDR) and trauma based cognitive behaviour therapy (CBT) are effective treatments for PTSD (109)(110). CBT is also effective in treating other trauma related disorders such as depression, anxiety and somatoform disorders. The presence of either PTSD or depressive illness, comorbid with mTBI in military patients, may be associated with a worse prognosis and quality of life (111), so effective clinical management of these comorbid disorders is important.

92. Two systematic reviews on the effectiveness of mental health treatments on mental health disorders comorbid with mTBI in military and civilian populations have appeared since the 2017 IMEG report. One review did not find any randomised controlled trials (RCTs), but suggested that the presence of mTBI in military patients does not necessarily reduce the effectiveness of psychotherapies for comorbid psychiatric disorders (112). The second review considered 23 longitudinal studies and 26 comparator case studies on treatment for PTSD in patients with TBI of mixed severity published between 1980 and 2019; only four of the studies were RCTs (113). CBT was the most common intervention, notably prolonged exposure (PE) and cognitive processing therapy (CPT). One RCT supported multidisciplinary interventions and another supported CBT for helping PTSD; a third found no difference comparing two cognitive processing therapies, and a fourth found a significant benefit with hyperbaric oxygen. Non-RCT results broadly support the present accepted use of CBT as best practice intervention for PTSD alone. Evidence has not yet emerged of a relationship between TBI severity and the magnitude of treatment gains. The review recommended further work through well-controlled studies, preferably randomised controlled trials, with more female civilian and military patients and cases of different severity of mTBI considered separately. These reviews highlighted the dearth of RCTs, which make all these findings provisional.

Vestibular effects of head injury

93. As discussed in the 2017 IMEG report, and referred to in paragraphs 18 and 23 here, dizziness is a very common symptom resulting from head injury, both acutely (114) and often persistently (115). It is frequently assumed that dizziness following head injury is due to brain injury, and the incidence of peripheral labyrinthine injury as the cause of such dizziness, rather than central nervous system damage, is underestimated. The distinction of peripheral and central dysfunction clinically may not be straightforward, and specialist audiovestibular assessment of patients in whom dizziness is a prominent symptom should always be considered, though this may not always be readily available. Peripheral labyrinthine pathologies occurring post-traumatically include bilateral/unilateral vestibular failure, unilateral and bilateral semicircular canal and/or otolith dysfunction, benign paroxysmal positional vertigo, vestibular nerve contusion, hydrops, superior semi-circular canal dehiscence, and labyrinthine fistula. Specialist clinical audiovestibular assessment includes examination otoscopically, detailed eye movement assessment including smooth pursuit, saccades, optokinetic, spontaneous, and positional nystagmus, Romberg's test, gait, and tandem walking, together with exclusion of other cranial nerve and cerebellar dysfunction. Labyrinthine involvement may include subtle auditory deficits in addition to disordered balance, and investigation should therefore include: audiometry, semicircular canal evaluation [video head impulse test (vHiT)] and/or bithermal caloric testing, cervical and ocular vestibular evoked myogenic responses testing of saccular and utricular function respectively, and video/electronystagmography to evaluate bilateral semicircular canal function and integration of visual and vestibular pathways in the central nervous system. Based on this detailed specialist test battery, peripheral and central vestibular disorders

can usually be distinguished, and appropriate management established. The prevalence of combined peripheral and central vestibular disorders resulting from mTBI is unknown.

94. The commonest causes of vestibular dysfunction following head trauma are treatable. Expert audio-vestibular assessment is important to define diagnosis, which determines appropriate treatment. Common underlying pathologies include:

- benign paroxysmal positional vertigo (BPPV) which, in most cases, can be effectively treated by a particle repositioning procedure (116) (e.g., Epley or Semont manoeuvre), although benign paroxysmal positional vertigo (BPPV) secondary to trauma has a poorer prognosis than idiopathic BPPV (117). It has similar prognosis to BPPV not due to mTBI occurring in the civilian population

- labyrinthine dysfunction, which is appropriately managed by vestibular rehabilitation (118), with customised exercises and appropriate psychological support where indicated

- vestibular migraine, the treatment of which is not definitively established but can frequently be effectively managed with the adoption of lifestyle strategies, vestibular rehabilitation physiotherapy, antiemetics, vestibular sedatives and simple analgesics or prophylactic medication and psychological support if required (119)

- Central vestibular dysfunction is rare with mild head injury, but may be ameliorated by specialised balance physiotherapy and, in certain cases pharmacological treatment

A recent systematic review of vestibular rehabilitation in sports personnel who had sustained mTBI identified two randomised clinical trials (RCTs) and eight non-randomised studies (120). Results were inconsistent but a majority confirmed that various strategies of vestibular rehabilitation physiotherapy were successful. One small RCT found that out of 15 patients, 11 (73%) of the treated group and 1 of 14 controls (7%) had recovered within eight weeks of starting treatment (121).

Management of mTBI

95. While general principles for pre-hospital and acute TBI management have emerged, including indications for CT scanning and the use of specialist centres, there are as yet no internationally accepted guidelines for management of TBIs of specific severities, and across the world there are significant disparities, particularly in long-term rehabilitation care plans. Future approaches must take account of the context and heterogeneity of TBI, and care pathways should reflect patient and family priorities and preferences including quality of life and disability. The present progress in specialist imaging and investigation, neuroinformatics, and discovery of genomic factors that influence long term outcomes, including the risk of development of neurodegenerative disorders, permitting patient stratification, is poised to support future precision care plans (122)(123).

96. A holistic approach informed by evidence-based guidelines, such as NICE Head Injury Clinical Guidance 176 (last updated Sept 2019) (124), delivered by a multidisciplinary team in a specialist unit, seems best able to meet requirements. For mTBI, both military and civilian, in the UK, management is community-based, multidisciplinary and 'stepped care' in design, beginning with patient education and information about PCS and expected progress. Where symptoms persist beyond about three months, specialist assessment is appropriate. PCS is diverse, and where there are cognitive problems, difficulty with information processing, multi-tasking and/or executive function, neurorehabilitation may be required.

97. Referral for neurological assessment allows, as required, objective deficits to be identified by further examination including psychometric testing, specialist neuroimaging, endocrine and audio-vestibular assessment. For cognitive deficits, compensation techniques in which the patient uses residual cognitive abilities are helpful. Long-term residual symptoms of mTBI are predicted by emotional distress and maladaptive coping (125), and poor function is associated with anger, irritability, comorbid depression and PTSD. Where present, PTSD and depressive illness should be treated according to current mental health best practice. CBT with training to use retained abilities is reported to benefit isolated tasks in a hospital or clinic setting, but evidence of positive impact on day-to-day function is less compelling. A recent systematic review of 14 RCTs testing therapy and rehabilitation identified significant positive results for CBT in six trials, similarly in four digital or video feedback studies and in one physical therapy trial (126). Headache is common after TBIs of all severities, of variable duration and not directly related to injury severity. It should be treated symptomatically. Headache pathogenesis is not well understood, but, in individual patients, muscular tension, cervicogenic, and migrainous headaches occur (127). Sleep problems related to pain or depression occur frequently and may respond to a brief course of CBT (128). Rarely, obstructive sleep apnoea may occur, which requires specialist assessment.

98. Overall, the individual studies on the effects of treatment and rehabilitation of mTBI share the limitations highlighted in the 2017 IMEG Report (3). These include use of different definitions for mTBI, limited patient matching in terms of age, sex, socio-economic group, and cases of different TBI severity. Interventions in studies may not be standard and are often multiple, with effects of the component parts not assessed and use of many different outcome measures, with few including return to work. All these factors limit pooling of studies for systematic review or meta-analysis.

Return to Work after mTBI

99. Concerning return to work, most studies relate to civilian injury and work (129). A prospective cohort study of 151 Norwegian patients with mTBI seen consecutively at outpatient clinics, considered predictors of return to work at 12 months for patients sick-listed at six to eight weeks after the TBI, with persistent PCS. Information on injury characteristics, demographic data, and sick leave data from one year pre-injury to one-year post-injury was gathered. There was a significant negative association between being back at work at 12 months and psychological distress, functioning post-injury and

being on sick leave during the year prior to the injury and at two months post-injury (130). Despite the small study size, such findings support the importance of addressing psychiatric morbidity in rehabilitation programmes. A high quality larger recent systematic review and meta-analysis on return to work in civilian patients with definite mTBI identified 14 eligible studies (131). More than half the patients had returned to work at 1 month post-injury and more than 80% at 6 months (132). This is reassuring.

100. A recent Danish thematic analysis looked at facilitators and barriers to return to work after mTBI in civilians. The study was qualitative and used semi-structured in-depth interviews with 22 adults 2-5 years after injury. While support services are not precisely as in the UK, the three themes identified as most adversely influencing return to work were relevant in the UK context. These included worker-employer relationships, including support for job access, tasks and hours worked. This was especially referenced as a problem if, before injury, workers had high work capacity and so there were high expectations. In addition, co-workers were reported as not always being sympathetic. General practitioners were recognised as potentially having a key role in rehabilitation options for mTBI, but in this group most patients felt primary care physicians‘ knowledge was limited. Lastly, local authority social workers and state benefit administrators were seen overall as focused only on return to work and not on improving symptoms or the well-being and quality of life of patients (132).

Compensation Aspects

101. From April 2005 until 31 March 2020, a total of 335 awards at levels 11 and 13 were made for mTBI. While the descriptors do not allow differentiation of mode of injury, the majority were related to combat-related blast incidents in Iraq and Afghanistan and had been clinically diagnosed using the Defence HQ Surgeon General definition. We have considered claims made since the 2017 IMEG report and conclude that, in relation to mTBI compensation under AFCS, clinical diagnoses and assessment based on the severity and duration of functional compromise, particularly for civilian employability, have been robust. We have also reviewed the current Descriptors and Tariffs for mTBI and find no indication to change these now.

AFCS ORDER 2011 Tariff TABLE 6 Neurological disorders - extract relating to brain injury

Level 1 Brain injury resulting in major and permanent loss or limitation of responsiveness to the environment, including absence or severe impairment of communication and language function, and a requirement for regular professional nursing care.

Level 2 Brain injury where the claimant has some permanent limitation of response to the environment; substantial motor and sensory problems; and one or more of substantial cognitive, personality or behavioural problems, requiring some professional nursing care and likely to require considerable regular support from other health professionals.

Level 4 Brain injury where the claimant has moderate and permanent motor or sensory problems and one or more of permanent substantial cognitive, personality or behavioural problems and requires regular help or full-time supervision from others with activities of everyday living, but not professional nursing care or regular help from other health professionals.

Level 7 Brain injury from which the claimant has made a substantial recovery and is able to undertake some form of regular employment, has no major cognitive personality or behavioural problems, but with substantial functionally disabling motor deficit in upper or lower limbs or both. (a)

Level 7 Brain injury from which the claimant has made a substantial recovery and is able to undertake some form of regular employment, has no major motor or sensory deficits, but one or more of residual functionally disabling cognitive deficit, behavioural change or change in personality.

(a) The claimant is unable to undertake work appropriate to experience, qualifications and skills prior to the brain injury, but able to work regularly in a less demanding job.

Level 11 Mild traumatic brain injury which has caused or is expected to cause functionally limiting or restricting central nervous system and/or audiovestibular symptoms of peripheral labyrinthine origin for more than 52 weeks including permanent sensorineural hearing loss of less than 50 dB averaged over 1,2 and 3 kHz.**

Level 13 Mild traumatic brain injury or head injury which has caused or is expected to cause functionally limiting or restricting central nervous system and/or audiovestibular symptoms of peripheral labyrinthine origin for more than six weeks, with substantial recovery beyond that date**

****Labyrinthine causes of audiovestibular symptoms must be excluded by detailed specialist audiovestibular assessment.**

Diversity and inclusivity

102. IMEG regards issues of equality and diversity as core values and aims to avoid unjustified discrimination on equality grounds whether age, disability, gender, gender reassignment, marriage and civil partnership, pregnancy, maternity, race, religion or belief and sexual orientation. During this updated review no diversity and equality issues emerged.

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Glossary

Absolute number: Actual total number, not qualified in any way.

Adjusted rate: A summary rate statistically adjusted to remove the effect of a variable (eg age or gender) allowing unbiased comparison between groups having different composition with respect to these two variables.

Algorithm: In mathematics and computer science, an algorithm is a plan set out in step-by-step, ordered instructions to solve a problem.

Bias: A systematic error in measurement that leads to a conclusion that deviates from the truth.

Biomarker: A characteristic that is objectively measured and evaluated as an indicator of a normal biological process, a pathogenic process, or a response to a therapeutic intervention.

Cognitive behaviour therapy (CBT): A talking, thinking and behavioural therapy, which helps the patient to change the way they think, feel and act regarding their ill health and function.

Computational biology: This includes many aspects of bioinformatics, the science of using biological data to develop models to understand biological systems and their relationships.

Confidence interval (CI): A range of values within which the true value lies. For example, a 95% CI means we can be 95% certain that the true value is contained within that range. As the study sample size increases the CI narrows.

Covariates or covariables: Characteristics of the participants of a study other than that of primary interest.

Cross-sectional study (survey): An observational study which is a snap -shot of a group of people at a given point in time.

EMDR: Eye Movement Desensitisation and Re-processing is a form of psychotherapy invented in 1988. It does not use ‘talking’ therapy or medication but the patient's own voluntary eye movements to reprocess and decouple emotionally charged memories of traumatic events. EMDR is used in the treatment of PTSD and phobias.

Genomics: The study of all (rather than single) genes in complex disorders caused by both genetic and environmental factors.

Incidence: A measure of the probability of a given medical condition occurring in a population within a specified period of time; it is expressed as a proportion or rate.

Incidence rate ratio (IRR): The ratio between two incidence rates.

Longitudinal study: An observational study that follows a group of people over a period of time.

MRI: A medical imaging technique for studying the anatomy and physiological processes of the body. MRI scanners use strong magnetic field gradients and radiowaves to generate images of the organs in the body; MRI does not use X-Rays or ionising radiation.

MRI DTI: A specialised MRI technique (using Diffusion Tensor Imaging) used to examine the white matter of the brain.

Odds ratio (OR): The odds of one outcome happening divided by the odds of another, which is a measure of risk used in observational studies. An OR of 1.0 implies no increase in risk; values above 1.0 indicate an increase, and those below 1.0, a decrease in risk.

Parameter: A measurable, quantifiable characteristic of an individual.

Positron emission tomography (PET): A functional imaging technique that uses radioactive substances known as radioisotopes to visualize and measure change in metabolic processes and in other physiological activities including blood flow, regional chemical composition, and absorption.

Poisson distribution: A discrete frequency distribution which gives the probability of a number of rare events in a fixed time.

Prevalence: The proportion of a particular population affected by a medical condition at a particular time point (= ‘point’ prevalence) or over a period of time (= ‘period’ prevalence).

Randomised controlled trial (RCT): An experiment that reduces bias by randomly allocating subjects to two or more groups, treating them differently and then comparing them with respect to a measured response. Commonly there is a treatment group which receives the intervention being tested and a control group who receive either no intervention, a placebo, or a comparison intervention. The trial may be ‘blinded’ to the participants including subjects, researchers and statisticians to reduce sources of bias.

Retrospective study: An observational study that looks back at a patient's history, lifestyle etc.

Sensitivity: The ability of a test to correctly identify those with a disease.

Specificity: The ability of a test to correctly identify those without a disease.

Standardised Mortality Ratio (SMR): The ratio of the observed numbers of deaths in a study population and the numbers of deaths 'expected', based on age- and sex-specific rates in a studied reference population. An SMR of 1.0 (or 100) implies no difference in risk of death from that expected. An SMR above 1.0 (or 100) indicates an excess of deaths; if the 95% CI of the SMR value does not include 1.0 (or 100) then the excess rate is considered to be statistically 'significant' and unlikely to have occurred by chance. SMR vales below 1.0 (or 100) imply fewer deaths than would be expected.

Variable: In research studies, the outcome under study is known as the 'dependent' variable; the variables (such as age, sex, treatment) that may determine this outcome are known as 'independent' variables.

Annex 1:

Magnetoencephalography (MEG) and Mild Traumatic Brain Injury, Interim Report, on behalf of IMEG. September 2019.

Annex 2:

Setting a National Consensus for Managing Mild and Blast Traumatic Brain Injury: Post-meeting Consensus Report. August 2020.

Annex 1: Magnetoencephalography (MEG) and Mild Traumatic Brain Injury: Interim Report, on behalf of IMEG, September 2019

Key Points

1. MEG is a relatively new functional neuroimaging technique, which relies on detection of magnetic fields induced by electrical activity in the cerebral cortex. It is providing research insights into brain function in a variety of neurological and psychiatric disorders. MEG's place in routine clinical practice is not yet established, except perhaps in epilepsy.

2. There are probably currently no more than 10 MEG scanners in the UK.

3. MEG has yielded insights into localisation and pathophysiology in both mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD). However, published research results are not entirely consistent.

4. There are ongoing methodological problems, particularly related to MEG data processing.

5. While MEG shows great promise as an investigation in mTBI and possibly also in PTSD, it is concluded on current evidence that it is premature to regard MEG as a specific diagnostic test in either disorder.

6. Both mTBI and PTSD remain clinical diagnoses.

7. It is important to note that the results of imaging studies of any type are not required for the assessment of military personnel for compensation under AFCS of either mTBI or PTSD.

8. The level of AFCS compensation is awarded in relation to the severity of loss of functional capacity, particularly for future civilian employment, as the consequence of attributable injury/disease, irrespective of specific diagnosis.

9. Furthermore, MEG currently has no role in informing clinical management of either mTBI or PTSD.

10. IMEG is currently undertaking a comprehensive review of MEG, due to be published in 2020.

Introduction

11. This short paper has been prepared in response to a request from Minister DPV for IMEG to examine evidence concerning the clinical utility of magnetoencephalography (MEG) in the investigation and assessment of military personnel with mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD). Further to that request, Brigadier Tim Hodgetts (Army Personnel Senior Health Adviser) and Air Vice Marshall Alastair Reid (Surgeon General), have informed IMEG of plans to convene an urgent high-level meeting on the role of MEG in mTBI and PTSD during October 2019. This paper addresses some key issues and published evidence, in order to assist that meeting. It is presented as a preliminary review of a complex topic in which detailed understanding of basic physics and computer-based analysis is key to the interpretation of the emerging research evidence. The paper has been prepared solely to inform the planned meeting in October and should be viewed as an interim preliminary assessment of MEG, a technologically complex new imaging modality.

12. This paper should be read in conjunction with the chapter on Traumatic Brain Injury (TBI) in the fourth IMEG Report published in December 2017 (IMEG, 2017 pp65-96, attached). The Report presented an extensive evidence-based account of many issues relating to TBI, including definitions, epidemiology, TBI severity, pathophysiology, clinical aspects, diagnosis of mild traumatic brain injury (mTBI), the relationship of mTBI and concussion, investigation and management of mTBI, functional outcomes and prognosis of mTBI, audiovestibular features of TBI, mental health and TBI, and distinguishing mTBI and PTSD. It is recommended that the reader reads that review before proceeding further with this paper.

MEG: basic considerations

13. Magnetoencephalography (MEG) is a functional imaging method for recording magnetic fields produced by electrical activity in the brain, using sensitive magnetometers. The weak magnetic fields generated are recorded by arrays of SQUIDS (superconducting quantum interference devices). An alternative recording method with SERF (spin exchange relaxation-free) recording devices is under development (Boto et al, 2018). Although MEG signals were first reported 51 years ago (Cohen, 1968; Cohen, 1972), the technical challenges of reliably recording the very small magnetic fields generated by cerebral cortex electrical activity are considerable. Synchronised neuronal electrical currents in the brain produce magnetic fields which measure in the region of 10 femtotesla (fT), and the larger amplitude alpha rhythm, 10^3 fT. Because the average ambient environmental magnetic field, including the Earth's magnetic field, is of the order of 10^8 fT, MEG recordings need to be made in a magnetically shielded room, which itself is elaborate and costly. The cost of a MEG scanner is currently approximately 2 million US$. Information available via the internet indicates that there are currently 10 MEG scanners in the UK, though it is likely that more will be established in clinical neuroscience centres in the near future.

14. The physics of recording and the accurate localisation of cortically-generated magnetic fields is complex (Hauk et al, 2011; Sheltraw and Cousins, 2013). MEG signals are produced from the net effect of ionic currents in the dendrites of neurons, generated during synaptic transmission (produced by action potentials in neurons). The synchronised discharge of some 50,000 neurons in similar spatial orientation in the cortex is required to generate a detectable signal (Okada, 1983). As a result, it is predominantly electrical discharge of pyramidal neurons, lying perpendicular to the surface of the brain (cerebral cortex), that give rise to detectable MEG signals. MEG does not record magnetic fields from deeper structures in the brain though as with EEG, pathology in sub-cortical regions of the brain may be reflected to some extent in recorded cortical activity.

15. MEG is a functional imaging technique with high sub-millisecond temporal resolution, and is far superior in this respect to functional magnetic resonance imaging (fMRI), which is dependent upon changes in blood flow and has a temporal resolution of hundreds of milliseconds, and single photon emission tomography (SPECT) which has a resolution of minutes. Electroencephalography (EEG) also has a high temporal resolution, but the advantage of MEG over EEG is that magnetic fields are not distorted by human tissue in the way that scalp-recorded EEG electrical signals are. This results in a spatial resolution for MEG of millimetres, in contrast to centimetres for EEG (Leahy et al, 1998).

16. Computational analysis and modelling in order to produce MEG-based images presents another major challenge, and a wide variety of methods have been described. The published research literature on MEG is characterised by lengthy descriptions of different computer models, which for those not working in the field are not easy to grasp (see for example Alhourani et al, 2016; Rowland et al, 2017; Huang et al, 2019a).The variety of computational methods used in different studies is an important factor in the need to adopt a cautious interpretation of published MEG research papers, and is indicative of a new technique with potential clinical application but one which is still under development. Indeed, discussion of the limitations and caveats of interpretation of their results by the authors of the research studies cited in this short paper is a consistent and notable feature. Removal of contaminating artefact signals, for example from blinking, eye and facial movements, and of cardiac origin is another important issue in data interpretation (Jung et al, 2000).

Clinical uses of MEG

17. The most advanced clinical application of MEG is in the pre-surgical assessment of patients with epilepsy. The high temporal and spatial resolution of MEG has proved valuable in the localisation of inter-ictal spike activity to within a few millimetres (Cohen and Cuffin, 1983; Sutherling et al, 2008).

18. The relatively unconstrained space available in MEG scanners (in contrast to MRI) means that evoked MEG activity can be measured in response to visual and auditory stimulation, and in response to cognitive tasks. MEG has an established role in determining hemispheric language dominance, important in the presurgical assessment

of patients with epilepsy (Simos et al, 2000) and potentially in a variety of other conditions including the pre-surgical assessment of patients with cerebral tumours. MEG is providing insights into the relationship between brain activity and cognition and behaviour, and there are research reports of application in a number of conditions including schizophrenia, stroke, Alzheimer's disease, chronic alcoholism, facial pain, multiple sclerosis and autism (Georgopoulos et al, 2007; Montez et al, 2009; Hirano et al, 2010; Ihara et al, 2012; Lee and Huang, 2014).

Magnetic Resonance Diffusion Tensor Imaging (DTI) in mTBI

19. The role of conventional imaging with CT and MRI scanning in the investigation of individuals with mTBI was discussed in the fourth IMEG Report (IMEG, 2017), and brief reference was also made to recent research concerning new neuroimaging techniques not yet widely available in routine clinical practice. These included magnetic resonance diffusion tensor imaging (DTI) and MEG (denoted mEEG in the IMEG Report, but now widely referred to as MEG).

20. The molecular pathology of mTBI was considered in the fourth IMEG Report (IMEG, 2017); this has been investigated principally in animal models of mTBI. Molecular changes can occur in the absence of cellular pathology. Molecular changes include abnormalities in neurotransmission, ionic changes, increased energy demands, changes in cellular metabolism, and excitotoxicity, which are all acute potentially reversible changes (see Iverson, 2005 for review), possibly explaining transient cognitive and mood changes in individuals with mTBI who make a rapid and complete recovery. However, a mismatch between increased oxygen demand and decreased cerebral blood flow, even in mTBI may be severe enough to lead to cell death (Arciniegas et al, 2005).

21. Studies in man have demonstrated that mTBI causes axonal stretching, inflammatory changes, disruption, and separation of nerve fibres, together comprising diffuse axonal injury (DAI), although complete axotomy is apparently unusual (Adams et al, 1989). However, damage less severe than axotomy may prevent nerve impulse transmission (conduction block), leading to functional disconnection, often referred to in this context as deafferentation.

22. Standard MRI scanning in mTBI is usually normal. Magnetic resonance diffusion tensor imaging (DTI) quantifies the diffusion characteristics of water, which are altered by changes in tissue microstructure, acting as a sensitive marker of white matter damage. The extent of DTI abnormality in mTBI correlates with cognitive impairment and is a useful guide to prognosis (see Sharp and Jenkins, 2015 for review).

23. Macdonald et al (2011) reported DTI findings in a large series of 63 military personnel with a clinical diagnosis of traumatic brain injury. All had suffered primary blast exposure plus another, non-blast-related mechanism of injury including a fall, motor vehicle crash or other blunt head injury. Controls consisted of 21 military

personnel who had experienced blast exposure and other injuries but who did not have a clinical diagnosis of traumatic brain injury. All those with a clinical diagnosis of TBI fulfilled the diagnostic criteria for mTBI. All were scanned within 90 days of the mTBI event. As a group, compared to the controls, those with mTBI showed marked changes in the middle cerebellar peduncles, the cingulum and in the right orbitofrontal white matter. Re-scanning with DTI in 47 subjects with mTBI 6-12 months later revealed persistent abnormalities, judged to be consistent with evolving injuries. However, many of the mTBI subjects did not have abnormalities on DTI, questioning the sensitivity of DTI in mTBI and leading the authors to conclude that mTBI remains a clinical diagnosis. They further concluded that the observed DTI abnormalities were evidence of axonal injury. However, because all those with blast injury had also suffered other forms of head injury, the authors cautioned against making the assumption that the blast injury event was responsible for all the abnormalities shown on DTI. Finally, attention was drawn to the high rate of post-traumatic stress disorder (PTSD) in those with blast-related mTBI (see systematic review of Carlson et al, 2011).

MEG in mTBI

24. MEG reflects abnormalities of the electrical activity in cortical neurons and their injured axons. As with EEG, damaged cerebral tissue gives rise to ongoing electrical activity of lower frequency. Recordings from normal cerebral cortex show activity predominantly with frequencies above 8Hz, while injured neurons generate delta (1-4Hz) or theta (5-7Hz) activity. This occurs with damage of any kind, including stroke, tumour, infection, inflammation or tumour. Localisation of such abnormal activity using MEG was demonstrated more than 20 years ago (Veith et al, 1998; Lewine et al, 1999).

25. The sensitivity of MEG has been demonstrated in two further studies. In the first (Lewine et al, 1999), MEG was compared with EEG and standard MRI in subjects who were symptomatic following concussion (mTBI). MEG detected slow wave abnormalities in 65%, whereas EEG was abnormal in 20-25% and MRI in 20%. In a later study, Lewine et al (2007) reported a series of 30 mTBI patients with persistent symptoms of more than one year's duration, comparing investigation with MEG, SPECT and MRI. Abnormal slow wave activity was demonstrated in 63% of patients, compared with abnormalities with SPECT in 40% and in 13% with MRI. In those subjects with psychiatric symptoms, MEG was abnormal in 86%, compared with 40% for SPECT and 18% for MRI. Regional abnormalities on MEG showed associations with cognitive deficits, temporal lobe abnormalities being associated with memory problems, frontal lobe with executive deficits, and parietal lobe with attention deficits.

26. Huang et al (2009) correlated MEG and DTI abnormalities in 10 subjects with persistent mTBI symptoms, concluding that abnormal MEG was detected from cortical areas with abnormal axons in the underlying white matter, as demonstrated by DTI. All 10 patients had abnormal MEG scans; of these, 7 had abnormalities on DTI.

27. With refinement of data processing using a specialised high-resolution time-domain MEG imaging solution programme (VESTAL), Huang et al (2012) increased the

sensitivity of MEG in detecting abnormalities in 87% of 45 subjects with persistent mTBI symptoms, half due to blast injury and half due to other causes.

28. Lee and Huang (2014) drew attention to the fact that in mTBI, multiple cortical areas may be affected in mTBI in an unpredictable pattern, in contrast to studies of MEG findings in patients with Alzheimer's disease (predominantly temporoparietal).

29. Two further recently published studies deserve mention. In the first, Huang et al (2019a) demonstrated an increase in gamma band activity (30-80Hz) in subjects with combat-related mTBI throughout frontal, parietal, temporal and occipital areas. Drawing on evidence from animal experiments, they suggested that this might result from damage to GABA-ergic interneuron dysfunction. Furthermore, the presence of increased gamma activity correlated with cognitive impairments.

30. In the second study (Huang et al, 2019b), MEG source-magnitude images were obtained for alpha (8-12Hz), beta (15-30 Hz), gamma (30-80Hz) and low frequency (1-7 Hz) bands before and during tests of working memory. Compared with healthy combat controls, those with mTBI showed increased MEG signals in all frequency bands in the frontal pole, ventromedial prefrontal cortex, orbitofrontal cortex and anterior dorsolateral prefrontal cortex, but decreased MEG signals in anterior cingulate cortex. Hyperactivations in most of these areas of frontal cortex were associated with slower reaction times on tests of working memory, and hyperactivation of the frontal pole, in particular, suggested that this part of the frontal lobe might be particularly vulnerable to damage and dysfunction in combat-related mTBI. However, the authors drew attention to an important potential limitation of this study: the lack of control for previous non-combat-related mTBI, including falls and sports injuries.

31. In keeping with the findings of Huang et al (2019b), Kaltiainen et al (2019) recorded MEG in subjects with mTBI (civilians, with a variety of causes) and control subjects, during performance of a comprehensive battery of cognitive tests of attention, working memory, reasoning, visual perception, visual memory, naming, verbal memory, word fluency and executive functions. Half the mTBI subjects were studied at 6 days to 2 months following the mTBI event, and half at 6 months after the mTBI event. Handedness was not recorded, but it is safe to assume that the great majority were right-handed and thus that they were left cerebral hemisphere dominant. MEG abnormalities were found in the left parieto-temporal cortex, left superior frontal gyrus and right parietal regions. The authors concluded that the observed alterations in cortical activity during cognitive load may provide measurable neurophysiological correlates of cognitive difficulties in subjects with mTBI, even at the individual level.

32. There are four important caveats to bear in mind in the interpretation of these MEG studies in subjects with mTBI. First, that slow wave activity is not specific to mTBI, but as outlined above, can be due to multiple other types of cerebral pathology. Second, in the absence of MEG recording prior to the incident mTBI event, it is not possible to be certain that the mTBI event in question is the cause of the recorded abnormality. Third, no prospective longitudinal study has yet been reported. It is possible that there are subjects exposed to blast injury and other causes of mTBI who show similar MEG abnormalities but who are asymptomatic. This would necessitate a reconsideration of

the significance of the results of the published studies. And fourth, MEG has not yet been sufficiently studied in other neurological disorders to be able to conclude that the reported findings are reliably specific to mTBI. This could be the case but has not yet been conclusively demonstrated.

33. Finally, in relation to the suggestion that MEG can be regarded as a diagnostic test for mTBI, the point should be made that imaging of any modality, including CT and MRI, is rarely 100% specific regarding causation for any neurological disorder. The diagnosis of mTBI is in the history, supported by clinical examination features (notably cognitive, and assessment of mood and other psychiatric features), and then potentially supported by special investigations such as DTI and MEG. Regarding MEG as a specific and sensitive diagnostic test for mTBI leads to the awkward and illogical conclusion that individuals exposed to blast or another potential cause of mTBI in whom the purported 'specific' changes are not demonstrated by MEG, might be denied correct diagnosis and the subsequent benefits of appropriate care and, indeed, compensation under AFCS.

MEG and Post-traumatic stress disorder (PTSD)

34. Interpretation of the published studies on MEG studies in PTSD is challenging, largely due to the differing methods employed in computer processing and analysis of MEG signals. Research publications up to 2017 are reviewed by Rowland et al (2017). A detailed appraisal of the published papers on this topic demands advanced technical knowledge of, and familiarity with, some highly complex computer-based principles and processing of raw MEG signal data. The following two paragraphs are intended to provide an indication of this complexity.

35. Using graph-based network analysis, Lei et al (2015) studied patients with PTSD resulting from an earthquake event, finding that PTSD was associated with higher values of clustering coefficient, global and local efficiency, with lower values of path length, but without a significant difference in Small-worldness (a mathematical concept that measures connections through the number of steps necessary to establish connectivity). In contrast, using the network-based statistic (NBS), Zalesky et al (2010) identified a subnetwork in which connectivity was reduced in those with PTSD. Using NBS to analyse resting state MEG, Dunkley et al (2014) identified a subnetwork in the high gamma bandwidth located primarily in the left hemisphere with increased connectivity in patients with PTSD. However, in several studies using both resting state MEG and fMRI, reductions in functional connectivity have been demonstrated in patients with PTSD. These studies are detailed by Rowland et al (2017), who comment that the findings are mixed concerning the effect of PTSD on the resting state network as measured with MEG, but that the most consistent finding is reduced functional connectivity in PTSD. Two studies in patients with both mTBI and PTSD, using fMRI with graph theory-based network analysis, have also produced mixed results (Messe et al, 2013; Han et al, 2014).

36. Against this confusing background, Rowland et al (2017) determined to investigate how mTBI and/or a diagnosis of PTSD altered the whole-brain resting state

network, as measured with MEG, in post-deployment veterans. As with many other MEG research investigations, details of the analysis of MEG signals described by Rowland et al (2017) are complex and dense. The calculation of Small-worldness, Rich Club (a measure of the extent to which well-connected nodes also connect to each other) and Modularity (a measure of the degree to which a system's components may be separated and recombined, often with the benefit of flexibility and variety of use), is essential to the understanding of the data analysis presented. However, this is not easily accessible to those not working in this field. Notwithstanding this reviewer's limited understanding of the data analysis methodology and its limitations, the findings of Rowland et al (2017) appear to be striking. First, in PTSD, particularly in the absence of a history of mTBI, there were lower values of network metrics, indicative of reduced functional structure and increased randomness, suggesting a shift away from local connectivity and hierarchical network structure towards larger more inclusive modules. Second, mTBI was associated with an increase in Small-worldness in the wideband network but was not associated with alterations in alpha network metrics. And third, differing results were obtained when restricting connectivity within the alpha bandwidth, causing important network connections to be missed at other frequencies.

37. In essence, interpretation of these results seems to be as follows: the reduction in network efficiency and increased randomness found in PTSD might relate to the poorer cognitive performance associated with this condition. By contrast, in mTBI, networks showed a greater degree of structure and less resemblance to random networks, as evidenced by higher levels of clustering coefficient and Small-worldness.

38. Rowland et al (2017) stated that this is the first study to evaluate wideband connectivity using a purely phase-based metric, allowing connectivity to be determined anywhere in the frequency range. In a wide-ranging discussion, they drew attention to the limitations of their study, including the lack of premorbid studies in the subjects investigated, and the possibility that some of the altered connectivity demonstrated in patients with PTSD might have represented risk factors for the development of PTSD rather than consequences of the disorder. In addition, the majority of those with PTSD were taking psychotropic medication, and the effects of these drugs on network metrics is currently not known. The authors concluded that their results demonstrated differing effects on brain function in mTBI and PTSD, as determined by graph-based network analysis of resting-state MEG data.

39. Overall, this study represents an important contribution, indicating that there are differences in MEG activity in mTBI and PTSD. Intuitively, this is perhaps not surprising. As a research tool to better understand brain function and its relationship to symptoms including cognitive, mood and psychiatric morbidity, MEG is likely to continue to make additional contributions. However, there are clearly many unresolved technical issues, notably concerning the selection and analysis of MEG signals. This is manifest by the sometimes widely variable results of different studies, employing different methods of analysis.

MEG and DTI in relation to compensation for mTBI and PTSD under AFCS

40. The fourth Report of IMEG (IMEG, 2017) set out revised descriptors and tariffs for traumatic brain injury, including mTBI. Within the last year, a new descriptor for Complex PTSD, with an enhanced tariff, has been added to the Mental Health descriptors, in recognition of increasing evidence of the persistence of severe symptoms of PTSD in a small minority of those who develop this condition as a result of military service. Results of investigations such as neuroimaging (including CT, MRI, fMRI, SPECT or MEG) are not required in order to either make the diagnosis or to assess the severity of these conditions. Diagnosis is based on clinical assessment of history and examination, including physical examination and examination of the mental state. Compensation is awarded in relation to the severity and loss of functional capacity, particularly for future civilian employment, irrespective of specific diagnosis.

41. The broad concept of mTBI, argued and recommended by IMEG in 2017, remains appropriate, judged on current evidence. Affected individuals present with a variable mix of persistent physical, mood and psychiatric symptoms. They are all included within the diagnosis of mTBI. Some individuals will also have symptoms that fulfil the diagnostic criteria for PTSD. Compensation under AFCS does not require a sharp distinction between these frequently co-morbid conditions.

42. This preliminary review of the recent evidence concerning newer neuroimaging techniques, including DTI and MEG, leads to the conclusion that while these techniques are beginning to provide important insights into the pathological basis for mTBI and PTSD, they should not be regarded as specific diagnostic tests. It may be appropriate in individual patients for one or both these investigations to be performed, based upon expert opinion and recommendation, and importantly, as part of approved research studies, but the results will not currently affect the assessment of compensation under AFCS.

43. IMEG is embarking on an in-depth evaluation of MEG in its next programme of work, extending into 2020. In line with its established practices, this will involve a thorough literature review and consultation with specialists experienced in MEG both in clinical practice and research, in order to gain understanding and insight into methods and the benefits and limitations of the technique. IMEG will include MEG as a topic in its sixth Report.

44. Finally, it is worth reiterating that IMEG adopts an objective evidence-based approach to all the conditions it considers in relation to AFCS, while at the same time striving to understand, respect and consider the impact on patients and their families in a compassionate way.

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Annex 2 – Setting a National Consensus for Managing Mild and Blast Traumatic Brain Injury: Post-Meeting Consensus Report

Setting a National Consensus for Managing Mild and Blast Traumatic Brain Injury: Post-Meeting Consensus Report

FOREWORD

I am grateful that so many came together to help address this important topic. The United Kingdom Ministry of Defence was pleased to support this event as part of our duty of care to Service personnel, yet I recognise this subject is of national and international importance to our allies and across many fields of healthcare, employment and sporting activity.

It goes without saying that people, and specifically patients and their families, are the priority. The aim was a consensus that will help direct our further research and clinical innovation in mTBI prevention, detection and treatment pathways. The focus was to address diagnostic imaging modalities, but the discussion ranged much wider and deeper. It was important to me that all stakeholders had a voice. Moreover, it was critical that we could reach enough consensus on which to act, understanding where evidence is contested or at equipoise and that consensus may not mean unanimous acceptance.

I witnessed genuinely new knowledge being appreciated amongst the attendees, which was a success measure in itself, reflecting the value of bringing together national and international expertise. I also witnessed debate and challenge, those essential components for due diligence on the evidence presented. With the follow-up exchange of discussion and clarification, the summit has reached a series of consensus statements that provide a framework to align behind and drive forward the next steps.

I commend the consensus statements to you. I look forward to translating the summit outcomes into tangible actions that ultimately improve our patient outcomes, safety or experience.

Air Vice-Marshal Alastair N C Reid CB QHP
Surgeon General

Setting a National Consensus for Managing Mild and Blast Traumatic Brain Injury: Post-Meeting Consensus Report

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* The opinions and assertions expressed herein are those of Dr David Brody and Dr Daniel Perl and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense.

SUMMARY OF RECOMMENDATIONS

1. **The military should consider the implementation of recruitment or pre-deployment screening as part of an independent research study**. Recruitment or pre-deployment screening of selected military personnel would allow for a comparison within the individual post-deployment and/or post-blast exposure or non-blast TBI event.
2. **The military should employ pre-emptive medical assessment for those experiencing an event likely to have caused m/bTBI.** This is rather than waiting for individuals to present later with symptoms.
3. **A diagnostic suite of tests incorporating imaging and neuroendocrine testing should be introduced within a 'one-stop research clinic' approach**. Expertise and resources would need to be carefully focussed. The one-stop research clinic should form part of a multi-modal clinical research protocol and the data collected should feed into a longitudinal research study.
4. **Regional Hubs are required** across the country with access to a one-stop research clinic. Hubs could be located in the South, the Midlands and Scotland based on research expertise and access to appropriate imaging facilities.
5. **Establish imaging and neuroendocrinology sub-groups for implementation**. Two sub-groups of experts will be established to help implement the recommendations from this Consensus Report, agree on protocols and/or technology to use, and ensure integration of research protocols within clinical settings. Joint coordination will facilitate collaboration and coherence.

INTRODUCTION

The purpose of the meeting held on Wednesday 15 January 2020 was to examine the current evidence for non-routine imaging and for neuroendocrine screening in the management of military personnel with brain injury and overlapping symptom domains. The Summit aimed to specifically address the relative utility of magnetoencephalography (MEG), diffusion tensor imaging (DTI) and susceptibility weighted imaging (SWI) in the UK context.

Those in attendance at the meeting represented the following organisations/expertise:

- Defence Medical Services;
- Scientists from the United Kingdom, Unites States of America and Canada – many of whom work with the military;
- The UK National Health Service (NHS) – which would be responsible for implementing any new assessment protocols shown by research to have clinical utility in routine practice;
- The Chair of the Independent Medical Expert Group – the group which advises on medical aspects of the Armed Forces Compensation Scheme; and
- Clinicians who treat brain injury.

The approach during the day split the discussions into those about imaging and diagnosis first, followed by discussions about neuroendocrine testing. Both sessions started with a veteran's personal experience of mild traumatic brain injury to help inform the clinical context for discussions. These were then followed by presentations about the current science and clinical practice in the fields of clinical diagnosis, imaging, and neuroendocrine testing in the context of the current understanding of mTBI. The presentations led to discussions and debate which helped to establish the points of consensus outlined below, identified divergence of opinion and highlighted major uncertainties and gaps in knowledge.

Following the meeting, a brief Summary Report was produced and circulated to all attendees. Comments were then solicited for inclusion in this Consensus Report. The Consensus Report has been drafted with input from the attendees named as authors on this report.

POINTS OF CONSENSUS

Mild impact/acceleration TBI (mTBI) due to blunt head injury and blast-related TBI (bTBI) may not be pathologically identical. mTBI due to impact or acceleration is a well-recognised problem both in military and civilian populations, and many of the injury causations are similar between bTBI and mTBI. The majority of overall TBI are in the mild category. The military are more likely to be exposed to blast injury during conflict, and therefore this Consensus Report deals with bTBI as well as military-related mTBI (from non-blast events). Blast exposure appears to result in a different pathophysiological entity. Repeated mTBI or bTBI may also have cumulative effects that may be different to a single exposure to a blast or non-blast cause.

Overlap in symptoms between TBI and mental health conditions. The mental health conditions include Post-Traumatic Stress Disorder (PTSD), depression, anxiety and functional neurological disorders. TBI and mental health conditions (including PTSD) are leading causes of morbidity in service personnel and veterans. The disorders are complex, and the underlying pathophysiology is incompletely understood.

Currently there is no consensus or adoption of a diagnostic test that provides a 'signature' abnormality for m/bTBI. Severity of TBI from mild to moderate-severe can be defined using different categorisations that include factors such as acute level of consciousness (e.g. Glasgow Coma Scale), duration of post-traumatic amnesia (PTA) and acute neuroimaging findings (e.g. the Mayo classification). Currently there is no diagnostic test for m/bTBI that has been adopted. The MOD currently use a combination of the WHO and DoD definitions which are based solely on clinical criteria to diagnose mTBI in UK military personnel. Advanced imaging and formal neurocognitive testing are also used in some individuals, but not in a routine way.

Treat and diagnose the patient's symptoms rather than the suspected diagnosis or imaging results. At the current time, there is no biomarker to distinguish m/bTBI as distinct from PTSD. The two conditions often co-exist. Diagnosis is based on a history of one or more m/bTBI events, and treatment depends on the nature of the symptoms in individual patients, rather than imaging results. PTSD also remains a diagnosis made on purely clinical grounds. Baseline data (both imaging and neuroendocrinology) should be acquired in both these domains as part of future research (see Recommendations section).

Consideration of different cohorts for bTBI. There are three different military groups affected by blast-related TBI which require investigation:

1. Those currently presenting with symptoms compatible with a diagnosis of long-term sequelae of previous blast-related TBI and/or PTSD:
   - This cohort requires the development of an evidence-based management protocol/pathway which is agnostic of injury sequelae, and which acknowledges that both blast-related TBI and mental health conditions may be present.
   - This cohort could also be involved in the investigation of the longer term structural, functional and neuroendocrine changes which can be assessed against controls and other groups.
2. Those exposed to blast but with no long-term symptoms.
3. Population at risk of future blast-related TBI and who require enhanced mitigation strategies.
   - For this cohort it is important to better understand blast injury, particularly in terms of load, biomechanical effects, physiological responses and assessment of mitigation proposals.

Assessing the severity of the initial blast injury is difficult. A greater length of time since deployment may render it more difficult to recall the specific details related to blast exposure. Any future studies and clinical research protocols in this area should focus on serving military as well as veterans, with careful consideration of the severity of injury, and number and intensity of blast exposures.

Multi-modal imaging potentially offers new opportunities for the investigation and management of patients with military-related mTBI or bTBI.

1. Magnetic resonance imaging (MRI) is routinely used to assess the structural and functional impact of TBI.
   - Standard MRI approaches can identify many types of brain injury in both the acute and chronic phase. However, diffuse axonal injury and diffuse vascular injury are often missed unless more advanced MRI techniques are used.
   - Diffusion MRI has been widely applied to the study of diffuse axonal injury produced by civilian and military TBI. Diffusion tensor imaging (DTI) can identify subtle but important signatures of diffuse axonal injury, which can inform clinical management and outcome prediction.
   - Susceptibility weighted imaging (another type of MRI) is a sensitive way to identify diffuse vascular injury.
   - MRI scanners are available in almost all hospitals and protocols for advanced MRI acquisition are available on modern MRI scanners.
2. MEG appears to offer the potential to:
   - aid in diagnosis and in differentiating the pathophysiological consequences of m/bTBI from PTSD through 'signature' MEG abnormalities (noting however that TBI and PTSD often co-exist);
   - predict recovery outcomes and stratify patients e.g. those who will make a full recovery versus those who will continue to experience ongoing problems;
   - better understand the pathophysiology of these disorders; and
   - correlate with neuro-behavioural measures, e.g. symptom and neurophysiological scores.
3. MEG data acquisition and analysis techniques should be standardised, but MEG data acquisition is straightforward when acquiring resting-state data.
4. The importance of acting now and not waiting for the imaging technology to mature further was agreed.
5. MEG scans performed on those in the military affected by mTBI or bTBI should be undertaken as part of ethics committee-approved research studies and compared with advanced MRI.

There are deficiencies in the current imaging literature. Whilst the imaging field is progressing (both in terms of research and clinical use), there are discrepancies and deficiencies in the existing literature:

1. Many of the imaging studies are performed on varying versions of technologies without standardisation of data analysis methodologies. Technologies have evolved rapidly over recent years making some of the previously published data difficult to compare with recent studies.
2. Significant variability of protocol and scanner capabilities complicates sound meta-analysis being reliably performed. Harmonisation methods are being developed by many groups globally, but there is currently no consensus as to the most appropriate methods of data analysis.

3. There is a lack of longitudinal data, particularly for MEG studies.
4. In some studies, images have been interpreted by non-specialists, putting the reliability of the conclusions into question.

There is potential to incorporate neuroendocrine testing in a multimodal clinical research pathway. Further discussion is required about how best to incorporate evidence-based neuroendocrine testing within the potential multimodal clinical research programme that will be taken forward.

POINTS FOR FURTHER DISCUSSION/ POINTS OF EQUIPOISE

The following points were established as requiring further discussions or investigation.

Study measures and study size. Imaging and neuroendocrine research studies in the literature have often included small patient groups, and rarely have been combined together in the same study. Global efforts to scan and test more individuals, with clearly defined clinical characteristics, with standardised protocols, and with pooling of data need to be pursued further.

Randomised Controlled Trials (RCTs) of treatments. Some believe that RCTs are required for the field to make progress, precisely because m/bTBI is a complex condition, hard to define, without a diagnostic investigative marker, with multiple co-morbidity, and without a clear pathology. It was noted that the only way to take management/treatment forward is well designed RCTs, preferably using just one treatment approach at the time so that one can be sure that any differences between the two samples are due to the intervention under study.

Longitudinal research is essential. Overall, the prognosis following m/bTBI is good. In a small minority, there can be a persistence and/or progression of symptoms, but there has not yet been an appropriate longitudinal study which follows the progression of abnormalities in the MEG signal, correlated with symptoms and cognitive deficits. The question remains as to whether a multi-modal longitudinal study should be used to assess the following:

1. MEG allied with the use of EEG – there is growing evidence of MEG's utility in the identification and differentiation of the pathophysiological changes found in mTBI and PTSD. Resting state MEG and MEG studies with cognitive loading are needed. Correlation with neuropsychological evaluation is essential (see below). The relative ubiquity of EEG across hospitals may prove advantageous if MEG derived abnormalities could be mirrored in EEG (albeit with perhaps lower sensitivity and vastly reduced spatial precision).
2. There are a number of areas that may prove particularly beneficial for the future assessment of m/bTBI using MRI:
   - The use of AI based software or computer aided diagnosis to assess advanced MRI (SWI and diffusion MRI, plus other novel sequences).
   - The use of high field strength magnets that can be used in clinical research protocols in multiple locations may be evaluated.
   - The use of diffusion MRI to assess white matter microstructure and identify evidence of diffuse axonal injury after m/bTBI.
   - The use of functional MRI to estimate the integrity of brain networks.
3. Assess the utility of neuropsychological testing in m/bTBI:
   - Research to identify the optimal cognitive loading testing required in the evaluation of individuals following m/bTBI.
   - Development and validation of neuropsychological/neurophysiological testing which may be more sensitive to subtle, but clinically meaningful changes in performance and functioning.
   - Assess the use of semi-structured interviews for assessment of mTBI and mental health across the studies to understand the broader neuropsychological symptom complex and relate to pathology.
4. Agree and assess a battery of neuroendocrine testing to measure the incidence and severity of dysfunction.
5. Accurate phenotyping of:
   - Military m/bTBI secondary to blast-related and non-blast-related mechanisms, that often co-occur.
   - Military moderate-severe TBI secondary to blast-related and non-blast-related mechanisms.
   - Military PTSD.
   - Military with both PTSD and m/bTBI (blast- and non-blast-related).
   - Military with blast injury but without symptoms of m/bTBI or PTSD.
   - Civilians with m/bTBI.
   - Civilians with PTSD.
   - Military and civilians with neither m/bTBI nor PTSD.

Test beyond the 'resting state'. Currently most published studies have reported resting state MEG data to assess abnormalities in those with mTBI, PTSD or both. While the recent literature has shifted focus from task-dependent to task-free paradigms, there is still a lot to be gained from the combined use of the two using study designs that are specific to the behavioural phenotype of the individual. Information may be gained, and more sensitive biomarkers found, via the use of cognitive tasks (working memory or attentional tasks) which probe patient symptoms.

Potential clinical research protocols for imaging and neuroendocrine testing. These are some suggestions for clinical research pathways which require further development and discussion:

1. Imaging and neuroendocrine testing undertaken before deployment so baseline data is established and then further testing employed post-deployment. Agreement needs to be reached on which individuals should receive recruitment or pre-deployment screening. Research may be required to provide criteria for selection, and there

needs to be clear evidence from the research that markers are stable over time.
   - We need to further understand whether doing post-deployment imaging and neuroendocrine testing without baseline data is valuable. This may be more useful for imaging, as false positive results may often be seen in dynamic neuroendocrine tests depending on test and reference ranges used.
2. Serving military personnel with agreed diagnostic criteria for a particular clinical research protocol (e.g. imaging and neuroendocrine testing).
3. Veterans and civilians with similar entry criteria to an NHS clinical research pathway.

Selection of appropriate control groups. This needs to be considered in relation to the potential use of databases from around the world which contain MEG data from healthy control participants (e.g. Human Connectome Project, Omega, UK-MEG-partnership), which could provide a normative database against which to test for statistical differences in individuals with m/bTBI. This could also be considered in the context of randomised control trials where a comparator group is created by randomisation. Special care must be taken to recruit a military battlefield exposed, non-injured, comparator group.

RECOMMENDATIONS

The military should consider the implementation of recruitment or pre-deployment screening as part of an independent research study. Recruitment or pre-deployment screening of selected military personnel would allow for a comparison within the individual post-deployment and/or post-blast exposure (or non-blast TBI event). The following options should be considered:

1. Pre-recruitment history enquiring about previous m/bTBI.
2. Scanning:
   - Pre first deployment MEG and MRI screening of medium and high-risk servicemen and women. The risk stratification should be operationally based;
   - acutely following exposure to blast and non-blast injuries;
   - at an interval when there are persistent symptoms which could be attributed to m/bTBI; and
   - at retirement from active combat service and had exposure (or expected exposure) to blast or known to have had an m/bTBI.

A consideration of recruitment or pre-deployment scanning raises the likely prospect of picking up asymptomatic but potentially serious unknown neuroimaging abnormalities in the recruitment or pre-deployment scan. If such a study were to be undertaken in the UK, we would advise that scans are reviewed by an independent neuroradiologist and neurologist if abnormalities are identified. These independent reviewers would then decide if action should be taken.

Employ pre-emptive medical assessment for those experiencing an event likely to have caused m/bTBI. Based on experience from the United States, this may be preferable to waiting for individuals to present later with symptoms. It would also provide the opportunity to address immediate problems and reassure individuals about the likely good prognosis.

A diagnostic suite of tests incorporating imaging and neuroendocrine testing should be introduced within a 'one-stop research clinic' approach. Expertise and resources would need to be carefully focussed. The one-stop clinic should form part of a clinical research protocol and the data collected should feed into a multi-centre longitudinal research study.

1. Such a multi-modal prospective longitudinal study would help with determining the answers to the following questions:
   - Can m/bTBI and/or PTSD be differentiated from non-head injured controls by measuring brain activity?
   - Can m/bTBI and/or PTSD be pathophysiologically differentiated from non-head injured controls by novel imaging techniques?
   - Can biomarkers provide prognostic information for m/bTBI and/or PTSD?
   - To what extent do MEG, MRI and other imaging abnormalities correlate with symptoms and cognitive deficits?
   - Does analysis of MRI, MEG and EEG recordings allow network modelling to predict seizure risk after mTBI?
   - What is the prevalence of neuroendocrine dysfunction after mild or moderate-severe blast or non-blast TBI in military, what are the risk factors, and can it be predicted by clinical features or multi-modal imaging to enable targeted screening?
2. The following imaging would be conducted: structural imaging including conventional and advanced MRI techniques (including SWI and DTI), as well as functional imaging including the use of fMRI and MEG. Where available, high spatial resolution MRI using high and ultra-high field MRI and high gradient strength microstructure imaging could also be used.

Potential clinical research protocols for imaging and neuroe for clinical research pathways which require further developmer

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2. The following imaging would be conducted: structural imagi techniques (including SWI and DTI), as well as functional imag available, high spatial resolution MRI using high and ultr microstructure imaging could also be used.

3. The defined multimodal imaging as part of a one-stop clinic approach would standardise the pathway provided whilst minimising the number of interactions for patients.

Regional Hubs are required. To provide benefit across the country, regional hubs should be established for the one-stop research clinic where the suite of imaging and neuroendocrine testing can be carried out. Hubs could be located in the South, the Midlands and Scotland (possibly London, Birmingham, Nottingham, and Glasgow), based on research expertise and access to appropriate imaging facilities.

Establish imaging and neuroendocrinology sub-groups for implementation. Two sub-groups of experts will be established to help implement the recommendations from this Consensus Report, agree on protocols and/or technology to use, and ensure integration of research pathways within clinical settings. It is important that the recommendations from the sub-groups are considered within the context of being able to deploy the research protocols within the NHS and, therefore, NHS participation is recommended. The sub-groups should clearly communicate with each other and coordinate activities for a seamless 'one-stop' experience.

CONCLUSION

There is an urgent clinical need to address the issues arising out of large numbers of military personnel and veterans with persistent symptoms of m/bTBI/PTSD. The exceptional promise of advanced imaging and new knowledge of neuroendocrine function in this area will only be translated into practice via an integrated, global, multi-modal research effort; acquiring new data, pooling existing data, integrating new experimental paradigms, initiating longitudinal metrics and standardising methods. The UK can achieve the first major step in achieving this translation to clinical practice through an appropriately resourced and supported research effort.

DECLARATION OF COMPETING INTERESTS

The following authors are employed by the Ministry of Defence: MC, IG, TGH, AM, ANCR, DS, AS, DRW.

AMJB is Director of the Centre for Blast Injury Studies that receives core funding from the Royal British Legion and support from the Ministry of Defence; AMJB serves on the project board of the Armed Services Trauma Rehabilitation Outcome Study funded by the Headley Court Trust, HM Treasury, Help for Heroes, Forces in Mind Trust, Blesma, the Limbless Veterans, and the Nuffield Trust for the Forces of the Crown.

APG has received research grant support from Pfizer.

AM is the Chair of the Clinical Reference Group for Complex Rehabilitation and Disability for NHS England.

JWS is Chair of the Independent Medical Expert Group, which makes recommendations concerning the Armed Forces Compensation Scheme.

DJS is a member of the Rugby Football Union Expert Concussion Panel.

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APPENDIX

Definitions and current status of imaging for TBI

Traumatic Brain Injury

- Traumatic brain injuries (TBIs) can be described as mild, moderate or severe and the mechanism of injury can be from blunt, penetrating or blast forces[1]. The severity, location, type, mechanism and physiological response to injury are also used as classifications of TBI1.
- Clinical diagnosis of an acute injury is usually based on use of the Glasgow Coma Scale and sometimes the evaluation of neurobehavioural deficits1[,2,3].
- Imaging techniques can be used to help with diagnosis. Each of the below imaging techniques have been used in TBI patients, either individually or in combination. Some of these techniques are also utilised in research.

Computed Tomography Scanning

- Computed Tomography (CT) scanning is the modality of choice when assessing a head injury in the acute setting3. It is able to detect haemorrhage, intracranial injury, trauma-related fractures, swelling of the brain tissue and the presence of foreign bodies that are radio-opaque (e.g. shrapnel).
- Patients with mild TBI will have normal CT scans, so this modality is a poor discriminator for the presence or absence of mild TBI2.

Magnetic Resonance Imaging

- Magnetic Resonance Imaging (MRI) is an imaging method that is non-invasive and allows the imaging of soft tissue and structures within the body[4]. Different tissues and structures have different magnetic properties, allowing clinicians to tell them apart[5].
- MRI is considered superior to CT in terms of sensitivity for identifying haemorrhagic axonal injury and contusions. This includes in patients that have shown normal CT scans2.
- MRI is more expensive than CT, and is usually less available in acute settings2 with particular patient safety concerns in the acutely injured patient but provides optimal definition of brain structural anatomy.

Functional MRI

- Functional MRI (fMRI) can identify changes in communication between and within neural networks. It measures the differences in the MR signal between deoxygenated blood and oxygenated blood. When there is increased neural activity in a region, the signal from the local tissue changes as there is an increase in oxygenated blood to the region[6].
- Functional MRI provides information about brain function, which can be used following TBI. It has been primarily used to investigate dysfunction seen after TBI at the group level[7].

MRI: Diffusion Tensor Imaging

- Diffusion tensor imaging (DTI) is an advanced type of MRI that produces a measure of white matter structure in the brain[8]. DTI has been extensively used to investigate subtle but important effects of TBI and other types of brain injury. It has been shown to be useful in assessing post-traumatic damage to the structure of white matter connections in the brain.

Diffusion-Weighted Imaging

- Diffusion-Weighted Imaging (DWI) is able to map the complex architecture of fibres within the brain, at the submillimetric level.
- DWI is particularly used to help identify brain tissue that is ischaemic in the early stages of TBI[9].

Susceptibility Weighted Imaging

- Susceptibility-Weighted Imaging (SWI) is a technique which uses the differences in magnetic susceptibility of different compounds, for example

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iron, calcium and blood, to give contrast images[10,11].

- SWI aids the detection of diffuse axonal injury and microhaemorrhages. Small haemorrhages can be missed when using other MRI sequences[12].
- SWI MRI is a sensitive way to look at blood vessels and iron deposition within the brain[13]. This has been shown to be useful in the evaluation of Traumatic Brain Injury (TBI)[14].

Electroencephalography

- Electroencephalography (EEG) measures the synchronous activity of millions of neurons and allows assessment of electrical activity during different brain states (e.g. sleep, attentive wakefulness) where different frequency bands are often present[15].
- Pathological changes can also be identified, for example because of axonal injury during TBI15.

Magnetoencephalography

- Magnetoencephalography (MEG) measures the magnetic field which is generated by neuronal electrical activity[16]. It provides high spatial and temporal resolution and is non-invasive16,17.

Neuroendocrine testing in TBI

Neuroendocrinology is the field that looks at the nervous system's control of hormonal secretion and the control of the brain via hormones[18]. Neuroendocrine systems control many bodily functions.

Neuroendocrine dysfunction in TBI

- Many papers have considered neuroendocrine dysfunction after TBI, with the prevalence varying between studies. Potential differences are attributed to different sample populations, time since injury, injury severity, differences in the screening tests used, as well as confounding effects of other medications and other diseases[19,20].
- Hormonal screening can confirm significant pituitary hormone dysfunction, but usually needs repeat testing, with multiple dynamic endocrine tests needed for growth hormone and cortisol deficiency, and if a single test is used may in fact result in overdiagnosis19,21.
- Pituitary dysfunction seen in the non-acute phase of TBI may recover in many patients within the first year after injury19,22.
- Hypopituitarism in TBI patients may be the result of a number of potential mechanisms such as compression of the pituitary, vascular injury, increased intracranial pressure, direct trauma to the pituitary, and autoimmunity, genetic susceptibility and side effects of medications may play a role19,20.
- Symptoms of pituitary hormone dysfunction after a TBI overlap with the neurological and psychiatric symptoms of the TBI itself19.
- Even though pituitary hormone dysfunction may not be common after TBI, their diagnosis and treatment may have an important role in the individual's cognitive, psychological and functional recovery22.
- Exposure to moderate-severe blast TBI appears to be a particular risk factor for development of pituitary dysfunction21.

Testing and diagnosis

- TBI-induced hypopituitarism and other pituitary

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dysfunction is diagnosed in the same way as diagnosis of classical pituitary disease. There are variable patterns of hormone deficiencies/excess in patients with TBI-induced pituitary dysfunction and so each pituitary hormone needs to be tested for.

- Dynamic testing is required for some pituitary hormones - growth hormone, ACTH/cortisol and vasopressin/ADH22.
- Evaluation of the functioning of the pituitary during the acute phase of injury, i.e. during the admission with TBI, is unnecessary because it is not clear at that stage whether the hormonal changes are because of an adaptive response or a deficiency21. Central adrenal insufficiency should only be investigated in the acute phase if it is suspected clinically[23].
- In the non-acute phase after injury, adrenal insufficiency is a priority for testing as although uncommon, it can be life-threatening19,20,23,24.
- Testing of anterior and posterior pituitary dysfunction, are usually undertaken in the chronic phase of the injury as hypopituitarism can evolve over several months20,24.

Measurements

- The availability of particular dynamic tests to diagnose growth hormone deficiency and central adrenal insufficiency may vary between countries and centres, and depend on resources available, while cut-off values vary between tests and may vary locally depending on the assays used22. Harmonisation of assays to national or international standards e.g. for growth hormone and cortisol helps this process.
- Defining cut-off values for diagnosis of growth hormone deficiency and central adrenal insufficiency is also made difficult because of the influences of other factors such as level of hypothalamic-pituitary damage, age, body mass index, and presence of other diseases such as diabetes mellitus.
- Several peripheral hormones (cortisol, testosterone, IGF-I) have circulating binding proteins whose levels can vary between individuals. While the binding proteins concentrations can be
- measured (cortisol binding globulin, SHBG, IGFBP3), interpreting their influence on total hormone concentrations can be difficult, and tests for measuring free, biologically active hormones, are technically difficult, expensive and time-consuming24.
- Basal pituitary hormone levels naturally vary because of circadian, pulsatile and situational changes in secretion of certain hormones e.g. from stress or food intake22. This requires rigorous attention to circumstances of sample collection and necessity to avoid making diagnoses based on single samples collected inappropriately.

SUGGESTED CITATION

Foss, LJ et al (2020), Setting a National Consensus for Managing Mild and Blast Traumatic Brain Injury: Post-Meeting Consensus Report, https://doi.org/10.25561/81286

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Non-Freezing Cold Injury (NFCI): an update

Summary and key points

1. The incidence of NFCI has decreased since the last IMEG report on this condition in 2015.

2. NFCI in the military is, overall, less severe than previously reported, reflecting increased awareness of the condition and the measures needed to prevent it.

3. The prognosis of NFCI has also improved, and this is likely to be directly related to better prevention strategies and less severely affected individuals.

4. Recent research has clarified the pathophysiological basis of the pain, which is the leading persistent and debilitating symptom in NFCI; this pain is neuropathic in type.

5. Diagnostic accuracy of those with NFCI and persistent pain has been improved by skin biopsy, with objective histochemical analysis showing small fibre neuropathy, but this is currently an investigation available only in a few specialist centres.

6. In relation to AFCS, it is concluded that at the time of publication of this report, no modification of existing descriptors for NFCI, or additional descriptors, is required.

Introduction

7. Non-freezing cold injury (NFCI, previously known as Trench Foot or Immersion Foot) was considered by IMEG in the 2015 report (1). Key findings were that, more than a hundred years since it became a major problem in the first World War, NFCI remained a significant source of UK military casualties, with a limited clinical evidence base and many gaps in understanding of the pathogenesis of the condition. Particularly relevant to compensation, these included its prevention, diagnosis, assessment of severity, prognosis, and best practice treatment. The present review includes updated data on military downgrading and medical discharge, and civil and AFCS awards made since 2015. It also considers the changing patterns of clinical presentation in the UK armed forces over time, and current military prevention and clinical management. There are short sections on recent research in pathogenesis and pharmacological treatment.

9. The most functionally disabling aspect of NFCI is pain, which can persist and, in a small proportion of those affected, can become long-lasting. Both vascular and neurological mechanisms have been proposed, but by publication of the 2015 IMEG report, there was some evidence that the pain was due to a small nerve fibre peripheral neuropathy, the clinical features indicating that the pain was neuropathic in type. The

present report focuses on recent studies on these and related topics, particularly with potential impact on accurate diagnosis and treatment of NFCI in a military setting. The review was informed by published peer-reviewed literature search, discussion with military colleagues and Dr Andreas Themistocleous, clinical lecturer in neurophysiology at the Nuffield Department of Clinical Neuroscience, University of Oxford, who has an internationally recognised research record in small fibre peripheral neuropathy.

Key points from the 2015 IMEG report

10. Military NFCI and its impact on casualty levels has been recognised from Roman times, notably Trench Foot in the Great War and Immersion Foot in the Second World War. While NFCI remains predominantly a military issue, during this century the growth of mountaineering, winter, water and extreme sports and urban rough sleeping has led to its greater visibility in civilian populations, with symptoms, signs, and treatment challenges as in the armed forces. Painful sensory neuropathy is a recognised feature of several metabolic conditions, most commonly diabetes mellitus, but also in several less common conditions, reviewed in (2). Based on observation of the clinical features, effective military NFCI preventative strategies were introduced following the Great War. While the climatic conditions in the 1982 Falklands conflict led to numerous cases in Royal Marines (3), in the second half of the 20th century NFCI was otherwise not a major disabling disorder amongst serving UK troops, nor in UK civilian practice. From the winter of 2005/6 onwards, more military cases began to appear, with consequences for operational capability, military healthcare and compensation, both civil and no-fault. Typically, NFCI was occurring in army recruits undertaking winter training in UK in the Brecon Beacons, North Yorkshire Moors and Northumbria. Despite refresher training and new instructions on prevention and management for soldiers and the chain of command, and a new Surgeon General Policy Letter on clinical care, cases continued to present during subsequent winters. Those affected were almost all foreign and Commonwealth troops, British born African-Caribbeans, or Caucasians born and raised in Africa.

11. For the 2015 report, IMEG had the opportunity of discussion of a 2014 clinical audit of 644 cases by the then recently retired head of the Cold Injury Clinic, at the Institute of Naval Medicine (INM). The average time interval between cold injury and being seen at the clinic was 7.8 months (SD 2.8), with a range of 2-15 months. The most frequent and troublesome presenting symptom was pain, usually continuous and typically exacerbated for more than two hours by rewarming after cold exposure. The proportion of patients experiencing pain decreased exponentially with time from the initial causative episode of cold exposure, but 23 (8%) still had pain 32 weeks after the injury and two patients reported pain 4 years after the initial cold exposure. In addition to pain, numbness was reported in 25% and cold sensitivity or allodynia (i.e., feeling pain on cold exposure), by 68%. Non-neurological signs, common in the Great and Second World War cases, such as change in skin colour, blistering and skin peeling, were uncommon. In the cases audited, diagnosis of NFCI depended on the given history and special investigations, including infrared thermography (IRT) and thermal threshold testing (TTT). However, while abnormal results may be consistent with the clinical diagnosis of NFCI, neither of these tests is now regarded as being diagnostic (1). In normal subjects there is a wide reference range of responses to a cold challenge. Abnormal results may be demonstrated in the absence of

symptoms, and in the case of thermography, even without a history of cold exposure. In the INM audit cases, 89 (14%) of the 644 cases did not have NFCI, but most commonly primary Raynaud's disorder (1).

12. In January 2012 the Surgeon General set up an independent expert Review Group chaired by Professor Hugh Montgomery, of University College London, to examine all aspects of NFCI (4). The report, completed in February 2013, drew attention to the lack of reliable scientific evidence in the international published literature on many aspects of NFCI, including its definition, pathogenesis, systematic description of its clinical features, its natural history, the role of specialist tests in diagnosis and assessment of severity, its prognosis, and best practice treatment. The report recommended studies on how NFCI should be investigated, diagnosed, and treated. It also recommended that to better understand the natural history of NFCI, a systematic prospective longitudinal study starting at the time of recruitment to the armed forces should be undertaken. IMEG strongly endorsed these proposals, going on to make recommendations on three new AFCS descriptors, based on existing evidence. These were accepted by Minister Defence People and Veterans and were introduced into scheme legislation in April 2016.

Medical downgrading and discharge due to NFCI

13. The 2015 IMEG report recorded that 518 personnel had been medically discharged due to NFCI as the principal or contributory cause between 6 April 2005 and 31 March 2014. For those with NFCI retained in service, there was a high likelihood of medical downgrading and employment restriction. Since 2015, one UK case series of 42 military patients referred with chronic pain after NFCI, reported that 36% had been medically discharged following pain assessment, with a further 24% being discharged because of persisting pain at longer intervals. Those still serving all required restricted exposure to cold environments and had reduced deployability, and so limited career prospects. Of the veterans in the group, all had restricted civilian employment options, with the need to avoid cold exposure, and 53% were unemployed (5).

Civil and AFCS awards

14. Of the 518 personnel medically discharged between 2005 and 2014, 330 had AFCS awards for NFCI while, of 707 civil claims made between May 2007 and 31 December 2014, 470 had been settled at the time of publication of the 2015 report, at a cost of £17.2 million damages and £11.3 million claimant legal costs. NFCI compensation claims, both civil and AFCS, continue. From 2016/17 to 2020/21 the cost of 626 settled civil claims, i.e., damages and associated legal costs, was £117.41 million, £72.57 million damages and £44.84 million legal costs (6). By settled claim, we mean where damages have been awarded to the claimant and both the damages and the associated legal costs have been settled. Please note legal costs are often settled later than damages, so the financial year of final settlement is not always the same year in which damages are paid and overall expenditure in different time periods should not be directly compared. Under AFCS over the same period, 2016/17 to 2020/21, 440 awards have been made, with the majority for lump sums only and about 10 including a Guaranteed Income Payment (GIP) (7). It is of

note that many claimants successfully claim both civil and AFCS awards. In that event, in line with the principle that people should not receive double compensation for the same injury, AFCS awards are discounted.

Prevention of NFCI

15. Early in the Great War, occurring commonly amongst infantry soldiers spending long periods in the trenches, a cold -related injury, distinct from frostbite, was recognised and labelled “Trench foot”. The main symptoms and signs in the feet described contemporaneously were “pain, hyperaesthesia often persisting for weeks, at first cold and practically anaesthetic, becoming very red and swollen” (8). Various causes were proposed, including fungal infection from trench mud and venous stagnation from standing guard in the trenches. Eventually, the consensus became that cold and wet conditions, immobility, and tight footwear led to circulatory compromise. During December 2014, 4,000 British peacetime casualties suffered such injuries (9). In response, preventative measures to address cold, wet, immobility and stagnation were introduced as a command responsibility. Pumps and trench boards reduced the need for soldiers to stand in wet mud and as far as possible, wet weather clothing, and long gum boots, dried before issue, were provided. Soldiers were encouraged to keep moving in the trenches and to rest and sleep with feet elevated. Foot washing centres gave regular opportunity, based on a rota, for groups of soldiers to wash their feet thoroughly with soap and hot water, dry them, apply foot powder, and change socks. Hot food and drinks were the final part of the strategy. As a result, the incidence of new cases dropped from 38 per 1,000 in 1915, 12.8 per 1,000 in 1916, and 11.3 per 1,000 in 1917, to 3.8 per 1,000 in 1918 (10).

16. NFCI cases continued to occur in the Second World War. However, the lessons of the Great War contributed to the reason the British incidence of NFCI in the 1943/44 Italian campaign was 1:45 (one of 45 deployed soldiers) compared with 1:4 amongst US troops experiencing the same conditions (9). During the Second World War, Immersion Foot was described in shipwreck survivors who had spent long periods on rafts with feet in cold water. Recognised as very similar to Trench foot, Immersion Foot was described by Surgeon Commander CC Ungley, RN, in a classification still sometimes used today, and comprising four phases. These included: exposure, pre-hyperaemic, hyperaemic, and post-hyperaemic (11). After exposure, presumed to be due to vasoconstriction, feet were cold, pale, numb, swollen and sometimes pulseless. This was followed by reperfusion, hyperaemia (redness due to increased blood circulation), swelling and severe pain, lasting up to several weeks, with reducing severity. In the post-hyperaemic phase, the feet were abnormally sensitive to cold, cooling excessively when exposed to cold, and remaining cold for up to several hours. Hyperhidrosis (excessive sweating) was also sometimes associated with this final phase. By contrast, NFCI occurred in about 14% of non-fatal British casualties in the Falklands conflict, where the cold, boggy peat moor battlefield conditions meant there was little opportunity to implement recommended preventive measures. More recently, small numbers of cold injuries, including NFCI, were reported during the Iraq and Afghanistan operational deployments.

17. While in operational deployments, exposure to conditions likely to cause NFCI may be inevitable; for cold weather training, the need for prevention is key. Current best practice prevention of NFCI involves maintaining a normal core body temperature and

protecting vulnerable parts of the body. These principles apply to all three service environments and depend on awareness and assessment of risk, adoption of appropriate control measures and training in the identification and initial medical management of those affected. All personnel need education and training on cold injury prevention, its recognition, and appropriate first aid measures. Based on current, standardised, and approved training material, this takes place during basic training, as mandated by service policy, and with additional refresher training ahead of relevant activities or environments. Commanders, training staff and Defence Medical Services personnel similarly undertake regular prevention update training.

18. Cold injury risk assessment is carried out for all Defence activities undertaken in cold environments and covers factors such as work type and duration, provision of adequate clothing, equipment and load, nutrition, hydration, and rest periods, still air temperature (i.e., ambient outdoor temperature and any wind chill), as well as individual and group risk factors such as age, experience, and ethnicity. Commanders should consider how risk might be reduced, perhaps by re-scheduling or modifying the activity. There needs to be effective preparation, briefing and supervision, development of a medical plan and a record of the risk assessment, and a decision on whether the activity should proceed. Risk assessment should be kept under review during the activity. Medical personnel should be actively involved in these considerations, providing advice/assistance to commanders, and clinical care, should cold injury occur during an activity. Any such injury must be reported and investigated, a responsibility of the chain of command.

Risk factors

19. NFCI currently seen in the UK military is generally milder than the injuries seen in the 20th century wars but, although relatively uncommon, the disorder remains a cause for concern. Confusingly, some of the few published studies have included freezing injury as well as NFCI. There are also important constraints in interpretation of the published literature, due to factors including heterogeneity in study size, design, and conditions. For example, some studies relate to a single acute cold exposure, while in others, participants were exposed to multiple cold environments without ill effect before developing persistent symptoms, and in most cases were then cold re-exposed (5). Some long-accepted risk factors, including ethnicity and cigarette smoking, are not described in all studies (12)(13). Currently recognised risks comprise a mixture of unmodifiable and situational features. The multiple factors include: previous cold injury, being young and inexperienced, ethnicity, reduced physical fitness, alcohol consumption in the preceding 48 hours, generalised hypothermia, stress/anxiety, previous cold injury, wet/damp environments, upright posture, inadequate or constrictive clothing, static tasks, sweating, wading, swimming, water and winter sports, hand-arm vibration syndrome, travel in open vehicles, air and sea craft (especially in exposed positions), lack of shelter/rest periods, and inadequate hydration or nutrition. Commanders should ensure that drills are carried out including the use and care of waterproof clothing, sleeping bags, headwear, layered clothing, boots, and socks, gloves, and mittens. Finally, using a “buddy-buddy” approach, personnel should be able to recognise early signs of generalised hypothermia and NFCI in both themselves and colleagues. In the field, regular foot inspections should take place and where a cold injury is identified, there should be early evacuation of the casualty to a

medical facility, and action taken to identify any other affected personnel in the group. If one person in the group is affected, it is highly likely that there will be others. All personnel should be familiar with the hypothermia and NFCI First Aid Treatment Guidelines, take immediate action to evacuate casualties to safety, and report the event (14).

Current clinical military management

20. Detailed guidance and clinical care pathways on generalised hypothermia and NFCI are provided for Defence medical personnel including: a) field care; b) primary care; c) Defence Primary Health Care (DPHC) NFCI or INM clinics; and d) specialist referral. These will ensure advice on pain management, management of disabling hyperhidrosis, managing re-exposure to cold conditions, the need for future protective measures, as well as advice concerning longer term employability, whether military or civilian. Guidance on recording and reporting all cases of climatic injury treated under their authority is provided for medical personnel. Complementary to chain of command records and reports, both medical and command reports are essential to mitigating risk (15).

Clinical presentation of NFCI in UK armed forces since the introduction of AFCS

21. The severe skin changes, blistering, gangrene, and the other clinical features described in trench foot, and immersion foot Stages 3 and 4 of the Ungley classification (11), are now very rare. The clinical pattern today, both in the acute phase and later, is milder and NFCI symptoms and signs often recover, making the accurate diagnosis, prevention, and management of NFCI more challenging. In the INM 2014 audit already outlined (1), the suspected NFCI diagnosis was concluded to be incorrect in 14% cases. These findings raise the question as to whether currently understood NFCI risk factors, preventive measures, and clinical management, still largely based on historic observation, together contribute to best practice today, particularly in the light of the paucity of recently published case series.

22. To assess diagnostic accuracy in a contemporaneous series of those with NFCI, and to identify possible early indicators of NFCI presenting now, a study of 100 suspected military NFCI cases, referred between August 2015 and July 2017 for diagnostic confirmation and advice on management, was carried out at a Defence Medical Services Regional NFCI clinic (16). In those referred, other causes of peripheral neuropathy were excluded. Most patients were Caucasian (67%) with 28% being African-Caribbean. Mean age was 27 (range 17-53) years, including trained and untrained personnel, and, on average, patients were assessed within four months of cold injury. Assessment comprised a full clinical history including of the cold injury itself, acute and ongoing symptoms, and medical examination, both vascular and sensory, of extremities. NFCI was confirmed if there was a history of cold exposure causing sensory symptoms lasting more than 30 minutes; and becoming painful, with continuing sensory symptoms and/or cold hypersensitivity on re-warming. Of the 100 cases reported, NFCI criteria were met in 76; the remaining 24 were diagnosed mainly with neuropraxia (nerve injury due to physical

trauma), Raynaud's phenomenon (pre-existing vascular sensitivity), and pre-existing cold sensitivity from previous cold injury. The proportion of African-Caribbean men was higher in those with a diagnosis of NFCI. Where symptoms were present for less than a week, Ungley Grade 1 (minimal) was diagnosed; when symptoms lasted more than a week, NFCI was graded Ungley Grade 2 (mild). There were no Grade 3 or 4 cases. NFCI was found to occur commonly during initial training affecting younger, lower ranks. Most had an unremarkable medical history with relatively few having previous NFCI (5%) or cold sensitivity (4%). Hobbies involving prolonged periods of cold, or vibration exposure were not seen and rates of current or previous smoking were no different in those with or without a diagnosis of NFCI. The context of cold injury was most frequently UK-based winter training. There was also a link to "feeling generally cold", and static duties. By contrast, the associations with wet clothing or boots, or with feet being immersed, were less marked than in earlier studies. There were no links to hydration or nutrition. Study limitations included relatively small size and power, and retrospective self-reporting of some risk factors, including after re-warming from the initial cold exposure. In some individuals, this pattern was repeated, leading to persisting (lasting a week to three months) or chronic NFCI (more than three months). Based on these observations a simple field assessment protocol for early identification, evacuation, and management of to-day's NFCI is being developed (17).

NFCI pathogenesis and treatment

23. When the IMEG 2015 report (1) was published the pathogenesis of NFCI remained unclear, with both neurological and vascular factors being proposed, but neither fully elucidated. By 2015 there was experimental animal evidence that cold exposure directly damaged nerve fibres, while impaired blood flow due to vasoconstriction led to ischaemic nerve damage, with neural and vascular elements then interacting to cause further ischaemic damage. Modern clinical experience is that in the majority of those with acute cold exposure leading to the diagnosis of NFCI, the symptoms and signs resolve completely over weeks or within a few months, while pain persists in a minority. Evidence from a meticulous clinico-pathological cross-sectional military study, including skin biopsy, now supports the pain as resulting from damage to small diameter sensory and/or autonomic nerve fibres (the latter controlling blood flow) supplying the skin and deeper tissues in the affected extremities, in other words a small fibre peripheral neuropathy (SFN) (5). The resulting neuropathic pain (NP) may be continuous and is frequently exacerbated by mechanical and thermal stimulation of the affected extremities. In addition, sensitivity to cold, due to abnormal vascular reactivity, is a common consequence of an acute episode of NFCI, and in many subjects this persists and can be demonstrated using thermography (though this is not now regarded as a diagnostic test, as outlined above). Symptoms arising from cold sensitivity develop when the affected extremities are exposed to cold; they are usually mild and resolve rapidly on re-warming. Abnormal thermography, a very sensitive measure of vascular reactivity, on the other hand may continue long after symptoms have resolved completely, shows a poor association with symptoms, and so cannot be regarded as a diagnostic investigation (1,4).

24. The 2017 study investigated the clinical features of NFCI in 47 UK soldiers and veterans referred with chronic pain following NFCI between February 2014 and November

2016 (5). Its aims were to explore whether chronic painful NFCI was accompanied by a peripheral neuropathy, to detail the sensory symptoms (numbness, paraesthesia, pain and altered temperature sensibility), grade the pain and determine whether it was neuropathic in type. Other causes of peripheral neuropathy were excluded. Participants were mostly male and African-Caribbean, mean age was 32 years, with a history of military cold, often cold and wet exposure or exposures, closely followed by sensory symptoms, which persisted for a minimum of three months. The median time from exposure to study enrolment was 3.58 (range 2.73-6.19) years.

25. Assessment included a detailed history of the injury, symptoms arising, and their development and evolution over time, as well as data from completion of published standardised questionnaires on the nature of the pain and its impact on employability and quality of life. The questionnaires included the Douleur Neuropathique questions (DN4), a validated screening tool for neuropathic pain (18), and the Brief Pain Inventory (BPI) (19), which assesses pain severity and interference with activities of daily living, including general activity, walking, work, relationships, and sleep. It was found that the most functionally disabling symptoms amongst soldiers in the study group were chronic pain and cold hypersensitivity.

26. Clinical examination included neurological testing of motor and sensory function, followed by quantified tests of light touch, pin prick, proprioception (joint position) and vibration (Quantitative Sensory Testing – QST). Further investigation included tests of standard nerve conduction, and punch skin biopsy for evaluation of intraepidermal nerve fibre density (IENFD). Nerve conduction was tested on sural (sensory) and peroneal (motor) nerves and was normal in all cases tested. IENFD was quantified from skin biopsy and compared with established normative data. Small nerve fibre pathology was demonstrated, with mean fibre nerve density in NFCI patients substantially reduced in over 85% of study participants compared to age and gender matched normative data. Twenty-seven of the 42 study participants underwent QST with a standardised protocol, to assess their individual somatosensory phenotype by detection and pain threshold of thermal and mechanical stimuli. Data were converted into scores normalized for age, sex, and test body site, indicating gain or loss of function. QST is a psychophysical investigation affected by, for example, examiner and patient training, baseline skin temperature, stimulus sites and recovery time between tests. While useful in population studies and for research, QST test result reproducibility is less suitable in routine clinical settings and for assessment of individuals, where it is best considered complementary to clinical assessment and objective investigation. In the study, QST showed that more severe neuropathy and pain were correlated, and that loss of function was associated with more recent cold injury.

27. This was the first study to systematically demonstrate that the persistent pain of NFCI is due to a sensory neuropathy and is neuropathic in type. Its findings represent progress in establishing firm diagnostic criteria for chronic NFCI. In addition, the study indicates validated methods for investigation of pain in NFCI, confirms the utility of early recognition and prevention of cold exposure, and supports the need for further research on targeted treatment for pain. However, as a relatively small cross-sectional study, some observations require further investigation. Seventy-six per cent of study participants were African -Caribbean and 95% were male. No published IENFD normative data are available specifically for this population, but age, gender and ethnically matched biopsy data were

obtained from healthy African Americans, analysed at Johns Hopkins University Hospital, and deemed to be reliable normative comparators. Similarly, the QST results need to be seen against the usual normative data set for this assessment which, although large, gender and age-matched, was Caucasian (5). IENFD showed a prominent small nerve fibre component but, as with over 40% of those suffering peripheral neuropathic pain (20), in patients with NFCI, QST confirmed additional large fibre involvement, in a pattern resembling diabetic neuropathy.

28. NFCI recovery over time from exposure was further investigated in a 2019 Norwegian study (21). Twenty-six naval cadets and officers, all exposed to acute cold injury on a winter open boat journey, were followed up for four years post-acute exposure, alongside 20 age-matched controls, unexposed and asymptomatic cadets from the Norwegian war academy. All were investigated once at the start of the study with assessment of large and small nerve fibre function using nerve conduction and assessment of thermal thresholds respectively. Physical fitness and subcutaneous fat layer thickness, a surrogate for nerve fibre insulation, was also assessed in the cold-exposed personnel. Subjects also recalled their symptoms immediately after exposure and during the next two weeks. At two months post expedition, exposed sailors were seen again. There was evidence of large and small fibre neuropathy, and 19 out of the 26 complained of numbness; 16 had cold hypersensitivity, particularly cold allodynia, which was inversely related to subcutaneous fat content. In the 4-year follow-up period, particularly during the first year, large and small fibre function became normal in most of those affected. In seven sailors who had developed cold hypersensitivity and cold allodynia, blocking of conduction of large diameter myelinated nerve fibres relieved these symptoms.

29. These results are concordant with the audited 2014 INM clinical experience and the Vale et al 2017 study (5) described above, showing a trend of NFCI improvement over time after cold injury. Unlike those in the Vale study, the Norwegian participants had chronic cold hypersensitivity/cold allodynia not proven to be due to sensory neuropathy. The authors of the Norwegian study suggested that these differences may reflect different severity of exposures and perhaps predisposing risk factors (21). The Norwegian subjects were Caucasian, with a different cold exposure experience from the Vale study participants, who had been exposed to repeated cold; the reported Norwegian boat trip was a single and symptomatically relatively mild incident.

30. In 1944, Ungley suggested that the sensory and vascular abnormalities of Trench and Immersion Foot were due to vascular and neural factors, referring to the causative pathology as ‘vasoneuropathies’ (8). This hypothesis has recently been assessed using contemporary clinical tests and skin biopsy. The 2017 Anand study looked at 30 cold-exposed soldiers with chronic sensory symptoms, including pain and cold hypersensitivity at four months following cold exposure (22). Assessment included QST, large fibre nerve conduction and intraepidermal skin biopsy, with examination using immune histochemistry to assess dermal and epidermal markers. These included vascular markers, von Willebrand Factor, endothelial nitric oxide synthase and vascular endothelial growth factor for assessment of small blood vessels. Objective clinical examination findings were consistent with peripheral neuropathy. Signs included abnormal pinprick in 20 patients (67%), abnormal thermal thresholds (in 67-83%), and impaired plantar nerve conduction (in 23%). On skin biopsy there were marked increases in all vascular markers and

increased numbers of sensory or regenerating subepidermal nerve fibres. This was the first published study of this type. Previous work suggested that this pattern, seen also in painful diabetic neuropathy, might be explained by ischaemia, an increase in blood vessels and abnormal nerve fibres, supporting the Ungley view that the underlying pathology of NFCI with persistent pain might include both neural and vascular factors amounting to a “painful vasoneuropathy”.

31. The 2018 Devigili research study aimed to develop standardised diagnostic criteria for small fibre neuropathy (SFN) in clinical practice and research, with accurate diagnosis, particularly important for clinical trials of treatment (23). The study was a review of 150 patients previously diagnosed with sensory small fibre neuropathy (SFN), followed by a prospective follow-up study of 352 patients with suspected SFN. Diagnosis of SFN in the participants was again by history, clinical examination, QST and IENFD. SFN was excluded in five (3%) of 150 re-appraised patients. At baseline, in the validation of suspected sensory neuropathy, SFN was diagnosed in 149 of 352 patients (42%) because of:

i) two signs on physical examination and abnormal QST and IENFD (69%)

ii) abnormal QST alone (5%)

iii) IENFD alone (20%)

32. Eight (5%) patients of the 149 had abnormal QST and IENFD but no physical signs, while 38 (25%) had sensory symptoms but no physical signs. Of the 38 with symptoms but no signs, 34 (89%) had normal QST and IENFD, while four (10% of the 38 patients) had abnormal QST and normal IENFD. None had abnormal IENFD alone. At 18-month follow-up, 19 (50%) of the 38 reported complete recovery of symptoms and had normal clinical signs, QST and IENFD. No individual having either abnormal QST or IENFD alone developed signs or showed abnormality in the other test, while all eight (21%) patients with abnormal QST and IENFD at baseline developed signs at follow-up. From these findings the authors concluded that the most reliable diagnosis of SFN was based on clinical signs, abnormal QST and/or IENFD. Abnormal QST or clinical symptoms in the absence of clinical signs were unreliable screening tools.

33. Reliable diagnosis of NFCI-related neuropathic pain in a clinical setting can be difficult, even in a specialist clinical environment. Access to skin biopsy, with assessment of IENFD, remains limited in the UK. The lack of a generally accepted definition and classification of SFN, from any cause, has meant that its epidemiology, incidence, and prevalence have not yet been fully documented. At present there are no universally agreed published guidelines specifically for the treatment of neuropathic pain related to SFN. Bodies such as the British Pain Society and European Federation of Neurological Societies (EFNS) have published guidance on interventions, with some treatments based on high quality evidence, but the reliability of the evidence is affected by the relative rarity of SFN and reported study outcomes being inconsistent and/or underpowered. More research on co-morbidities, quality of life, and standardized diagnosis is required for definitive guidance (24) (25). In October 2020, NICE published a neuropathic pain treatment guideline for non-specialist settings (26). The guidance is first to use amitriptyline, duloxetine, gabapentin or pregabalin (gabapentinoids). If these are ineffective

or not tolerated, the pain is localized, and the patient wants to try topical treatment, then 30% capsaicin cream might be appropriate. A trial of short-term tramadol might be considered. The gabapentinoids and tricyclic anti-depressants should be introduced singly and titrated for efficacy and side-effects. If single analgesic agents are ineffective, there is some evidence that combination of drug classes may be effective, but this carries the risks of polypharmacy, and of the clinical picture being obscured by medication side-effects. Pregabalin and gabapentin are Class C controlled drugs, and duloxetine is currently licensed only for diabetic neuropathy, so use for pain due to other causes is “off label”. Second line medications are available, including cannabis derivatives, lacosamide (see paragraph 26 below), venlafaxine and topiramate, but should not be used without specialist supervision. In many cases of neuropathic pain, including military NFCI, recommended management is to refer to multidisciplinary pain clinics, which will include psychological assessment and support as part of long-term rehabilitation.

34. A novel approach to the treatment of NP due to SFN is the use of lacosamide, a specific sodium channel blocking drug. This is cutting edge clinical neuroscience, but as a potential treatment of NP due to NFCI, should be mentioned here. In brief, gain of function mutations in voltage-gated ion channels Na 1.7 and Na 1.8 (encoded by the genes SFN9A and 10A), underlie dorsal root ganglion cell (small sensory neuron) hyperexcitability and pain in some patients with SFN (27). Lacosamide, already used as an anticonvulsant in the treatment of epilepsy, blocks these ion channels, with pain reduction noted in some patients with SFN. A recent small, placebo controlled, double blinded crossover therapeutic trial has been published (28). The trial assessed the effect of lacosamide in 24 patients with SFN and carrying multiple Na1.7 variants (28). There were 15 different mutations in the group with five patients sharing mutation variants. Mean pain decreased by at least 1 scale point in 58% of those receiving lacosamide, compared to 22% in the placebo group (odds ratio 5.65 (95% CI: 1.83–17.41); $p = 0.0045$) (28). In a moderator analysis, responders were found to be more likely to have specific Na 1.7 mutations in comparison to non-responders (29). This preliminary work needs replicating. However, in summary, lacosamide shows promise in the treatment of NP due to NFCI.

35. Where pain is localised, as in the extremities in NFCI, topical therapy, with 5% lidocaine plasters and capsaicin preparations, has been used for many years. But until recently, capsaicin treatment has been formulated in low concentration, due to the potential for symptom exacerbation. More recently, a high concentration patch, containing 8% capsaicin for single application of 30-60 minutes’ duration, under the supervision of a healthcare professional, has become available (30). Capsaicin is a selective exogenous agonist for the transient receptor potential vanilloid 1 (TRPV1) receptor, a cross-membrane receptor ion channel complex responding to both temperature and acidity. On activation, the cross-membrane receptor in small nerve fibres may open briefly and trigger depolarization by sodium and calcium ion influx. The nerve impulses generated then travel to the spinal cord and brain and are experienced as burning pain or itching. With capsaicin, a more prolonged initial activation effect is seen, followed by a prolonged subsequent desensitisation of the skin receptors stimulated. This results in analgesia. In essence, an initial stimulating effect, which may exacerbate the pain, is followed by prolonged pain relief. More work on the site and mechanism of action in the skin, and the molecular basis of action, is ongoing.

36. In a recent UK case series of this treatment, an 8% capsaicin patch treatment was applied to 16 military personnel with NFCI affecting the feet (31). Pain was assessed by self-report using a pain diary, and skin biopsy was carried out before, and three months after, treatment. A small but statistically significant decrease in pain, both spontaneous and cold-induced, was recorded at three months' follow-up. The reported pain reduction, both spontaneous and cold-induced, correlated with skin biopsy results at baseline and three-months' follow-up. These demonstrated increases of intra and sub-epidermal nerve fibre densities. Much more work is needed, especially for translation to practical safe use for NFCI in a military operational context, but these results show promise in directing NFCI-related personalised effective treatment of pain due to SFN.

Findings and Recommendations

37. NFCI today mainly affects UK land-based soldiers undergoing winter training. It can be very disabling, leading to medical downgrading, discharge, and difficulty with civilian employment, with high personal, operational and compensation costs. Since the 2015 IMEG report, and beginning ahead of the COVID-19 pandemic, numbers of cases presenting have declined, and the clinical pattern is milder and may be more difficult to diagnose clinically than the classic 20th century injury. Although predisposing factors are identified, some of which cannot be modified, for example, ethnicity, in peace-time service, NFCI is a largely preventable injury. Since the 2015 IMEG report the emphasis, led by the chain of command, has been on awareness raising, in theatre and winter training through feet checks and early detection of NFCI. This is accompanied by greater flexibility as required on training schedules and content. Where NFCI is detected, the affected individual should be quickly evacuated and, as others are likely to have similar problems, feet checks should be extended more widely. Lastly and importantly, the matter must be reported. For clinical management, accurate diagnosis is a priority. At present, diagnosis is largely reliant on the history and clinical examination. Availability of skin biopsy investigation in UK clinical practice, although not yet routine, is becoming more widely available, providing an objective assessment of intraepidermal nerve fibre density, which can now be regarded as a biomarker diagnostic test in this clinical context. Treatment of the most prominent disabling symptom, neuropathic pain, shown in the 2017 Vale paper to be due to small fibre neuropathy, is largely by the analgesic measures described here. These vary in efficacy, and side-effects may limit treatment. As touched on in our review, this is an important area of active research, not just for NFCI but for the pathologically similar neuropathic pain associated with diabetes and other causes of SFN. In compensation terms, about 2000 awards have been made since the introduction of the AFCS in 2005, with the great majority being at the level of lump sum only. At the time of this report, IMEG does not recommend any additional descriptors or revalorised awards.

Descriptors and Tariffs for NFCI

38. The current descriptors replaced the then descriptors on 31 May 2016 and apply to claims made from that date.

Item 5 Level 14

Non-freezing cold injury which has caused pain in the feet or hands or both, with functional limitation or restriction at 6 weeks and substantial recovery by 12 weeks. Continuing cold sensitivity may be present beyond 12 weeks.

Item 55 Level 13

Non-freezing cold injury which has caused neuropathic pain in the feet or hands or both, with significant functional limitation or restriction at 26 weeks and substantial recovery beyond that time. Continuing cold sensitivity may be present beyond 26 weeks.

Item 27 Level 9

Non-freezing cold injury in feet or hands or both, with small fibre neuropathy diagnosed clinically and by appropriate tests* with continuing neuropathic pain beyond 26 weeks, and severely compromised mobility and, or dexterity.

***Diagnosis should be by a non-treating consultant neurologist**

Diversity and Inclusivity

39. IMEG regards issues of equality and diversity as core values and aims to avoid unjustified discrimination on equality grounds, whether age, disability, gender, gender reassignment, marriage and civil partnership, pregnancy, maternity, race, religion or belief and sexual orientation. During this updated review numbers of claims and awards made for NFCI amongst non-Caucasian African-Caribbean soldiers fairly reflected their pre-disposition and representation in the military “at risk” groups e.g., undertaking required winter training.

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An audit of AFCS decisions for initial mental health disorder claims notified in 2019/20

Summary and Key Points

1. In the light of the interest and concerns expressed about AFCS awards for mental health disorders, IMEG undertook a statistical review and audit of such claims and contrasted these against those for other conditions.

2. Methods included a review of Defence AFCS statistics since scheme introduction in 2005, and an audit of a sample of 150 claims and service medical records for mental health disorders, which included two sub-samples to assess timings of the steps in the care pathway and medical discharges.

3. Results showed that 76% of all mental health claims were awarded, compared to 45% of all other claims; 22% of the former attracted guaranteed income payment (GIP) pensions, compared to 5% of all other awards.

4. Level 4 awards were uncommon.

5. Awards were most commonly made to young male soldiers from the Army, often following deployment, with post-traumatic stress disorder (PTSD) being the commonest diagnosis made.

6. Interim awards were frequently made, in the context of incomplete treatment programmes.

7. In the Armed Forces overall during this period, medical discharges occurred most commonly in those with musculoskeletal disorders, followed by mental health disorders and a mixture of both.

8. The results from examining the time intervals in the care pathway steps were limited by missing data, but suggested that delay in seeking help in general, and delays in accessing specialist care for veterans, are common.

9. We found no evidence that mental health claims were assessed inappropriately, or without parity of esteem.

10. Issues for further systematic study include the time interval between stressful incidents and seeking help, and the role of comorbid alcohol misuse, in determining response to treatment and prognosis.

11. We make more detailed recommendations at the end of this report and conclude that interim awards and the current table 3 tariffs should be retained.

Introduction

12. The promotion of good mental health and well-being is part of the national agenda. Prevention of mental health disorders, reducing stigma and encouraging early detection, access to multifaceted support, and, as required, best practice treatment are challenges for both the general population and the armed forces. Since its introduction, AFCS provisions for mental health disorders have attracted criticism in individual cases and of the scheme's legislative principles. IMEG has addressed the AFCS approach to mental health, providing clarification and making recommendations in four reports, all of which have been accepted. In the early years from 2005, AFCS claims and awards slowly built up, but with in-service claims and large numbers related to the Iraq and Afghanistan conflicts, steady state was reached quickly and an audit of decisions became appropriate.

13. The aim of this audit was: -

- to confirm that decision-making reflected scheme legislation and policy, and IMEG recommendations
- to detect any emerging trends in claims
- to examine level of awards made in the audited sample, and since scheme introduction, to compare them with awards for physical injuries and conditions
- to gain some insight into the steps and time intervals on the pathway into care, and on the nature, availability and accessibility of treatment interventions, their duration, and outcomes

14. Since the Great War, awards for disablement and death caused by service-attributable mental health disorders have been made under the UK no-fault military compensation schemes, with generally low numbers of claims and awards. By the late 20th century however, media and parliamentary interest in mental health, understanding of the impact of mental health problems on patients, family, friends and colleagues and their functional and economic effects, had much increased. In the UK, campaigns to raise awareness and reduce the stigma of mental illness and its treatment, encourage recognition and acknowledgement of symptoms, support from colleagues, friends and family, and early engagement with expert help, have been run regularly, aimed both at the general community and the armed forces.

15. In the armed forces context, the rate of claims has risen since the 1991 Gulf War (where the War Pension Scheme applies) and again since the introduction of AFCS in 2005. AFCS has a normal time limit of seven years, but also includes provision for late onset disorders and late presentations. Article 3 of the AFCS Order 2011 defines late onset illness for both delayed first clinical manifestation and delayed presentation or expert help seeking:

"A late onset illness is—

(a) a malignancy, or other physical disorder which is capable of being caused by an occupational exposure occurring 7 or more years before the onset of the illness or the date of death, as the case may be;

(b) a mental disorder which is capable of being caused by an incident occurring 7 or more years before the onset of the illness; or

(c) a mental disorder capable of being caused by an incident occurring less than 7 years before the date of onset of the illness, which disorder is capable of causing the person suffering from it to be unable to seek medical help for the disorder within 7 years of the date of onset of the illness."

16. To provide rigour and consistency, the legislation requires psychiatric disorders claimed to be diagnosed by a clinical psychologist or psychiatrist at consultant level and in line with International Classification of Diseases (ICD) or Diagnostic and Statistical Manual (DSM) criteria. The AFCS standard of proof is the balance of probabilities, and recognising the multifactorial nature of aetiology, awards are made when claimed disorders are predominantly due to service on or after 6 April 2005. At introduction of AFCS and since, UK armed forces have experienced high levels of combat and deployed service. Advances in evacuation from the front line, in anaesthetics and critical care medicine have led to higher survival rates in personnel with the most severe polytrauma. Against this background the development of psychological symptoms and discrete psychiatric disorders are a high risk. In many cases, symptoms manifest and present soon after the traumatic event and within AFCS normal time limits. In other cases, clinical onset or presentation is delayed and Article 3 is relevant.

17. As a selected population with pre-enlistment health screening, severe and enduring mental health diagnoses, such as schizophrenia, are rare in serving personnel (1). Common mental health diagnoses (CMD) such as depressive and anxiety disorders have broadly similar prevalence rates to the age and sex matched wider community (2). Post-traumatic stress disorder (PTSD) is not the most common diagnosis found in surveys of service personnel and veterans, although it is the commonest diagnosis in those awarded military no-fault compensation (3). Traditionally, alcohol has been used to encourage bonding and social cohesion in the armed forces and while, as in the wider community, hazardous and heavy drinking levels have declined in regulars in recent years, they remain higher in both male and female regular serving personnel than in reservists and the equivalent civilian population (4). Alcohol misuse often accompanies other mental health diagnoses in armed forces personnel. AFCS legislation precludes awards for substance misuse.

18. Traumatic physical injuries and physical disorders always have physical, psychological and social effects, and all AFCS awards include an element for psychological symptoms short of a discrete psychiatric diagnosis. AFCS is a tariff-based scheme and the legislation includes nine tables of injury and disorder categories likely to occur in armed forces personnel. Table 3 concerns mental health disorders. These are described generically rather than by specific diagnosis. AFCS assessment is based on the

associated functional limitation or restriction and its duration, measured from first presentation for medical help, with account taken of social, interpersonal, and occupational function. Each tariff table lists a series of descriptors and corresponding tariff award levels, reflecting functional compromise and duration, including in relation to capacity for suitable paid civilian work. There are 15 tariff levels and from April 2018, award values range from level 1, £650,000, to level 15, £1236. A lump sum is paid for pain and suffering and, where function is impaired and the disorder likely to compromise civilian employability, an additional tax-free income stream or reduced earnings allowance, called the Guaranteed Income Payment (GIP), is paid from service termination for life. There are four levels of GIP dependent on the degree of functional compromise, based on 25%, 50%, 75% and 100% of final military salary, reflecting also rank, service duration, age at service termination and adjusted for standard expectable promotion.

19. The aim is to pay full and final AFCS awards as quickly as possible after a claim. They are made full and final when the claimant has had an adequate course of best practice clinical management and a stable optimal medical and functional state has been reached, or prognosis established. The legislation includes a definition of "permanent" at Article 5 (7):

“Functional limitation or restriction is "permanent" where following appropriate clinical management of adequate duration-an injury has reached steady or stable state at maximum medical improvement; and no further improvement is expected.”

20. The scheme aims to address claims for any injury or disorder, and care is taken to maintain horizontal and vertical equity in awards. Vertical equity means that in any one category table, the most disabling disorders attract the highest award, while horizontal equity provides that injury and disorder from across the different category tables, paid at the same tariff level, should make similar allowance for impact on function.

21. Unlike War Pension claims, AFCS claims can be made while the person is still serving. The aim of early payment of awards and GIP (with no reduction/award recovery if the disorder resolves), is to encourage early engagement and commitment to best practice treatment and rehabilitation, and where appropriate, enable a return to a military role or, where that is not possible, a suitable civilian role. (Military health and fitness standards are generally higher than that required for civilian employment, a particular issue for those with mental health problem being safe access to weapons.) Early payment allows award recipients, many of whom are young, to continue their contribution to family and community, maintaining their confidence and self-esteem. Settlement of civil awards for mental health problems may be much delayed, often taking years after the claim has been made. AFCS claimants may also make civil claims but for civil damages to be paid, negligence or lapse of duty of care must be shown. In line with government policy that there should not be double compensation, where there are both AFCS awards and civil damages, the final award paid is adjusted.

22. Delayed AFCS final award notification may also occur in some complex or multiple disorder/injury claims. This may include mental health problems claimed soon after the index event or first manifestation of the claimed disorder, often before treatment has begun or is in in early stages. In this circumstance a fair and just final award is often not possible. To address this delay in payment, an interim award may be paid. Article 52 AFCS Order 2011 refers. Interim awards are effectively payments on account. They may be made where the prognosis for the claimed disorder is uncertain, and it is not possible to determine the appropriate descriptor. An interim award is made in the first instance for a maximum of two years. If prognosis remains uncertain at the end of that time, there can be further extension but a final award, with the right of appeal, must be made by four years from notification of the initial interim award. If the final award is higher than the initial award an additional sum is paid; while if there is improvement and a lower award is now determined, no amount of the initial award is recovered from the claimant.

23. Interim awards have been criticised by claimants, their supporters, clinicians and solicitors. IMEG has commented on the concept, the role in upholding scheme principles of fairness and consistent equitable awards, in several reports. About 5,000 interim awards have been made on all claim categories in the Scheme between 2005 and 31 March 2021. This compares with total awards for the same period of over 75,000 and equals 6% of the total. The numbers of interim payments in most tariff categories are small. The exceptions are musculoskeletal disorders, fractures and dislocations, and in particular, mental health disorders. The last group accounts for almost half the total interim awards from 2005 with by far the majority being for PTSD. From Scheme introduction to 31st March 2021, 2165 of 2415 (90%) PTSD awards were made interim, from an overall total of 4870 mental health awards.

24. War Pensions legislation provides that a request for a case review for deterioration may be made "on any ground and at any time". This dates from the interwar years and reflects the then limits of medical treatment where, in many cases of significant injury, the expectation and reality was of inexorable decline and worsening disablement over time. For many AFCS disorders and injuries, including polytrauma and complex disorders, treatment to optimal steady state or a clear prognosis, can today be established soon after the claim is made. Modern clinical management investigates, makes a diagnosis, assesses the patient's problem, going on to provide effective treatment and rehabilitation. The patient is likely, regardless of age, to reach optimal steady state in about two or three years. He or she is then largely able to self-manage with healthcare and other support available as required. That is the reality for most AFCS claims. Where the claimant disagrees with the notified final award, the AFCS legislation, AFCS Order 2011 includes provision for reconsideration and appeal to an independent Tribunal and, under certain circumstances, limited review of awards (Articles 53, 55, 56, 57, 58 and 59), including on the grounds of unexpected worsening.

25. In 2010 Lord Boyce reviewed the AFCS, concluding that it was generally fit for purpose. He recommended that the robustness of scheme policy and decisions would be enhanced by the appointment of an independent medical expert group, IMEG, made up of established clinicians and academics in relevant specialities, including mental health. Their role would be to provide expert independent evidence-based advice to ministers reflecting contemporary medical and scientific understanding of cause and course of disorders. Importantly, IMEG has no role to play in assessing individual cases. Since the Boyce

review, and its designation as a non-departmental public body (NDPB), IMEG has discussed mental health issues in four reports (link). These have included responses to questions and criticisms and resulted from literature scrutiny and discussion with appropriate experts and claimants. Topics to date have included: interim awards, the legislative requirement for discrete diagnoses to be based on ICD or DSM criteria and made by specialists at consultant level, the value of awards and parity of esteem for mental and physical disorders, maintenance of horizontal and vertical equity across disorders, and how to address and fairly compensate service-connected disorders where symptoms co-exist and overlap, such as mTBI and PTSD. In the 2017 report, IMEG acknowledged that a small minority of service personnel and veterans were so severely and permanently affected by mental health disorders, that an additional descriptor paid at level 4 with 100% GIP paid for life, was justified. The report emphasised that such awards would be rare. All IMEG recommendations have been accepted by ministers and introduced. IMEG also advised that where there are co-morbidities, such as anxiety disorder and depressive disorder, apportionment of disabling symptoms and functional effects on the basis of aetiology is very difficult, and so one tariff value and award is paid, encompassing all functionally disabling effects and their duration. Where co-morbid disorders clearly respond to treatment, at different rates, the award paid reflects the duration of the longer-lasting disorder.

26. AFCS is administered by lay staff. A key aim of successive governments has been to develop low-cost no-fault public compensation scheme delivery systems, maximising the value of awards paid. Defence Business Services (DBS) has a team of medical advisers with wide clinical background and trained in the compensation schemes and medico-legal determinations. Lay colleagues request their advice whenever they judge appropriate, and for some claim categories, including mental health, departmental policy is that DBS medical advice should always be obtained.

Medical discharge

27. Service personnel with medical conditions or fitness issues which affect their ability to perform their military duties will generally be referred to a medical board for an examination and review of medical grading. In clear-cut cases where the individual's fitness falls below the service employment and retention standards, the board will recommend a medical discharge, as laid down in the medical policy and/or the services retention standards for their career group. In many cases, the patient will first be downgraded, allowing treatment, recovery and rehabilitation. For personnel who do not make a total recovery, the board may recommend retention, permanently downgraded with limited duties, or medical discharge. Medical advice is forwarded to personnel administration units for decision and action. Where possible, and following discussion with the injured person, he /she will be retained in service either in their principal occupation or in some other suitable role.

28. Published medical discharge statistics are for regular armed forces personnel only. This is because the medical discharge process and medical record information for reservist personnel is not comparable to that of regular personnel with most reservists' primary medical care provided by the NHS. In recent years the groups significantly more likely to be medically discharge have included:

- Other Ranks (OR) in each of the three services
- females in the army and the RAF
- Royal Navy/Royal Marines aged 30-34 years; army personnel aged 20-24 years; RAF personnel aged 50 years and over
- Royal Marines compared to Royal Navy personnel
- untrained personnel in the army and Royal Marines

29. Historically, musculoskeletal disorders and traumatic physical injuries have been the most common cause of medical discharge across all three services with, more recently, mental disorders being the second commonest reason. Even before the Covid pandemic, the proportion of medical discharges for the army and RAF for mental disorders had been increasing, and for the RAF was higher than that of musculoskeletal disorders and injuries in 2019/20. Both for the UK general community and armed forces' populations and veterans, successive governments have prioritised raising mental health awareness, health and well-being, tackling stigma, and the provision of enhanced and, for veterans, culturally sensitive NHS mental health services. A subsequent increase in mental health problem presentations and compensation claims across the three services has been observed.

AFCS mental health disorder awards

30. AFCS Tariff Table 3 Mental disorder AFCS order 2021

Item Tariff Descriptor

A1 4 Permanent mental disorder causing very severe functional limitation or restriction(aa)

1 6 Permanent mental disorder, causing severe functional limitation or restriction (a)

2 8 Permanent mental disorder, causing moderate functional limitation or restriction (b)

3 10 Mental disorder, causing functional limitation or restriction, which has continued, or is expected to continue for 5 years.

4 12 Mental disorder, which has caused, or is expected to cause functional limitation or restriction at 2 years, from which the claimant has made, or is expected to make, a substantial recovery within 5 years.

5 13 Mental disorder, which has caused, or is expected to cause, functional limitation or restriction at 26 weeks, from which the claimant has made, or is expected to make, a substantial recovery within 2 years.

6 14 Mental disorder, which has caused or is expected to cause, functional limitation or restriction at 6 weeks, from which the claimant has made, or is expected to make, a substantial recovery within 26 weeks.

In assessing functional limitation or restriction in accordance with article 5(6) account is to be taken of the claimant's psychological, social and occupational function.

Mental disorders must be diagnosed by a clinical psychologist or psychiatrist at consultant grade.

(aa) Functional limitation or restriction is very severe where the claimant's residual functional impairment after undertaking adequate courses of best practice treatment, including specialist tertiary interventions, is judged by the senior treating consultant psychiatrist to remain incompatible with any paid employment until state pension age.

(a) Functional limitation or restriction is severe where the claimant is unable to undertake work appropriate to experience, qualifications, and skills at the time of onset of the illness and over time able to work only in less demanding jobs.

(b) Functional limitation or restriction is moderate where the claimant is unable to undertake work appropriate to experience, qualifications and skills at the time of onset of the illness but able to work regularly in a less demanding job.

Defence Statistics data

33. The acceptance rate for mental health disorder AFCS claims is high, and the most common diagnosis claimed is PTSD. Defence Statistics present AFCS claims and awards data by the financial year in which an initial claim was registered. If a claim has subsequent activity (a reconsideration, appeal and/or review) and an increase in tariff, the latest outcome is still presented by the financial year the initial claim was registered. The figures presented for the 2012/13, 2017/18, 2018/19, 2019/20 and the 2020/21 financial years (including totals) should be considered 'provisional', as over 1000 claims were pending at 31 March 2021. As mental health claims require consultant level verified ICD or DSM discrete diagnoses for consideration/award, most claimants claim a specific diagnosis. Defence Statistics present mental health data including, as a sub-group, PTSD where it is the claimed condition and can be obtained from the claim form.

34. From April 2005 until 31 March 2021 there were 5335 awards for mental health disorders notified including 4080 (77%) for PTSD. Total awards in the scheme for the period were over 75,000 of which about 70,000 were for non-mental health disorders. 22% (1175 of 5335 total) of mental health awards included a GIP - a figure that has been steadily rising since 2011. In comparison only 5% (4005 out of 75425) of other awards received a GIP. Of mental health awards in receipt of a GIP, 102 were at level 8, 98 at level 6 and less than 5 at level 4, attracting a GIP of 50%, 75% or 100%, paid for life.

Audit methods

35. The original intention was to sample claims from a study population representative of the contemporary armed forces. While digitisation of military compensation processes is under way, AFCS claims administration remains largely paper based, so, for full scrutiny, access to paper files stored remotely from the Scheme administration hub was required. The COVID 19 pandemic, working from home and distancing requirements made case file access difficult, and as a consequence, case examination was restricted to a sample of first claims (made at earliest in mid-2018), and decided and notified in 2019/20. A total of 150 files were sampled, with medical and lay colleagues asked to forward first mental health claim files crossing their desks. The sample size was chosen as feasible given the available time and resources. Despite obvious limitations, for example on wider applicability of findings, this sample size was considered likely to be sufficient to detect trends or issues worthy of possible future systematic review or study.

36. A standard case report form was used to record: sex, year of birth in five-year intervals, service, regular or reservist, rank at the time of claim, principal service occupation, whether there had been deployed service, whether the claim was made during service or as a veteran, the disorder claimed, the reported stressor incident/event(s), the

outcome of the claim, level of any award and whether it was interim or final. Examination of case service medical records provided information on the time course between the stressor event/experience, symptom onset and initial help-seeking (e.g., from peer, padre, website, or GP). Where relevant, similar information was obtained for cases treated post-service. Further information included: specialist referral, assessment and interventions, and time interval between the various steps along the care pathway into treatment. Other variables recorded included: whether referral was in- or post-service or both, the claimant's engagement with treatment, numbers and type of providers involved, whether these were sequential or simultaneous, and finally whether treatment was completed in the opinion of the senior treating clinician at the date of claim.

37. In AFCS, mental disorder award level depends on the severity of functional disability and its duration from the date the claimant first sought medical advice in respect of the disorder (Article 5 AFCS Order 2011). Since the path from stressor exposure to treatment is complex, it may adversely impact patient recovery and compensation received if prolonged. So, in this audit it was thought appropriate to gain some impression of time course between the various steps. This information was not always recorded or easily visible in case files and an indicative investigation was carried out with scrutiny of 25 in-service and 25 post-service claims from the original 150, again collected opportunistically. Militarily based clinical management and rehabilitation, including for mental health disorders, aims wherever possible to restore function with retention in service. In addition to the care pathway time course sample, 60 additional files from the total sample of 150, where a decision to discharge or actual medical discharge was recorded, were examined to establish the reasons for discharge.

Audit Results

Table 1: Sample basic characteristics (N 150)

Sex	Year of birth	Service N (%)	Regular	Rank	Claim in or post service N (%)	Principal service Occupation	Deployment
M 147, **F 3**	<1985: 7 85-90: 42 91-95: 58	Army 123 (80) RAF 17 (12) RN 10 (7)	Regular 145 Reserve <5	Pte/equiv 67 Junior NCO 56 Senior NCO 22	In service 65 (43)[1] Veteran 85 (57)	Infantry 59 Medic 22 Engineer 15 RA (gunner) 15	Yes 120 (multiple 68) No 27 Missing 3

	96-01: 43			Officer <5		RLC (logistics) 12 Other 27	

[1] 53 (35%) still serving at notification

38. Table 1 sets out basic sample characteristics. While tri-service, the resultant sample did not precisely reflect the demography of today's armed forces. It included males from all three services, different ages and ranks, but females and reservists were under-represented. The large majority were from the Army, reflecting the underlying numbers per service. The largest group were junior soldiers, and thus young, with an age range 19-34 years old, with less than ten years' service at claim or service termination. The officers and senior NCOs had longer service; on average, over twenty years. The majority of principal service occupations were infantry. Most claimants had been deployed, the majority combat related, and 68 claimants had had multiple deployments and conflicts over ten or more years.

Table 2: Claim and outcome details

Diagnoses N(%)	Self-reported initiating stressor N (%)	Outcome N (%)	Tariff award
PTSD 133 (89) **Other 17 (11)**	Combat 92 (61)[1] Work related 30 (20) Bullying/ harassment/ discrimination 11 Overwork 7 Disciplinary offence/service complaint 5 Refused posting/leave <5 Failed promotion <5 TRIM[2] not provided <5	Awarded 108 (74) Declined 38 (26)[3]	**Level 14:** Interim 0 Final 2 **Level 13:** Interim 61 Final 30 **Level 12:** Interim 3 Final 5 **Level 10:**

	Others 28 (19)		Interim 3 Final 4

[1]Afghanistan 66 (44%), Iraq 12 (8%), Multiple 14 (9%)

[2]TRIM Trauma Risk Management

[3] 4 claims transferred to war pensions scheme, 3 of which were awarded.

39. Table 2: By far the most commonly claimed condition was PTSD, and the reported causal stressors were similar whether claims were made in or after service, regardless of service, or principal service occupation. 92 stressors were combat related (61% total stressors). These included where the claimed disorder arose in the context of personal traumatic physical injury, injury to colleagues or the enemy, or related to events witnessed by the claimant. Of combat related stressors, 66 (44% total) were from Afghanistan, 12 (8% total) from Iraq service, and 14 (9% total) were from multiple combat theatres. Deployment related stressors were commonly multiple and claim forms identified these as causes of contemporaneous mildly disabling symptoms, typically disturbed sleep. Most commonly support and treatment were not sought or provided for such symptoms either in theatre or early on return to base. In most cases initial symptoms remitted or were coped with over time often using alcohol (see below). Some claims histories contained no reference to the contended deployment related problems in contemporaneous service medical records.

40. There were 30 (20%) home base work related stressors with 11 of the 30 for reported discrimination, racism, harassment, and bullying, and seven that were causally linked by the claimant to “overwork”, including covering for absent colleagues and unfilled posts. Five of the harassment and less than five of the “overwork” group described stressor events as repetitive or continuing for six months or more.

41. The final “others” stressor group of 28 (19% total) comprised road traffic accidents (RTA), adventure training accidents with, in eight cases, serious injury to the claimant and /or colleagues or the claimant witnessing a death. Other stressors included the death of a close relative or colleague, particularly if sudden or by suicide, or having a chronic painful disorder such as non-freezing cold injury (NFCI) or non-specific low back, neck or knee pain.

42. Consultant verified psychiatric diagnoses in the sample, other than PTSD, included adjustment disorder, depressive episode or disorder, anxiety disorder and obsessive compulsive disorder (OCD). For each of these diagnoses there were fewer than five cases. Overall psychiatric claims’ acceptance rate was 76% compared with an average AFCS acceptance of around 45 % for all claims since 2010.

43. Table 2 records awards paid at levels 14 (lowest), where substantial recovery occurred or was expected at 26 weeks, to 10 (highest) where expectation was of a continuing disorder for five years. Forty awards were final and 68 interim, with a review at

two years. Most awards in this sample were at level 13, two thirds being interim, for review at two years. These data refer to initial claims made when treatment was rarely completed to optimal state or a firm prognosis, making an interim award with review appropriate.

The care pathway

Table 3: Time course from stressor incident to treated optimal steady state (N = 50 of which 22 included adequate care pathway information)

A. Time from stressor to initial help-seeking

Duration	Number	Breakdown
Less than one year	**3**	**(3 in service, nil veterans)**
One to three years	**3**	**(3 in service, nil veterans)**
Three to five years	**12**	**(11 in service, 1 veteran)**
More than five years	**4**	**(all veterans)**
Missing data*	**28**	

B. Time from initial help-seeking to specialist assessment

Duration	Number	Breakdown
Less than six months	**16**	**(13 in service, 3 veterans)**
Six months or more but less than a year	**6**	**(2 in service, 4 veterans)**
One year or more than one year	**0**	

C. Time from specialist assessment to treatment

Duration	Number	Breakdown
Immediate	**14**	**(12 in service, 2 veterans)**
Less than six months	**2**	**(2 in service)**
Six months or more	**6**	**(6 veterans)**

D. Duration of specialist treatment at date of claim

Less than a year	**12**	**(8 in service, 4 veterans)**
Treatment complete / prognosis determined at date of claim	**0**	
Withdrawn from treatment	**0**	

A year or more than a year	**10**	**(4 in service, 6 veterans)**
Treatment complete / prognosis determined at date of claim	**7**	**(4 in service, 3 veterans)**
Withdrawn from treatment	**1**	**(veteran)**

*Data were missing on 28 of the 50 claims assessed for all variables. Because of the potential clinical and functional importance of interventions, care pathways and their duration, case narratives for the 22 with adequate time course information were examined in detail. Some of these qualitative findings provided further support on issues and topics for more detailed study.

44. Table 3: Fifteen claimants reported combat or training related stressors, with 8 having also sustained physical injury. Fewer than 5 of these 8 claimants required hospitalization and all were treated to physical fitness levels enabling retention in service. The remaining seven stressors contended were home base related, mainly described as “overwork”.

45. For the 22 claimants for whom we had data, the reported time interval between stressful incident and help-seeking was more than 5 years in four claimants. When personnel sought formal help, it was usually directly from medical sources, while a few case notes (three of the 22) recorded first approaches to peers, the padre or welfare staff. Initial contact with medical help was often shortlived, the patient assuming “he could handle it” and symptoms would usually resolve. In some cases, symptoms recurred, sometimes triggered by other unrelated stressors and either increased over time or presented episodically. While in service, even with the changing attitudes around mental health, there remained concern about confidentiality, stigma from chain of command,

peers and family and possible negative impact on career progression. Some personnel were concerned about time required for treatment appointments.

46. Time to specialist assessment from first help-seeking was less than six months for the majority and quicker for those in service. In service, there was early onward referral to specialist Defence Community Mental Health services, varying from a few days to at most two-three weeks. For veterans presenting to NHS specialist veterans' services, waiting times and clinical models varied with region and the devolved administrations. This observation relates to the date of audit. Roll-out of NHS Veterans services has been gradual across the country. The position has now improved with more complete nation-wide NHS Veterans' services (1). Time to veteran specialist assessment in the audit was typically several months with often a further delay of several months to treatment. While awaiting clinical care, veteran claimants continued with primary care support and medication. Some sought help from both service and non-service charities, while others used on-line support and treatment, often from multiple providers. This was mainly sequential but, in some cases, by simultaneous multiple approaches. While NHS and Defence Medical Service interventions reflected best practice, that was not always the case for private or charity based treatment. Dual therapy, addressing both the mental health diagnosis and co-existing substance misuse, was rare. There were no documented suicidal behaviours in the sub-sample of 22 or total 50 claimants, whether claims were in or post-service, but there was much missing data.

47. In most specialist services, DMS and NHS therapists were likely to be clinical psychologists, nurses, social workers with occasional input from consultant psychiatrists. Contact with multiple clinicians both in and post-service was the norm, in all patients in the sample, requiring them to repeat their history several times. Unfilled therapist posts were not uncommon. This occurred in service when a therapist had deployed or been posted or as was common, both in and post-service, had otherwise moved on, but without replacement. Clinic notes both in and post service and after transfer to a new clinician, recorded patients reporting their concerns about confidentiality, as well as reluctance in older more senior personnel to share sensitive personal issues and events with therapists of perceived "junior rank". In cases affected, the resultant prolonged treatment duration sometimes led to the conclusion by both treating and non-treating clinicians that the disorder was treatment resistant and so "permanent" and that this should be reflected in the AFCS award.

48. While in service, clinic attendance amongst the sample claimants was generally regular and none opted out of treatment. Inpatient admission was uncommon, particularly in service (one out of 15 serving personnel in the sample of 22) and brief. At date of claim 12 claimants had received less than a year's treatment. None of the 12 had completed an adequate course of best practice treatment to optimal clinical and functional state or reached a firm prognosis, according to the senior treating clinician.

49. Some claimants struggled on, often employing maladaptive coping mechanisms, such as increasingly heavy and binge drinking. Although rarely recorded as a co-morbid diagnosis for treatment or medical discharge in service medical records, there was frequent reference to alcohol misuse, hazardous drinking, or binge drinking in younger personnel, with these terms undefined. The armed services are running an opportunistic alcohol misuse screening programme, using the shortened version of the WHO AUDIT

tool, (4) but in this sample, not all claimants had documented AUDIT scores. In a sub-sample of 30 cases with recorded AUDIT scores covering the full age spectrum and where alcohol was referenced in consultation notes, 25 (80%) had started drinking either occasionally, weekly or two or three times a month, before service and most commonly in early teenage years. Of the 25, 18 had deployed service. There was no case where the documented evidence or claimant history supported drinking having started after deployment but in 10 of the 18 there was evidence of its escalation, in some cases for a short-term but in others persisting.

50. A new trend detected in the audit was that initial claims (15 out of total 150) were made with claimants providing specialist medico-legal reports, not necessarily from the treating clinician, or with help from solicitors (8 cases), who routinely commissioned reports from non-treating consultant clinical psychologists/psychiatrists. Most of the solicitor commissioned reports followed a face-to-face clinical interview but even before the pandemic, some were based on a single remote /telephone interview. The reports were often heavily reliant on claimant self-report and focused on service history. A comprehensive history and examination was not always present and while most reports routinely provided description of mental state, psychometric scores were rare. Comment was often unsupported by corroborated evidence. Brief binary responses without reasons to closed questions posed by the solicitor and based on the scheme descriptors, were common, “Does the claimant meet descriptor X on the AFCS Table 3 list?” and “Is the disorder ’permanent’? “. Consultants also commented frequently on the potential adverse impact on the claimant's condition of interim awards.

Medical Discharge audit results

51. A further sample of 60 files from the overall 150, where a decision or actual medical discharge was recorded, was examined to establish the reasons for discharge. Musculoskeletal disorders (MSK) or mental health disorders were the most common reasons for medical discharge. MSK disorders were the principal invaliding condition or a contributing condition in 26 cases, with mental health disorder in 12 cases and in 22 cases, jointly physical disorder /injury and mental health disorder. This was most often amongst those with deployed combat service and was in line with Defence Statistics 2019/2020 data where 42% of medical discharges were for multiple diagnoses. These findings were also consistent with independent research (3).

General Discussion of Results

52. The Defence Statistics’ data show that from AFCS introduction, 76% of mental health claims were awarded, compared to 45% of other claims, and 22% of mental health claims attracted GIP, which compares with 5% of all other claims. Claimants were young regular army males of junior rank, commonly infantry or combat medics, with less than ten years’ service. Most had deployed service to combat zones with multiple deployments to both the same and different theatres. PTSD was by far the commonest diagnosis given to claimants. Interim awards were common and associated with incomplete management programmes. Although there were many missing data, sub-sample results suggested most

delay occurred in the first decision to seek help, and, in this sample, veterans suffered delays receiving specialist help more than service personnel. Multiple agency involvement, with frequent therapist turn-over prevents good care and may affect outcomes. Alcohol misuse is commonly reported but seemingly not often addressed (4).

53. Limitations of this audit are its relatively small size and constraints on its sampling and the amount of missing data in the sub-sample. Other limitations to generalisation include the continuing uncertainties and impact of COVID on present and future service life, compensation administration, and variations in clinical practice; collectively these make most of the findings indicative, requiring replication. Scrutiny of case narratives provided greater detail and, together with the quantitative data, suggested topics for possible further study, outlined below.

54. The high frequency of the diagnosis of PTSD in claimants requires comment, since it contrasts with the much lower prevalence of this diagnosis in the military in general, when compared with the commoner mental diagnoses such as depressive illness and anxiety disorders, which were uncommon in this sample (5). It may be that PTSD is more chronic and disabling than mood disorders, and thus attracts compensation more often, but this seems unlikely (6). The finding in this audit of high rates of deployment and combat exposure may help to explain the high proportions with PTSD (7). However, the audit also found that PTSD was frequently diagnosed following stressful events that were not life-threatening, such as work-related stressors. While there is research evidence that PTSD may arise in such circumstances it may be that PTSD is a less stigmatised and therefore more acceptable diagnosis in service personnel and veterans than a mood disorder. This suggestion requires more research. There seems to be a strong and widely held belief that PTSD in military personnel is not best considered multifactorial with predisposing, precipitating and perpetuating factors but results solely from stressful events or exposures occasioned by service. This is not the case (8).

55. This audit also suggested that alcohol misuse is not uncommon and may be neglected in management. It seems likely that comorbid substance misuse affects prognosis in the UK military population (9) (10). If both confirmed and addressed, prognosis and outcomes might improve. Current research may throw more light on this relationship (https://www.kcl.ac.uk/kcmhr/research/kcmhr/alcohol).

56. Time course of steps in the care pathway was explored in the opportunistic sub-sample of 50 in and post-service claims (Table 3 refers), with information clearly recorded only in 22 (44%) claims. In this 2018/19 sample the most delayed step in the care pathway was the original decision to seek help. This occurred despite positive in-service action to tackle stigma, raise awareness, encourage early recognition and help-seeking for mental health problems in self and others (8). Time to specialist assessment was then up to a year at most and, in service, accessing treatment was then rapid. By contrast, a different and regionally varied pattern was seen with NHS services, where waiting times for treatment of six months or more were the norm. With further extension of the NHS veterans' services, across the UK, this finding needs replication in a representative sample. Both Defence Medical Services and the NHS provided treatment in line with best practice. Quality published studies on what constitutes an "adequate" course of trauma based cognitive behaviour therapy, or eye movement desensitisation reprocessing (EMDR), are few and reach different conclusions based on patient and trauma

characteristics (11). In the sub-sample, 12 out of 22 claimants had received less than a year's treatment by the time of claiming, none of whom had completed treatment or reached a final stable state. Of the 10 remaining claimants who had been treated for a year or more, 3 had not completed treatment or reached a final stable state. This suggests that interim awards were appropriate for most of this group.

57. Given the continuing mental health and well-being focus and expansion of clinical services in the UK and globally, the number of unfilled therapist posts, which require years of training, is likely to increase. In contrast to the evidence of this audit, where the majority of in-service cases were treated a few years ago, this situation is now impacting in-service military services so that frequently military personnel are managed, as in the NHS, in primary care. Culturally sensitive veterans' NHS Services continue to be rolled out but are not established in every area and use different care and pathway models.

Claims and decisions

58. As this was a sample restricted to initial claims, where, in the majority, treatment was yet to commence or was still in progress, 60% of awards were interim and 40% final. Interim awards do not carry appeal rights, so AFCS legislation requires awards to be finalised, with a right to appeal, four years after initial award notification. This is regardless of whether optimal treated state or established prognosis has been reached. In the sampled cases, the 2 final level 10 awards had not reached steady state four years after initial interim award notification. There were no final awards in the sample at level 8 or above, attracting 50% GIP or more.

59. We noted a varied quality of medical reports supporting AFCS claims. From information documented in the reports few of the experts had military or trauma experience, or familiarity with the scheme. A particular issue is that AFCS is no fault, so awards do not address restitution, but rather reparation. It is also important to bear in mind that the scheme is not restricted to mental health disorders. AFCS addresses any injury or disorder predominantly causally related to service after 6 April 2005 service and must reflect both vertical equity in that more severe disorders and injuries in any category will receive higher value awards. Similarly horizontal equity across the Tariff categories provides that accepted conditions with similar functional impact attract the same award level. IMEG consider that an advice leaflet for consultants providing reports setting out the background and criteria for the scheme would be helpful.

Decisions and awards

60. Parity of esteem between AFCS awards for physical and mental health disorders was raised in the early days of the AFCS and at a time when the same debate was being held about NHS clinical provisions. IMEG considered the issue in its 2017 report, confirming that scheme tariff award levels in the legislation were appropriate. The present review of AFCS awards notified from April 2005 until 31 March 2021 showed that 22% of mental health awards included a GIP - a figure that has been steadily rising since 2011. In comparison, only 5% of awards for other conditions received a GIP. Although we have not

examined how appropriate these levels of tariff were in individual cases, these data suggest that mental health awards are assessed at least as carefully as awards for physical injuries and illnesses. Of mental health awards in receipt of a GIP, most were either at level 6 or 8, with fewer than five at level 4. The level 4 award was introduced following IMEG recommendation in April 2018, with advice that eligibility was likely to be rare. This seems to be the case.

61. The evidence of this audit suggests that DBS decision-making was reasoned and reasonable, in line with case specific evidence, contemporary medical understanding, scheme legislation and policy, and IMEG recommendations. This included the level of awards, including level 4, and the use of interim awards. 76% of mental health claims were accepted. This contrasts with an overall AFCS 45% acceptance rate.

Conclusions and recommendations

1. The audit of Defence Statistics data from 2005-2021 revealed good evidence that AFCS mental health awards are considered appropriate, with higher proportions receiving awards and GIPs when compared to awards received for physical disorders.

2. Although interim awards are common for mental disorder awards, their justification is supported by the audit finding that claims were often made before best-practice clinical management had been completed, with neither optimal functional abilities nor prognosis yet established, and thus were appropriate.

3. Level 4 awards have been awarded, but uncommonly, reflecting the anticipated rarity of very severe disability in people with mental health disorders.

4. The preliminary findings on the care pathway, and the time interval between steps, suggest that delays in seeking help, and later treatment delays and their consequences, should be further investigated and mitigated, particularly in veterans.

5. The unfilled therapist posts, both in military and wider general community mental health settings, and the underlying factors mitigating against early resolution, suggest that treatment priorities, interventions and method of delivery might benefit from further review and research into possible alternatives, such as modification of interventions or their delivery.

6. More research is required to investigate the management of comorbid alcohol misuse in service, and engagement of personnel and veterans with other mental disorders.

7. Military service duration, particularly for junior personnel, is typically around only ten years. That may at least in part explain the rarity of chronic alcohol-related physical disorders or effects presenting in service. By contrast, recent veteran studies, including the recent fourth follow-up of nuclear test veterans (12) and a matched military control group, record higher mortality from chronic liver disease compared with the general population. It is recommended that alcohol education includes the risk of physical effects, which may only present after service termination, including obesity, hypertension, certain cancers, and liver disease.

8. An advice leaflet or other more available guidance for consultants, instructed by claimants or solicitors, providing reports setting out background to the scheme, would be helpful.

9. The audit confirms that the table 3 mental health disorders list of descriptors and award levels should be retained at present.

Diversity and Inclusivity

62. IMEG regards issues of equality and diversity as core values and aims to avoid unjustified discrimination on equality grounds whether age, disability, gender, gender reassignment, marriage and civil partnership, pregnancy, maternity, race, religion or belief and sexual orientation. During this updated review no diversity and equality issues emerged.

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Suicide and compensation

Summary and Key Points

1. There is understandable public concern regarding service personnel or veterans who tragically end their own lives.

2. The incidence of death by suicide in service personnel is lower than is seen in those of the general population of similar age and sex.

3. The incidence of death by suicide in veterans is similar to that seen in those of the general population of similar age and sex.

4. The one exception is a higher risk of suicide in young men with short army service and who have recently left the armed forces.

5. It is very difficult to prevent suicide or predict whether any individual will take their own life, but the strongest risks occur generally in men, those with adverse childhood experiences, those with a mental health disorder (particularly mood disorders and/or alcohol misuse) and in those who have previously harmed themselves. Suicide occurs in those without these risks, and this varies across cultures.

6. One of the most effective ways to prevent suicide is the removal of access to lethal means. Improved access to mental health and social care may also help, and the NHS Transition and Liaison Service, and devolved equivalents, may have a particularly important role to play in supporting veterans.

7. Compensation to families of those who have ended their lives is appropriate when there is a predominant attribution to service activities, on the balance of probabilities. Claims should be determined on an individual basis.

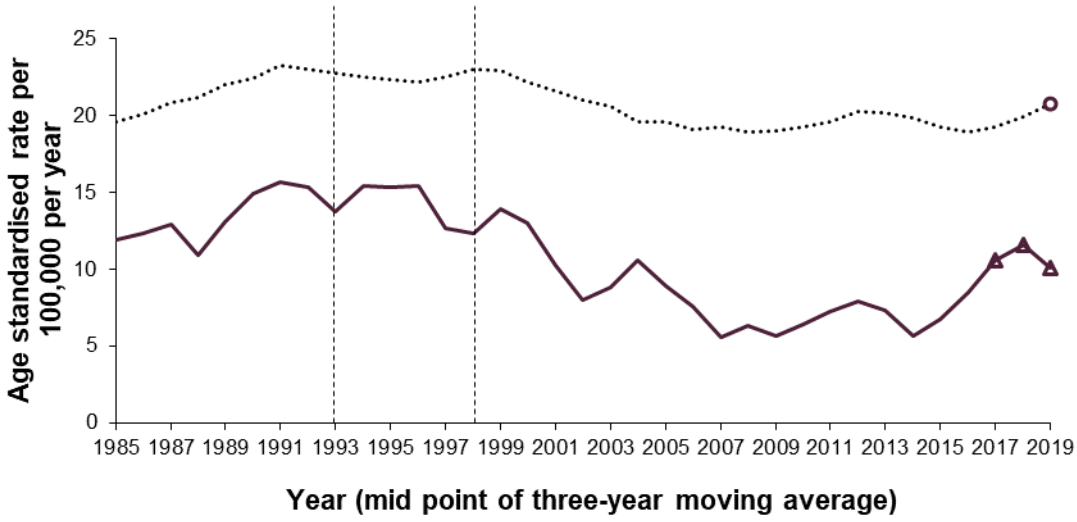
Introduction

8. AFCS pays survivor benefits to entitled partners and dependents for deaths in and after service due to suicide. AFCS awards are made where death can be accepted, on the balance of probabilities, as predominantly due to activities of military service on or after 6 April 2005. Sudden death, especially where a person has taken their own life is highly distressing to family, friends, colleagues, and carers. For AFCS survivor benefit determination, establishing case facts in sudden death cases may be prolonged, relying on coronial investigation and report, and often service inquiry. If a compensation claim is then rejected, reconsideration and appeal will cause further delay. The purpose of this note is to consider the epidemiology of suicide in the UK population and in the armed forces and veterans, contemporary understanding of the risk factors for suicide, prevention

interventions, research in UK military populations in progress and planned, and AFCS compensation aspects. A glossary is included at the end of the review.

9. Suicide, defined by the Office for National Statistics (ONS) as deaths given an underlying cause of intentional self-harm or an injury/poisoning of undetermined intent recorded as an open or narrative verdict, is a major public health issue in the UK general community and the armed forces and often the subject of misinformation (1). By convention, analysis of suicide is by deaths registered in a given year, not those occurring in a given year. Suicide rates in groups and at different time points are usually expressed per 100,000 where the number of deaths in the group is divided by persons at risk, multiplied by 100,000. For comparison with deaths in the UK general population, Standardised Mortality Ratios, (SMR) adjusted for age, gender and year are used. SMR is the ratio of the actual number of deaths observed in a study population to the expected number if the study and reference populations had the same age and gender specific rates, multiplied by 100 and applicable to specific years. An SMR of 100 in a study means its death rate is the same as that of the reference population. Confidence Intervals (CI), used to show the degree of uncertainty of the estimated SMR, represent the range in which the true mortality ratio value lies and are based on the margin of error, – for example, 1.96 times the standard error is used to calculate a 95% CI. The wider the range in the CI, the less precise the estimate. 95% confidence intervals are generally used, implying that the estimates derived for 19 out of 20 random samples would contain the true population value, while 1 would not. Derived for 19 out of 20, CIs for 19 out of 20 random samples would contain the true population value, while 1 would not. An SMR where the 95% CI encompasses 100, implies no statistically significant difference in rates when comparing a study population, such as the UK armed forces, with the general UK population. It is sometimes thought that death by suicide is more common in military personnel than the wider community. In fact, suicide in the serving military is a relatively low-frequency event, as can be seen in figure 1 (2).

FIG. 1 1984-2019 UK regular armed forces and UK general population male suicide, three year moving average, age standardised rate per 100,000



…… general population _____regular armed forces

1. The year shown is the mid-point of the three-year moving average, e.g., 1985 refers to the period 1984-6.

2. Rates have been age standardised to the 2020 armed forces population per 100,000 at risk.

3. If there are any awaiting verdicts in the three-year period, the data point is hollow. Note: rates may change as the inquest results are known.

4. Values are to two decimal places.

5. Legislative change in 1993 catalytic converters fitted to all vehicles.

6. Legislative change in 1998 to restrict over the counter (OTC) painkiller pack size.

Epidemiology of suicide – general

10. Globally, about 800,000 people are estimated to die by suicide annually, with many more making suicide attempts (SA) (3). Internationally, data from death certificates probably under-estimate the number of deaths, as suicide (and suicidal behaviours) are stigmatizing to all those affected, including bereaved family, friends, and carers. In some countries, to take one's own life is shameful, and, in others, it may still lead to a criminal conviction. Most reported investigation of risk factors for suicidal behaviour has been in high- income countries but a recent systematic review in medium and low-income countries suggests broadly similar risk factors (4). Suicidal ideation (SI) refers to repeated thoughts of suicide (contemplation, considering the act and/or the means), or ambivalence about dying. Self-harm (SH) is defined as an intentional act of injury or poisoning. Suicide attempt (SA) normally describes non-fatal injury or poisoning despite intent to die. Suicide

attempts (SA) are overall 30 times more common than death by suicide, and three times more common in females than males; SH is also more common in women (5). SI and SA are predictors of repeated SA, SH, and death by suicide. Studies suggest almost half of those who end their lives by suicide from the general population, and over half of young people who do so, have previously harmed themselves (6) (7). The means of self-harm are also predictive, with violent means, as opposed to poisoning, having higher risks of subsequent suicide.

11. People who self- harm do not always present to GPs, emergency departments or other health professionals, so studies based on hospital /emergency department admission may under-report SH and be misleading. Overall risk of SA and SH in the general population is low but greater in those with discrete psychiatric diagnoses (8). Risk of SA and SH is further raised if the psychiatric disorder has required hospital admission (9), or there has been prolonged adverse childhood (10). Socioeconomic factors, poverty and deprivation are also relevant. Risk of suicide in those who self-harm, particularly in the year after the SH episode, is increased and remains elevated through life. One study found risk of suicide raised by 30-100 times in the year after SH (11), and a Swedish study found it still raised 32 years later (12). All-cause mortality rates are also increased. A six-year follow-up of around 31,000 patients admitted to six hospitals in one English city with self-injury or poisoning, found an overall raised risk of death (SMR 36 CI 35-38). 21% died by suicide, 13% due to accidents, and in the majority of the rest from natural causes (13).

12. Since the late 1990s, in the UK there has been a concerted effort to tackle SH and suicide using a public health prevention perspective and a biopsychosocial approach, with collaborative working among mental health professionals, emergency departments, GPs, social services, counsellors, charities, as well as employers, local communities, friends, and families. Reports on suicide and self-harm in the general community and sub-groups (children and young people, older people with chronic physical or mental illness and those in contact with the judicial system) have been published by the UK health departments, NICE and the Royal College of Psychiatrists (5, 14, 15). Topics considered are the prediction of suicidal behaviour, risk factors for suicide and the relation between suicidal ideation, suicide attempts, self-harm and death by suicide, protective factors, interventions, and evidence of effectiveness.

Factors associated with increased risk of suicide

13. Suicide is a complex phenomenon, not due to a single or simple cause, but is always multifactorial with risk further increased in the presence of multiple factors. The relevance of a risk factor in a population depends on the size of the relative risk and its prevalence. Much investigation has centred on socio-economic factors, income, education, health services, occupation, and unemployment. These factors are highly prevalent at a population level, but individually have a low relative risk compared with psychiatric disorders where the opposite is the case, i.e., low population prevalence but high relative risk. Measures to address population risk factors inform public preventive policy, but by their very nature take time to make a material difference to deaths by suicide. They are less useful in predicting which individual will go beyond thinking about self-harm or death by suicide and take lethal action. Of those seen by a medical professional in the week

before their deaths by suicide, estimated at 25%, few are identified as at risk contemporaneously, but subsequent psychological autopsy frequently suggests the presence of psychiatric symptoms or disorder (16). Psychological autopsy is often heavily reliant on accounts by those close to the deceased person and provides a context where they are encouraged to think and recall mental health symptoms and illness. This may encourage effort after meaning, being necessarily post hoc. As a result, the idea that suicide risk is caused by psychiatric symptoms and disorder has been controversial with some experts taking the view that studies based on psychological autopsy are not reliable enough to confirm disabling psychological symptoms or discrete psychiatric disorder, so that conclusions based on such studies will over-estimate the risk (17). The likelihood is that psychiatric disorders increase the risk of suicide considerably (see below), as prospective studies suggest, but are not always sufficient by themselves to cause a person to commit suicide, and some people end their lives without having evidence of a psychiatric disorder.

14. More evidence that mental health disorders play a role in deaths by suicide has come from record linkage studies based on mental health service use (18)(19). Most of these studies have used service attendance as a proxy for a mental health problem or discrete disorder but different populations studied, study design, quality and size, presence of controls, and adjustment for confounders have led to highly heterogeneous results. A 2019 Australian systematic review and meta-analysis aimed to address some of these limitations by using pooled data from single studies selected to defined quality criteria (20). Following scrutiny of eight English language databases, twenty articles and thirteen age and sex adjusted cohort and case control adult general population studies, published between 2000 and 2018, were identified. The authors calculated a risk ratio for each study based on the number of reported suicides associated with presence and absence of mental health disorders, going on to determine risk ratio for the pooled data on mental disorder categories. The pooled risk ratio (95% CIs) for psychotic disorders was 13.2(8.6-20.3); for mood disorders 12.3 (8.9-17.1); personality disorders 8.1 (4.6-14.2); anxiety disorders 4.1 (2.4- 6.9); substance misuse disorders 4.4 (2.9-6.8). The overall risk ratio for any psychiatric disorder was 7.5 (6.6-8.6). All the studies were general adult population of all ages; when older adults were excluded the pooled overall risk ratio rose to 9. This review may have overestimated associated risks, by including studies of patients who had had severe enough ill health to have needed mental health services, including inpatient admission. A more recent review excluded such patients, while limiting the search to fewer psychiatric disorders. The fully adjusted relative risks (CIs) were lower, ranging from 4·1 (2·1, 8·1) for dysthymia to 7·6 (4·3, 13·6) for major depressive disorder (21). The RR (CI) for anxiety disorders was similar at 4·9 (2·8, 8·7), perhaps reflecting how uncommonly such patients receive specialist care.

15. Although reported absolute risk ratios for different mental health disorder categories vary, dependent on study size, design and quality, the relative order of risks is consistent among studies. There is now substantial evidence that risk of suicidal attempts and death by suicide is increased in people with discrete psychiatric diagnoses. The risk of suicide is raised in just about every psychiatric disorder (with the possible exception of simple phobias), the evidence being especially strong for depressive, bipolar and substance use disorders, and psychotic disorders such as schizophrenia. Co-morbidity is important; where there is more than one diagnosis, the risk is increased further (22). Those who die

by suicide do not all have a mental disorder and studies where participants have died by suicide are not always able to determine whether around the time of death the person was symptomatic.

16. Suicide is more common in those with chronic physical illness with most research focussed on long-term debilitating, painful, physical disorders as well as neurodegenerative disorders, haemodialysis, autoimmune disorders, ischaemic heart disease, diabetes, epilepsy, hypertension, or stroke (23). Social factors such as isolation and loneliness may mediate (24). As discussed in the mTBI (mild traumatic brain injury) paper in this Sixth IMEG report, it is now accepted that there is an association between mTBI and psychiatric disorder and between TBI of all severities and suicide. A 2018 retrospective cohort study used nation-wide registers with more than 7 million adults living in Denmark between 1980 and 2014, and more than 164-million-person years of follow-up. 7.6% had a medical contact for TBI including mild TBI, skull fracture without documented TBI and severe TBI. Data were adjusted for relevant co-variates including fracture other than of the skull, psychiatric diagnoses, and deliberate self-harm (25). The association between TBI of all severities and suicide showing a positive interaction between pre-TBI psychiatric history or self-harm and later suicide. Similarly post-TBI diagnosis of psychiatric disorder predicted a higher incidence of later suicide than TBI alone (incidence rate ratio (IRR), 4.90; 95% CI 4.55-5.29). That was also the case for those who had engaged in self-harm after experiencing their TBI (IRR, 7.54; CI, 6.91-8.22). Thus, a history of either self-harm or a psychiatric disorder, either before or after TBI, largely mediated the increased risk for later suicide.

17. Despite the multiple identified risk factors, suicidal attempts and suicide remain incompletely understood. Several models have been developed (26)(27). Most commonly it is proposed that individuals have a background vulnerability, such as mental health disorders, adverse childhood experience, family history of suicide, older age, male sex, lower income, being a member of the LGBT community, or with a history of previous suicide attempts (28)(29). In addition, much closer to the death, the person may experience a highly stressful trigger event. These may particularly involve feeling defeated or humiliated while also trapped in their situation. A large study of Finnish people who died by suicide found 80% had had a life event in the three months prior to death. These included: “job problems (28%), family discord (23%), somatic illness (22%), financial trouble (1 %), unemployment (16%), separation (14%), death and illness in family (13% and 12%).” Job problems and unemployment were more common in men and loneliness in women (30). A review of studies of psychological “autopsies” suggested that interpersonal conflict was the commonest event before suicide (31). A Danish population-based study of 7,115 people who died by suicide found that imprisonment (particularly), being a victim of violence and divorce were significantly more likely to have occurred in people who later died by suicide (32).

18. Protective factors and preventive interventions have also been proposed (33). Where self-harm or illness are present, there should be timely access to appropriate assessment, clinical management, and other support services, including for substance misuse. A meta-analysis found that psychosocial multi-level interventions were moderately effective in preventing both future suicide and suicide attempts in at-risk people, who had had a suicide attempt or reported suicidal ideas (34). Responsible media reporting including on digital websites and social media is also relevant. The present generally low

suicide rate in the general UK and armed forces populations, owes much to restricting access to lethal means, control of potentially toxic substances such as by limiting pack sizes of analgesics, detoxification of domestic gas, the introduction of catalytic converters, restriction of ligature points, notably in secure and hospital accommodation, and reduced access to suicide location sites such as by bridge barriers (35,36,37). There are reports of declines in suicide rates with reduced availability of alcohol (such as due to price rise) found in time series analyses, particularly seen in men, but these studies may suffer from known and unknown confounders, such as the effects of Perestroika in Eastern Europe and Russia (38). The World Health Organisation has recently published its guidance “Live Life” on suicide prevention, targeting four promising areas for prevention: limiting the means to suicide, working with media accounts, improving social and emotional skills of adolescents, and providing appropriate care to those who either self-harm or contemplate it (39).

Suicide and occupation

19. There is an extensive international literature on suicide and occupation (40)(41). Given the multifactorial nature of suicide, results are heterogeneous and vary by study date, changes in job nomenclature and associated defined tasks. Proportional Mortality Rates (PMRs) express the proportion of all deaths in the occupational group due to suicide, compared with the proportion in the wider general population. Care must be taken in interpretation, as a higher PMR in a particular occupation group may reflect a lower proportion of the total deaths due to some other cause e.g., lifestyle related disorder. Raised PMRs may be found in occupations with access to means such as poisons (dentists, doctors, veterinary surgeons, pharmacists) (42,43), while SMRs are increased in male-dominated, generally low skilled jobs with seasonal or periodic unemployment, job insecurity, isolated working, often poor working conditions and health and safety provision, poor terms of service and high accident rates (44). Occupations may attract people with particular personalities, previous experiences, education and training or lifestyles such as high alcohol consumption. Evidence on factors like bullying by peers or managers and increased death by suicide is limited and inconsistent, although there is some evidence that bullying may be linked to suicidal ideation (45).

Epidemiology of suicide – UK armed forces

20. Military principal service occupations do not precisely mirror civilian jobs and working patterns, promotion, and changes of role over a career, as well as overall average service durations are also quite different. In contrast to most civilian occupations, service enlistment involves medical screening and meeting defined physical and mental health standards and regular medical examinations take place throughout service. Service life, regardless of specific role, goes well beyond normal working hours. For many personnel it is not just a job but their family, a 24/7 lifestyle. Most people, including those in the armed forces who experience traumatic events, do not go on to develop mental health disorders (46,47). For some, stressful experiences lead to better appreciation of their good fortune in family, friends, material possessions and freedom (48).

21. Suicide data in the UK serving armed forces have been collected and analysed by Defence Statistics (Health) since 1984 (49). Between 2001 and 2020, 284 suicides occurred among UK regular armed forces personnel: 267 men and 17 women. UK military suicide analysis is based on male data and shows that rates in the UK regular armed forces have been declining since the 1990s and have been consistently lower than the UK general population rates over the last 35 years (see Figure 1 above). However, in the last five years the numbers of army male suicides have been increasing and from 1 January 2016 to 1 June 2021 suicide risk among army males was approaching that for the general population for the first time since the mid-1990s with SMR of 81 (CI 62-104). Higher suicide rates occurred in army personnel aged under 24, with 21 per 100,000 for those aged less than 20 years and 28 per 100,000 in age 20-24 years. A similar increase was also seen in males in those age groups in the UK general population (1). For all other ages suicide risk remained significantly lower than general population equivalent rates. Because of their heterogeneity and lack of discharge information, data on suicide are not collected for armed forces reservists. The Royal Navy (includes Royal Marines), Army and Royal Air Force all have different age structures from each other and the UK general adult population. For comparison amongst the services and with the general population, suicide rates per 100,000 were calculated from SMRs over the period 2001-2020. The tri-service SMR was 42 (CI 37-48) with RN 35 (CI 26-47), Army 53 (CI 46-61), RAF 24 (CI 27-33), giving age adjusted rates in tri-service of 8 per 100,000, Royal Navy 7 per 100,000, Army 9 per 100,000 and Royal Air Force, 5 per 100,000. To conclude, suicide rates for the armed services have been lower than the general population rates for many years.

22. Recent studies of SA and SH are rare in the UK armed forces (50,51). Data collection may be difficult based on self-report (with risk of recall bias and false responses) (52). Another factor is that until relatively recently SH was a disciplinary offence (53). A 2019 study provided a more contemporary account of UK military self-harm in serving personnel and veterans using self-reported survey data from the three phases of the Kings College Military Heath Research (KCMHR) cohort study (54), to measure SA and SH rates at three time points between 2004 and 2016. The study went on to consider the socio-demographic, and mental health related associations of SA and SH, in serving personnel and veterans who had consented to follow-up by telephone interview, having reported a mental health, emotional or stress problem in the previous three years. Participants were asked about their mental health, alcohol use, well-being, help-seeking, SA SI and SH episodes. For both serving personnel and veterans the prevalence of lifetime SH increased significantly at each of the three time points. In 2004 –2006 rates were 2% in serving personnel and 5% in veterans while in 2014-2016 the serving rate was 4% and 7% for veterans. Lifetime SA was reduced in commissioned officers and the RAF and associated mental health disorders were “probable“ anxiety disorder and PTSD. (The label “probable” is applied because diagnosis was not based on clinical interview /examination); rather mental health diagnoses were made using psychometric scales during the telephone interview and SH was recorded by self-report). Interestingly this study did not find an association between alcohol misuse and SA or SH in contrast to this often being reported with suicide (54). The study did confirm social support as an effective protective factor for either lifetime SA or SH.

23. Risk and protective factors for suicide relevant in the UK general community apply to military personnel and may be either reinforced or mitigated by military lifestyle and

factors. An example of risk reinforcement might be the loss of the close military support network at or around transition to civilian life. This can be especially difficult following long service or, for early service leavers, perhaps returning to a challenging environment which they left behind to join up, with hopes of more success and enhanced life trajectory. Factors like social cohesion within service units, strong effective leadership, availability of welfare and medical services, stable employment and salary potentially mitigate suicide risk during service. The increased risk of suicidal behaviours and suicide in the presence of psychiatric disorders apply to military populations. Military populations traditionally use alcohol for bonding and misuse is more prevalent in armed forces populations (10%) than the general community (3%) although misuse rates are reducing in both populations (55). Typically, military personnel start drinking pre-service with consumption often increasing as a coping mechanism for psychiatric symptoms and sleep problems post combat or other stressor experience. This reflects the belief amongst military personnel that they can deal with issues themselves and do not need expert help, often perceived as having a potential negative impact on career trajectories. Such thinking and pattern of behaviour is not unique to the armed force. Recent promotion of healthy drinking in the armed forces includes opportunistic screening, at dental appointments, development of an app and alcohol education (56,57).

24. As a selected young fit male population, suicide associated with prolonged debilitating physical disease is rare in serving military personnel. Following recent advances in anaesthesia, casualty evacuation from the front line and innovative clinical management of very severe polytrauma injuries, a much higher proportion of those experiencing severe disabling trauma of all types now survive. At the time of the index serious trauma those affected are generally young, highly motivated, fully engaged and committed to best practice clinical management and rehabilitation and return to their military career. Injured UK armed forces personnel are normally retained in service until treated to optimal clinical and functional state. In severe polytrauma, such as spinal cord injury or multiple amputations, reaching this point is through collaborative patient-centred treatment, both physical and mental, and early rehabilitation. This involves working with MOD medical and welfare services, NHS, social services, charities, colleagues, spiritual advisers, friends, family, employers, and local community, and may take four years or more. Typically, the great majority of the most disabled UK personnel are assessed as highly functional in activities of daily living (ADL) by service termination.

25. US evidence on severely injured Vietnam veterans, mainly above knee bilateral amputees, suggests that with ageing, complications such as poor prosthesis fit, or symptomatic atherosclerosis may develop (58). Mobility may be compromised, and the person’s motivation may decline with resultant despondency, often development of discrete psychiatric disorders and co-morbidities, loss of independence and feeling a burden. In that situation the risk of suicidal behaviours may increase, unless mitigated (59). However, in previous generations in the UK, and, to date, in those injured in Iraq and Afghanistan the evidence is that discrete mental health diagnoses and suicidal behaviours are uncommon amongst amputees in the early years post incident. The position in more recent service personnel and veterans with very severe polytrauma is being closely monitored via the ADVANCE study (60).

Suicide research in the armed forces

26. Defence Statistics track all in-service "possible" suicides and monitor all changes in trends. A new UK wide study, by Defence Statistics and the NHS, on the long- term consequences of service, including deployments, on deaths from all causes is presently being planned and will include all who have served from 2001 and those yet to serve in the future.

27. Recent analysis of risk factors derived from Service Inquiries and Learning Accounts following in service army suicide and open verdict deaths, identified welfare related issues as the most common triggers or superimposed crises, particularly financial stress, and relationship breakdown. This means that a successful prevention strategy must include wider welfare aspects as well as mental health and resilience and be based on client centred multifaceted collaborative social and medical support. Current interventions include HeadFIT (61), a mental fitness tool to support the armed forces community, the Combat Stress 24-hour mental health helpline for personnel and families (62) and Togetherall (63), a 24-hour staffed digital forum providing access to trained counsellors for armed forces personnel. The Samaritans deliver culturally aware workplace training for the armed forces and have produced a peer support pocket guide on talking to and supporting colleagues struggling with mental health problems (64). The single services each have a Mental Health Resilience and Fitness programme reflecting the different contexts, age groups etc, of the three services and sharing best practice as appropriate, such as with vulnerable service leavers at transition to the civilian community and beyond. The Defence Suicide registry has been set up to investigate the background and risk factors in real UK suicide cases in serving personnel (65). In turn this should help identify the most cogent data to be collected by a standardised protocol and inform suicide prevention policy development. Initial findings are expected in 2022/23. MOD also discusses and shares best practice on suicide prevention with our allies.

Veterans' studies that have been published, are in progress or planned

28. The Kings College Military Health Research (KCMHR) study of serving personnel and veterans, mentioned in paragraph 14, found higher rates of lifetime reports of self-harm in veterans compared to serving personnel (39). But what of suicide? In the UK there have been few published peer-reviewed studies on suicide in military veterans. In 2008 a Manchester University led study examined suicide risk in all those leaving the armed forces, in total 233,803, between 1996 and 2005 and with a mean follow-up period of 5 years (66). It linked national databases of service leavers with suicide deaths and compared the leaver cohort with both the serving and general populations. There were 224 suicide or undetermined deaths in leavers. The overall rate of suicide was not greater than that of the general population but the risk for men aged 24 and younger was 2-3 times higher than risk in those in the same age group who stayed in service or were from the general population. The risk was highest in army males of low rank and short service. The study also found rates of contact with specialist mental health services was lowest in the

highest risk age groups. For serving personnel much has changed since this 2008 study in terms of awareness, anti-stigma campaigns sponsored by the senior commands as well as through service education, support, and mental health care services. For veterans there are similar nation-wide general population anti-stigma campaigns, mental health, and substance misuse services, as well as new dedicated multifaceted veterans' mental health services. A further Manchester study, jointly commissioned by MOD and NHS E and I, is presently investigating the risk factors for suicide in veterans who served between 1996 and 2018. The study uses MOD military service information, National Confidential Inquiry data and coroners' reports to understand the factors which may lead a military veteran to take his /her life. Work started in September 2020 and is due for completion in late 2022.

29. In 2017 a retrospective cohort study of over 56,000 Scottish veterans, born between 1945 and 1985, and 172,000 matched non-veterans, compared the risk of suicide and fatal self-harm by sex, birth cohort, service length and year of recruitment (67). The maximum follow-up was from 1981 (or if later, date of leaving service) to 2012. The results suggested no overall difference in long-term risk of suicide between male veterans and non-veterans. There were 267 (0.48%) suicides in veterans compared with 918 (0.53%) in non-veterans (hazards ratio, HR 0.99, CI 0.86-1.13). The study has recently been updated to the end of 2017, now including 78,000 veterans and 253,000 non-veterans born between 1945 and 1995 again matched for sex, birth cohort, service length and year of recruitment (68). At 31 Dec 2017, 388 veterans (0.5%) and 1531 (0.6%) non-veterans had died from suicide, so confirming the earlier findings. Most deaths, as in the wider community, occurred in the fifth decade of life, using similar suicide methods as in the general population and around 20 years after leaving service. As a data linkage study, this design is a source of its strength in terms of study size and duration of follow-up and clinically determined causes of death. Limitations included lack of information before 1981 on disorders managed in primary care or as out-patients, on service branch, rank, deployed service, and importantly, adverse non-military related events.

30. Defence Statistics monitors deaths in Falklands and Gulf 1991 veterans (69,70). Both UK studies are presently undergoing ethical clearance and data update in preparation for the next five-year review. Regrettably the findings in both studies have frequently been misrepresented by the media. Beginning in 2002, the twentieth anniversary of the war, the media sound bite "more Falklands veterans have taken their own life than were killed in the war" has been often repeated (71). In fact, at the last review, covering the period 1982-2012, 95 suicides had been recorded in Falklands veterans compared with 237 deaths among UK armed personnel during the campaign. Twenty-five thousand, nine hundred and forty-eight personnel received the South Atlantic medal, having taken part in the Falklands War. For the period 1984-2012 there were 1,335 deaths in Falklands veterans compared with 2079 expected. Overall, all cause SMR for the period was 64; disease related deaths accounted for SMR 60 and for external causes of death, the SMR was 80. The SMR for suicide and open verdict deaths was 65. For Gulf 1990/91 a total of 53,409 personnel deployed. Mortality statistics over the period 1 April 1991 to 31 December 2015 were compared with an era group of 53,143 personnel, matched for age, sex and rank who served around the same dates but did not deploy to the Gulf. There were 1,858 deaths in Gulf veterans compared with 1,804 age adjusted deaths in the era cohort. Compared with the UK general population this gives SMR 59 (56-62) for Gulf veterans and 61 (59-64) for era veterans. There were 216 suicide or open verdict deaths in Gulf veterans and 204 in the era group, equivalent to SMRs of 73 (64-83)

and 70 (61-80) compared with the general population. These data reveal no negative effect on both all cause and suicide mortality of deployment to for the Falklands campaign and the 1991 Gulf War. This adds to the previous studies that showed no excess mortality by suicide in UK veterans.

31. These reassuring results contrast with studies from other countries. A follow up was undertaken of 1.3 million US veterans who had served between 2001 and 2007 during the Iraq and Afghanistan war eras, and left service by the end of 2007, with follow up until the end of 2009. The authors found higher rates of suicide in veterans, compared to the US general population (SMR (CI) for deployed 141 (126-156), non-deployed 161 (153-169)). There was no higher risk following either single or multiple deployments (72). The US Department of Veteran Affairs (DVA) has confirmed the higher rate of suicide in veterans, compared to the age and sex matched general population. The highest risk period for US veterans seems to be in the transition period of the first year following leaving the services. Shen and colleagues undertook a retrospective analysis of all US personnel (3.8 million) who had served sometime between 2001 and 2011. They found the highest risk was during the transition period of the first year after leaving service (HR 2·49, CI 2·12–2·91) (74). In the UK, the NHS England Transition Intervention and Liaison Service (TILS) and devolved equivalents may provide vital support during this challenging period (see paragraph 27 below). The reasons for the higher incidence of suicide in US veterans in comparison to UK veterans are unknown but may be partially related to easier access to lethal means (75).

Moral injury

32. The concept of moral injury is not new nor unique to armed forces settings. Moral injury is the psychological, social, and sometimes spiritual suffering caused by challenge to moral beliefs about the person's own conduct or another people's actions (76). An ethical dilemma, it affects first line responders, emergency services, and journalists, as well as armed forces personnel. Recent interest and research study was triggered by the 9/11 Twin Towers New York bombings. In addition to traumatic stressors, which may lead to depressive disorder and/ or PTSD, armed forces personnel in combat often face ethical and moral dilemmas. Effective rules of engagement, training, strong leadership, and the shared sense of purpose found in established units generally help personnel to manage these, but the experience of recent conflicts with no clearly demarcated battle lines and increasing use of artificial intelligence (AI), remotely piloted aircraft weapons systems with harm to civilians while the operator is not at risk, may transgress deeply held beliefs. As well as witnessing intense human suffering amongst civilians and colleagues, their own acts of commission or omission, the observed behaviour of others, including perceived poor leadership, may lead to guilt, anger, self-loathing, and shame, as well as significant psychological distress and maladaptive coping mechanisms. Such feelings may complicate PTSD, depressive disorder, and suicidal behaviour, and raises the question of whether moral injury should be considered a discrete psychiatric diagnosis. Published studies on moral injury, how and why it may develop, and its relation to co-existing mental health diagnoses remain limited (77). A 2015 systematic review found that 60-70% of US veterans with PTSD failed to respond to adequate courses of treatments of cognitive processing or prolonged exposure therapy, continuing to meet the criteria for PTSD (78).

One explanation was that this might be due to the presence or co-existence of moral injury, whereby repeated therapeutic exposure to the memory of a morally ambiguous event may cause harm (79). New treatments are proposed and being explored. In the UK compassion focussed therapy and trauma focussed cognitive behavioural therapy, in the US adaptive disclosure and acceptance and commitment therapy are being trialled. To be effective, interventions will unlikely be purely clinical but will need to address both psychological and ethical matters. PTSD diagnostic criteria have changed over time and in both recent DSM and ICD classifications, guilt, shame, and anger are included. This suggests there is no need for moral injury to be added as a separate psychiatric disorder (80). To do so risks medicalising a predictable human dilemma, depriving the individual of opportunity to come to terms with their action, and leaving the moral injury unresolved potentially creating another victim with limited hope of recovery. The view is that the person is affected not by any of their actions but because they have been put in a challenging situation from which there was no escape. As yet, it is too early to detect any impact on mental health, moral injury, or suicidal behaviours by the COVID-19 pandemic especially on front-line clinical staff. The sudden withdrawal from Afghanistan may pose a similar risk for those who served there and more widely, combat veterans in general (81). The preventive medicine model, a major element of Defence mental health strategy and primarily a matter for the single service chain of command, aims to build resilience and cohesion, minimise risk of ill-health in self and colleagues, early detect developing problems and as necessary, support access to early treatment.

Other current work to raise suicide awareness

33. An NHS England and NHS Information funded suicide prevention package is presently being piloted In the Sussex and Kent armed forces network and will soon be rolled out to all regions. Work from Suicide Bereavement UK on the types of information likely to be supportive to those who lose family, friends and colleagues through suicide is also in progress.

34. In March 2021 NHS England launched a new mental health service for veterans including those suffering a mental health crisis. The NHS and military charities will work together to provide therapy, rehabilitation services and, if necessary, inpatient care to former military personnel, regardless of when they served. Named Operation Courage this will combine under one umbrella the existing veterans' Transition Intervention and Liaison Service (TILS), the Complex Treatment Service (CTS) and High Intensity Service (HIS). TILS supports veterans with a wide range of disorders and symptoms as well as alcohol and drug misuse. It works with MOD to offer mental health support for those approaching service discharge. Its clinicians are culturally aware of armed forces life and support veterans without complex mental health needs to access mainstream services. The CTS, which is accessed via TILS, provides specialist community mental health services for veterans and their families transitioning out of the armed forces and beyond. The HIS provides care and treatment for veterans in crisis who need urgent help. It does this by working with local mental health services that are already treating the veteran, to improve their experience, health and ultimately their lives.

Coroner's reports: what are they and what do they provide?

35. Coroners (in Scotland, procurators-fiscal) are independent judicial officers appointed by local authorities. Although previously they could be either doctors or lawyers and many were or are dual qualified, today and for the future all appointees will be lawyers. Most deaths are not reported to the coroner; reports are made where deaths are unnatural, violent, where cause of death is unknown, or the deceased died in custody or state detention. When a death is reported a coroner's statutory duty is to investigate deaths that they have reason to suspect are violent, unnatural or of unknown cause. There will usually be a post-mortem and, if the cause of death is still unresolved, the coroner will open an inquest, a fact-finding inquiry to establish who the deceased was, and where, when, and how they came to die.

36. The most common inquest conclusions are death due to natural causes, accident or misadventure, industrial disease, dependence on drugs / non-dependent abuse of drugs, attempted /self-induced abortion, disaster, lawful killing (war/self-defence), unlawful killing, suicide, and an open verdict (where there is insufficient evidence for any other conclusion). From July 2018, in England and Wales, the standard of proof for suicide was changed from the criminal standard of "beyond reasonable doubt " to the civil “on the balance of probabilities”. That does not apply to deaths in Scotland or Northern Ireland.

37. For a finding of suicide, it must be established as fact that the deceased committed an act that resulted in death and that was the intended outcome. Suicide can never be presumed, and if the two criteria are not met an open verdict must be recorded. Until 2009, the coronial process was not required to explore why a person took his life but simply that they i) committed an act of self-harm and ii) intended by so doing not to call for help but to kill themselves. There may be witness evidence, but inevitably the viewpoint of such witnesses may be partial, and it is only in very few cases that intent is documented, such as in a note from the deceased person. The 1984 Coroners’ Rules gave coroners the discretion, where something giving rise to concern was revealed at the inquest, to provide a Rule 43 report. That position was revised by the 2009 Coroners and Justice Act which replaced Rule 43 reports with a duty for coroners to provide a report on anything coming to light in the investigation, not just at the inquest, suggesting reasons for suicide and/or actions to prevent further deaths (82).

COMPENSATION ASPECTS

38. Compensation claims are common from eligible partners and dependents where serving personnel or veterans have died by suicide and especially where there has been combat service. A common contention, often supported by clinicians involved in the case, is that where the service person was subsequently diagnosed with a mental health disorder, particularly PTSD, and it is accepted as due to service, the PTSD led to the death. PTSD is not the mental health diagnosis most likely to be associated with suicide

(which is depressive disorder), but the presence of another comorbid psychiatric disorder increases that risk. The relationship between service activity, such as combat deployment, and a consequent mental health diagnosis, with later suicide is an example of an indirect causation, with no inevitable and direct link between the service activity and suicide (see figure 2 below). In other words, for AFCS survivor award, to be likely, there must be a service attributable mental disorder, which is followed by suicide, itself predominantly attributable to the same disorder, where the disorder has been present and symptomatic, with adverse impact on function since service. As paragraphs 6-8 (above) explain, assuming that a psychiatric condition is a sufficient cause of someone dying by suicide is not straightforward.

39. Evidence to inform decisions on all survivor benefits, where the deceased was either serving or a veteran, include recruitment medicals with past medical and social history, family history and evidence of family circumstances and function, service medical records and the personnel file. If relevant, service inquiry or service complaint and coroner's reports (or equivalent in NI and Scotland) may be informative.

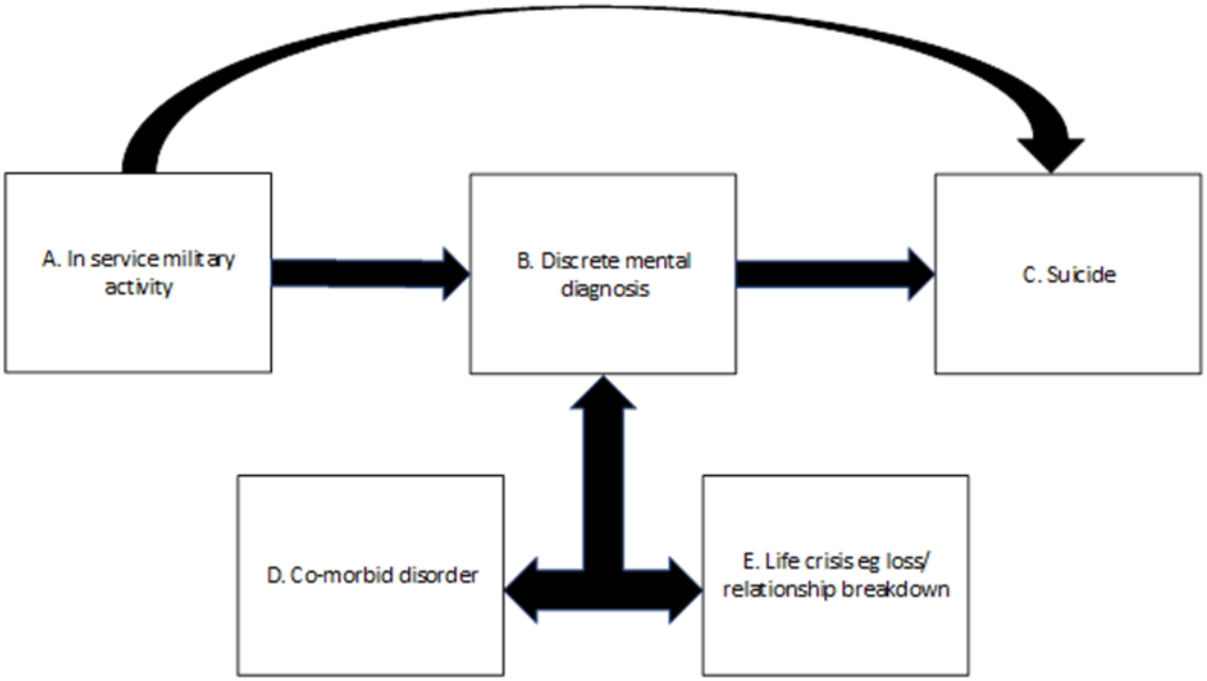
40. Defence Business Services (DBS) administrative and medical staff will use these sources to decide whether death by suicide, as determined by coroner or procurator fiscal, was predominantly due to service in the armed forces on or after 6 April 2005. Administrative officers will focus mainly on armed forces' factual issues, such as: service, service dates, rank, deployed and operational service, if so dates and role, physical injuries, disciplinary issues, service complaints or inquiries, involvement with the judicial system before or in service, evidence or perception of bullying or harassment, and discrimination issues. Medical advisers will assess pre-service risk factors, such as family and childhood adversities, mental health symptoms, specialist referral and diagnoses, family history including of SH and suicide, and bereavement through any sudden death (especially in a close relative). Other issues include previous suicidal ideation or self-harm; mental health disorder treatment, including whether in patient or outpatient, by whom delivered and their expertise, treatment duration and progress; alcohol and/or other substance use; any relation of onset or episodes of mental health problem to disciplinary and forensic issues; alleged discrimination on any count, missed promotion; or physical health problems. Was there a significant injury? What was the context, e.g., combat? And finally, personal issues: was the deceased sociable or a loner? What about family and relationships? Was there any domestic violence?

41. Where the claim concerns death of a veteran, evidence will cover similar issues but including post-service information on the above topics. Additional sources are NHS primary care and specialist notes, NHS or charity provided, covering inpatient treatment, crisis intervention, and attendance at veterans' mental health services. Other relevant topics concern: substance misuse and any treatment, gambling, employment since service discharge and reasons for leaving jobs, involvement with the police and judicial system, and debt.

42. An audit of a convenient (sequential) sample, not representative of UK armed forces, of 20 AFCS survivor compensation cases (deaths during or since 2005) provides the strong impression that the majority of those who died by suicide, mainly men after their service, had a discrete mental health diagnosis, most frequently PTSD and comorbid alcohol misuse, but also a superimposed life crisis often in the personal domain. Sound

decisions on attributability rest on careful scrutiny and evaluation of the overall case facts on an individual basis. For an AFCS award, death must be found by evidence to be predominantly due to service on or after 6 April 2005.

FIG 2 The possible relations between suicide and clinically diagnosed mental disorder



(1) A --------->C

(2) A--------->B--------→C

(3) A---------->B------→C
plus
D

(4) A-------->B-------> C
plus
E

KEY: A = in service military activity, B = discrete mental diagnosis, C = suicide, D = co-morbid disorder, E =life crisis, e.g., loss / relationship breakdown.

43. In case 1, For an award to be made there would need to be evidence of a clear causative relationship between service activities and suicide.

44. In case 2, if there were a clear causative relationship between service activities and a discrete diagnosed mental health disorder, which itself led to death by suicide; the claim would likely be accepted.

45. In cases 3 and 4, the claim would be accepted if the evidence showed a diagnosed mental health disorder was predominantly caused by service activities and, when symptomatic and adversely impacting function, was followed by death by suicide with factors D and E shown by the evidence to play a less important role than factors A leading to B in the death.

Diversity and inclusivity issues

46. IMEG regards issues of equality and diversity as core values and aims to avoid unjustified discrimination on equality grounds whether age, disability, gender, gender reassignment, marriage and civil partnership, pregnancy, maternity, race, religion or belief and sexual orientation. During this updated review no diversity and equality issues emerged.

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Glossary

1. **Standardised Mortality Ratio (SMR)** is the actual number of deaths observed in a study population to the expected number if the study and reference populations had the same age and gender specific rates. This is multiplied by 100 and applies to specific years. An SMR of 100 in the study and reference populations means death rates in both populations are the same.

2. **Confidence Intervals (CI**), show the degree of uncertainty of the estimated factor. For SMR, the CI represents the range in which the true mortality ratio value lies, based on the margin of error - 1.96 times the standard error. The wider the range, the less precise the estimate. 95% confidence intervals are used implying that the CIs for 19 out of 20 random samples would contain the true population value, while one would not. An SMR where the 95% CI encompasses 100 implies no statistically significant difference in rates between the reference and study population. E.g., such as the UK armed forces compared with the general UK population.

3. **Relative risk (RR)** is the disease rate among the study subjects divided

by the rate among the controls.

4. **Standardised Incidence Ratio (SIR):**

The incidence of a disease over a year in the group of interest divided by the number expected if that group had similar risk as the general population (multiplied by 100).

5. **P value**: this measures the strength of the evidence provided by the data. A p-value of 0.05 represents the point in the sliding scale of evidence where a result more extreme than that observed would be expected to occur by random chance only 1 in 20 times if there is no difference between the two groups. A p-value less than 0.05 can be considered to provide good evidence while a value between 0.05 and 0.1 can be considered to provide, but weaker, evidence. These values are not absolute cut off points but rather a sliding scale between 0 and 1.

For RRs greater than one the p-value measures the strength of the evidence that the rate among the participants is greater than that among the controls. For RR's less than 1 this is the strength of the evidence that the rate among the controls is greater than that among the participants. For SMR/SIR measures the p-value measures the strength of evidence that the measure differs from 100 in either direction.

6. **Proportional mortality ratio (PMR)** is a ratio of how more or less likely a death in a given occupation is to be from suicide as opposed to other causes, than a death of someone of the same age and gender in England and Wales as a whole. To calculate a PMR the proportion of deaths in the general population from suicide is needed. This proportion is applied to the number of deaths in the occupation group being considered to produce an expected number of deaths from suicide. The ratio of the actual number to the expected number is multiplied by 100 to give the PMR. A PMR of 100 means that there is no difference in the ratio of suicide deaths to all deaths in the given occupation compared with the general population.

Coronavirus (COVID-19) and the AFCS

Summary and key points

1. This report provides an overview of scientific and medical knowledge on the adverse health effects of coronavirus (COVID-19) infection at publication date, together with comment on the UK military experience of the pandemic to date.

2. COVID-19 infection can cause severe, sometimes fatal acute illnesses. What is less clear is the range of longer-term complications arising from acute infection, and the prognosis of persistent symptoms.

3. The sequelae of infection generally reflect the severity of the initial disease. Patients with less severe symptoms during acute infection usually recover completely and rapidly, although a proportion report persistent fatigue and shortness of breath, probably at a rate similar to survivors of other forms of community-acquired pneumonia.

4. Well-understood are the diffuse and sometimes disabling cognitive and physical symptoms, termed post-COVID syndrome or long COVID, which are not easily explained by organ damage.

5. The pandemic has brought uncertainty, anxiety, fear, and loss with, in some cases, development of mental health problems meeting the diagnostic criteria of discrete psychiatric diagnoses. Studies to date suggest that psychological effects are relatively short-lived in the majority of those affected.

6. As a young, selected group with few pre-existing co-morbidities, the UK armed forces personnel were not expected to be generally at high risk of disabling or prolonged illness from COVID-19, and to date that has been the case.

7. COVID-19 AFCS claims to date divide into: -

- asymptomatic, minimal, or mildly symptomatic polymerase chain reaction (PCR)-test positive cases - by far the most common claim
- acute COVID-19, with symptoms and/or signs for up to four weeks
- ongoing symptomatic COVID-19, with symptoms and/or signs for four to twelve weeks
- COVID-19 complications related to acute COVID-19
- post COVID-19 syndrome with symptoms and/or signs that develop during or after a COVID-19 infection, continue for more than twelve weeks and are not explained by an alternative diagnosis: usually, these are clusters of symptoms which can fluctuate and change over time and affect any system in the body
- deaths from COVID-19

Background

8. Understanding of the acute illnesses and longer-term problems caused by COVID-19 infection continues to emerge. This report provides an overview of scientific and medical knowledge at the time of its publication, together with comment on the UK military experience of the pandemic to date. It also considers compensation for COVID-19 under current AFCS legislation. We recognise that a comprehensive description of the clinical features is inevitably incomplete in this rapidly developing pandemic, but there is an urgent need to consider existing knowledge and clinical experience in relation to compensation under AFCS, with the clear understanding that this guidance will require updating over a short timescale. It is already obvious that COVID-19 infection can cause severe, sometimes fatal acute illnesses. What is less clear at present is the range of longer-term complications arising from acute infection, and the prognosis of persistent symptoms.

9. Clinical features of acute COVID-19 infection are manifold, reflecting differences in the virulence of distinct strains of the virus, in infective dose, in host immunity including that acquired through vaccination, in pre-existing comorbidities and in developments in, and the application of, effective therapies. In the early phase of the pandemic, 25% of patients admitted to hospital were treated on intensive care units (ICU), where their mortality rate was around a third (1), with about a sixth dying in hospital post -ICU understanding of community rates of infection, less virulent virus strains and enhanced population immunity, it has been evident that most infections incur fewer and relatively minor symptoms, seldom require hospital admission and rarely need intensive care and mechanical ventilation.

10. The clinical features of acute COVID-19 infection are now sufficiently well-described to include discrete diagnosable disorders, sometimes requiring treatment in critical care settings. These include Acute Respiratory Distress Syndrome (ARDS), venous thrombosis and pulmonary thromboembolism, cardiovascular disorders including stroke and myocardial infarction, and acute kidney, liver, and other organ injury, in some cases these lead to lasting organ damage. Recovery from these is generally slow and sometimes incomplete, and may be complicated by impairments in cognition, psychological health, and physical function – particularly muscle weakness - which are common to those who have undergone care in an intensive care unit (2). Lesser degrees of this so-called ‘post-intensive care syndrome’ will affect many patients who have had any prolonged hospital care, a period of ensuing convalescence being universal.

11. For the most part, it seems now that the sequelae of infection reflect the severity of the initial disease. Patients with less severe symptoms during acute infection generally recover completely and rapidly, although a proportion report persistent fatigue and shortness of breath, probably at a rate similar to survivors of other forms of community-acquired pneumonia (3).

12. Less well understood, at the time of writing, is the pattern and extent of diffuse and sometimes incapacitating cognitive and physical symptoms, which are not readily explained by organ damage. Together, they are termed ‘post-COVID syndrome’ or ‘long COVID’. Their incidence is poorly understood, although it seems not to reflect the clinical severity of the original infection, and most cases have arisen in those who did not originally

require hospital care. The pathogenesis of these symptoms and the reasons for their persistence are largely unknown, and while they generally improve over several months, in some individuals there is emerging evidence that longer term problems may develop, with potentially severe restriction or limitation of functional capacity (4, 5).

INFECTION RISK REDUCTION IN THE UK

13. The transmission of infection with COVID-19 is predominantly by aerosol spread; factors identified include contact with an infected person who may be asymptomatic but able to infect others. Early studies suggested higher risks of infection in children and young people, in certain occupations and in those living in large households or care homes. The risk of being seriously ill, hospitalized, or of death, depends on age and sex, with older people and males at any age being more at risk, and on co-morbid conditions, including obesity, diabetes, cardiovascular disease, and being immunosuppressed. Both infection rates and risk of mortality are reported to be increased in ethnic minorities (6). The precise reasons for this remain under study, but socioeconomic factors including large and multigenerational households, are established risk factors and taking them into account substantially reduces the reported effect of ethnicity associations in many studies (7). Occupation-related infection risks also remain under study. Relevant factors probably include proximity to others in the workplace, as observed in health and social care settings and in other jobs with direct, frequent, and close contact with fellow workers or the public, including taxi and bus driving, and shop and process work (especially with food). Additional risk factors include high density of people in the workplace; working in a confined, poorly ventilated space; lack of specific infection controls, and the absence of effective respiratory protection.

14. The risks of infection and illness from COVID-19 have not been constant over the duration of the UK epidemic, with periods of increasing and decreasing infection rates in different locations, related to emerging variants of the virus, including alpha in September 2020, delta in December 2020, gamma in February 2021 and omicron and sub-variants from autumn 2021, as well as the effectiveness of the introduction of risk reduction measures. These have included social distancing, face masks, and national and local lockdowns. Because public health is a devolved responsibility, precise policy and implementation dates were different in the four UK nations, varying in response to local infection and illness rates. The measures introduced included restriction of gatherings and movements of all but essential workers, closure of all hospitality venues, places of worship, theatres and cinemas, non-essential shops, and schools; and working from home was encouraged.

15. Early in the pandemic, testing for COVID-19 virus became available first for health and social care workers, and later in 2020 and beyond, more widely. Immunisation (vaccination), starting with health and social care workers, was extended to older and other vulnerable adults by the end of 2020, and to the general community during 2021. As with other RNA viruses, such as influenza, COVID-19 shows substantial genetic variability, so that the virus can mutate to new strains, of different infectivity and virulence. In some recovered patients, the antibody titre drops rapidly, and it is now established that patients may be re-infected within three months of a first infection (8). While the different COVID-19 vaccines offer significant protection against the more serious outcomes of COVID-19, and

to a degree against infection, they do not eliminate infectivity to others, and those vaccinated may be asymptomatic but still be spreaders of infection.

PERSISTENT SEQUELAE OF COVID-19 INFECTION

16. Most people, particularly the young, who have been infected with COVID-19 variants to date, experience mild short-term symptoms with good recovery. In describing longer-term sequelae, terminology and definitions vary. The National Institute for Health and Care Excellence (NICE) uses the following clinical definitions (9): -

- **ACUTE COVID-19:** symptoms and signs for up to four weeks.

- **Ongoing symptomatic COVID-19:** symptoms and signs for four to twelve weeks.

- **Post COVID syndrome:** symptoms and signs that develop during or after a COVID-19 infection, continue for more than twelve weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body.

- **'Long COVID'** is a term commonly used to describe symptoms and signs that continue or have onset after acute COVID-19. It covers both ongoing symptomatic COVID-19 and post-COVID-19 syndromes, but has been variably adopted in the medical and scientific literature. This is related to the established observation that "long covid" is clinically heterogeneous (see below).

17. In 2020/21 the International Classification of Diseases (ICD), ICD 10 and 11, (10) introduced emergency designated codes including for:

- COVID-19, virus identified
- COVID-19, virus not identified
- COVID-19 personal history
- multisystem inflammatory syndrome associated with COVID-19
- post COVID-19 condition

18. Recognising that the lack of standardised, globally agreed definitions impedes progress in research on epidemiology and potential treatments, a Delphi exercise to develop a consensus definition for post COVID-19 was convened by WHO in 2021 (11). This included 265 experts (patients, clinicians, researchers, and WHO staff) from around the world, and followed a two-round process, with 14 domains and 45 items. The exercise concluded that:

"Post COVID-19 condition occurs in individuals with a history of probable or confirmed COVID-19 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others* and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time."

*** including cough, chest pain, shortness of breath, headache, memory issues, muscle pain, altered smell /taste, sleep disorder.**

19. WHO noted that there was no minimum number of symptoms required for the diagnosis and that symptoms involving different organs systems and clusters have been described.

20. As with the NICE guidelines and ICD classification categories, this definition is likely to be revised and unified over time as further evidence emerges.

21. A recent review of 27 international studies listed the pooled prevalence of persisting symptoms in cases of post COVID-19 condition. Fatigue (47%) was the most common, followed by shortness of breath, (32%), muscle ache, (25%) joint pain (20%), headache, cough, chest pain and altered smell (each 14-15%) and then altered taste (7%) and diarrhoea (6%). A smaller percentage reported cognitive impairment (so-called "brain fog"), amnesia, sleep disorder, palpitations, and sore throat (12). Patient reports in early follow-up studies, of varied quality and size, suggest persisting adverse impact in many individuals on quality of life, mental health, and employment.

Mental health and well-being and the pandemic

22. The pandemic has brought uncertainty, anxiety, fear, and loss, with widespread international reports of adverse mental health and well-being, in some cases satisfying criteria of discrete psychiatric diagnoses. Studies addressing these aspects have been heterogeneous in size, design, and outcomes. Adverse psychological effects have occurred most frequently in younger people, women, those who had the infection, were isolated or lonely (predominantly older people), and in healthcare staff. A number of longitudinal studies on psychological distress have been published, including a report following more than 14,000 adults from the nationally representative UK Household Longitudinal Study (13). Participants were first surveyed in 2017-19, pre-pandemic, and then followed up in April, May, and June 2020, when psychological problems were assessed using the 12-item General Health Questionnaire (GHQ12). Before the pandemic, 24% had psychological distress; this increased to 38% in April 2020, was 35% in May 2020 and 32% in June 2020. Those most affected were young people aged 18-34 years, women and those in high income and education groups. Another study on over 5,000 UK and republic of Ireland frontline emergency, critical care and anaesthetic medical staff assessed distress, again using the GHQ12 questionnaire in the pandemic acceleration,

peak and deceleration phases (14). High scores were found in 45% in the acceleration phase, 37% at its peak and 32% at deceleration. Twenty-four % had trauma symptoms at the peak, dropping to 18% at deceleration. At the peak, 13% had probable PTSD, reducing to 10% at deceleration. More work is needed, but these results suggest that psychological effects do occur, and are relatively short-lived. The doctors' study is especially interesting because throughout they were all continuing their normal clinical work, albeit at likely greater intensity and for longer hours, and above all in an unknown context, with high patient mortality. Against such a background, good leadership, teamwork, peer and management support, effective communication and direction, good personal protective equipment (PPE), opportunity for adequate sleep and food and feeling appreciated, are key in maintaining morale, good health, and well-being. A positive aspect is that there has been no published evidence of an increase in deaths by suicide during the pandemic (15).

23. A not dissimilar environment of high stressors and uncertainty is found in aspects of military life, especially in combat service. The Defence response is to build resilience, provide good leadership, maintain morale, and promote good mental health and well-being. At the same time, it is also important to avoid over-medicalisation of normal life.

UK military covid arrangements

24. As a young (average age 32 years), selected group with few pre-existing co-morbidities, the UK armed forces were not expected to be generally at high risk of disabling or prolonged illness following infection with COVID-19 variants seen to date, and that has been the experience. However, communal living and sometimes restricted space, poorly ventilated workplaces, e.g., aircraft cockpits, operation rooms, and submarines which do not permit social distancing, increase the risk of virus exposure. At initial lockdown, in line with wider government policy, PPE and social distancing measures were put in place across Defence, and about 50% of military personnel, averaged across the three services, were able to work from home. Defence Primary Health Care (DPHC) moved to a blended consultation approach with mainly remote, telephone, video and e-consultations and a cloud-based instant messaging app for deployed primary care. As the pandemic continued, a series of COVID-19 rapid medical policy leaflets were produced (16). Regularly updated, they covered a range of circumstances including dental treatment for service leavers, vaccine administration for phase 1 trainees, testing of deployed personnel, and clinical and occupational assessment prior to return to duty and training post symptomatic COVID-19.

25. During the pandemic, groups of military personnel were diverted from non-essential military work to support the national general community response to COVID-19. In addition to Defence Secondary Health Care (DSHC) personnel who continued their clinical work in NHS Trusts, engineering and logistics specialists moved from their principal service occupations making a major contribution to the Nightingale hospitals, the setting up of ventilatory equipment, delivery of PPE and other hospital supplies, ambulance driving and to the test and trace and vaccination programmes.

26. Because of the many uncertainties about COVID-19, estimates of infectivity rates and casualties in the armed forces, especially for those with mild short duration illnesses,

are not reliable. Symptomatic cases have however occurred. Healthcare for injury or illness in the armed forces routinely goes beyond acute clinical management to optimise recovery and incorporate rehabilitation to levels of function and performance for return to a military role or, if that is not achievable, suitable civilian employment. Soon after UK lockdown, in late March 2020, Defence rehabilitation clinicians systematically reviewed the contemporary evidence on the health effects of coronaviruses (Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and COVID-19) and developed recommendations for an Armed Forces clinical management and rehabilitation programme. The resultant consensus statement covered general principles; for acute covid complications, specific recommendations on pulmonary, cardiac, exercise, psychological, neurological complications, particularly for those severely ill and requiring Intensive Care Unit admission and ventilation, as well as on musculoskeletal deficits and weakness (17). A remote assessment tool for use by video-teleconference to allocate patients to appropriate rehabilitation management in the community or the residential recovery service at Defence Medical Rehabilitation Centre (DMRC), Stanford Hall was also designed (18).

27. With a high proportion of young single men in the armed forces, the high infectivity of the virus and the natural history of the earlier SARS and MERS epidemics, it was judged that some personnel with acute infection might become too unwell to look after themselves in single living accommodation while not being ill enough to require hospitalization. In response, Defence Primary Health Care (DPHC) developed a national network of residential supported facilities. As in the wider community, most affected military personnel had a mild-to-moderate illness lasting about a week and responding to symptomatic and supportive treatment. Requirement for hospitalization, interval persistence or return of symptoms, and sometimes prolonged disabling illness occurred in a few (number currently unknown) military cases (19). Risk for such a clinical course in the military population was higher in those with more severe initial acute illness, and significant symptoms, physical limitation and abnormal lung function or imaging, lasting more than eight weeks.

28. A clinical pathway starting in primary care with onward referral as required to Defence and NHS specialists was developed by DMRC Stanford Hall. The approach, patient-centred and multidisciplinary, was informed by contemporary published understanding of the disorder and the experience of DHSC clinicians, rehabilitation specialists, occupational physicians, and NHS consultants in respiratory and cardiac medicine, neurology, and pain. Patients at presentation in primary care who met thresholds of symptom severity and objective evidence of cardiopulmonary dysfunction (ECG, resting and post exercise peripheral oxygen saturation), were referred from DPHC to DMRC where more detailed tests and questionnaires on fatigue, cognitive function, mental health, and quality of life were carried out. Results were then jointly reviewed by Defence secondary care and DMRC clinicians. Where appropriate, further joint DMS and NHS case conference and investigation followed at Oxford University Hospitals NHS Foundation Trust, with results informing expert advice on precise diagnoses, clinical and rehabilitation needs and ultimate likely employability (20). An observational study of clinical, occupational, and operational outcomes received ethical approval and is under way. The integrated service pathway and research study were developed and delivered in less than three months; as the first of its type, it has had significant influence on early NHS approaches.

DMRC Residential Rehabilitation Course

29. Up to October 2021, of 774 total referrals to DMRC, 444 have a full data set. Of these, 80 had required a hospital admission for COVID-19, 17 having had an ICU admission. Of 155 referrals to DMRC from primary care between May 2020 and April 2021, 78 were reviewed three months after admission to DMRC, when 91% had returned to work. Some patients, having been referred and awaiting admission, improved to no longer meeting the admission criteria, suggesting that not all patients actually needed DMRC referral. Both among those admitted to DMRC and the wider serving UK military community, there was little evidence clinically of disabling mental symptoms, discrete psychiatric disorders, or suicidal ideation /behaviours in relation to covid 19. These outcomes suggest that primary care level delivery of treatment of ongoing post-Covid symptoms, as seen to date in the military population, is likely to be appropriate for most military patients. This is now being developed.

30. Other findings from the DMRC pathway included: -

a. there were fewer than 10 referrals per month to DMRC from each Defence Primary Healthcare region
b. acute COVID-19 severity did not predict rehabilitation needs nor, excepting patients requiring ICU admission, the development of post COVID-19 condition
c. ICU admission was closely related to developing post -COVID condition
d. for the 6-minute walk test, 66% of the 78 patients showed improvement between DMRC admission and discharge
e. at three-month follow-up, 91% had returned to employment

31. As of 6 January 2022, 247 UK Armed Forces personnel have had Long COVID entered in their medical record at some time, representing 1.4% of personnel who had tested positive for COVID-19, and less than 1% of the UK Armed Forces population. Of the 247, 182 (74%) were male. 124 (50%) were medically downgraded with long COVID, 17 had medically limited deployability (14 temporary, 3 permanent), while of 108 who were medically not deployable, for 99, that was temporary and for 9, permanent.

UK armed forces compensation issues

32. Compensation arrangements for civilian work-related COVID-19 are being considered across the world, but few definitive schemes are yet established. Where schemes have been set up, eligible groups have been based on best available contemporaneous evidence, with health and social care workers the main beneficiaries at present. UK academic and government statistical surveys over time since March 2020, show that incidence and prevalence of infection, both test positive carrier state and symptomatic illness, have not been uniform across health and social care sector occupations nor consistently elevated, compared with the general community over the duration of the pandemic (21).

33. So that awards focus on those who are most disabled, many publicly funded occupational injury compensation schemes have a compensation threshold. For benefit to be paid for UK Industrial Injuries, the injury/disorder must have lasted a minimum of 90 days with at least a minimum level of functional compromise based on scheduled assessments in the legislation. In Table 4 AFCS Tariff, Physical Disorders and Infectious Diseases, the threshold is set out in the descriptor: "Physical disorder which has caused or is expected to cause, moderate functional limitation or restriction at six weeks, from which the claimant has made, or is expected to make, a substantial recovery at thirteen weeks." Where there is evidence of having been infected with COVID-19 due to service, but claimants are asymptomatic or the effects very mild and of short duration, the threshold is not met, and no award is payable. To date this is the most common category of claim.

34. The low standard of proof of the War Pension Scheme meant that war pension claims for endemic infectious diseases with clinical onset during service had to be accepted unless there was evidence positively dissociating a causal link to service. i.e., proof of a negative association. Case law also established that entitlement was appropriate even where service was only a potential, and not necessarily, the most likely, cause of the disorder. Awards were therefore payable for disorders such as rheumatic fever and pulmonary tuberculosis, each carrying high risks of complications. When such complications did arise, they were also accepted as consequential disorders, often attracting high compensation assessment, despite no evidence of increased occupational risk.

35. AFCS legislation set out a new approach, aimed at restricting awards for endemic exogenous infections but acknowledging exogenous infection acquired on deployed service. The legislation provides that “no award is payable when the infection is acquired in a temperate region unless as part of an outbreak, but awards can be paid if infection was acquired in a non-temperate region where the person was exposed to the infection in the course of service.”

AFCS Order 2011, Part 2, Article 12(1) (f) (iv) refers to infection due to or worsened by service or death. It provides that:

“benefit is not payable to, or in respect of, a person by reason of an injury (includes illness) sustained by a member, the worsening of an injury, or death which is caused wholly or predominantly by an exogenous infection except where the infection is acquired in a non-temperate region and the person has been exposed to the infection in the course of service or where, in a temperate region, there has been an outbreak of the infection in service accommodation or a work-place.”

36. “Outbreak” is defined in the legislation as follows: “an outbreak involving exogenous infection means the occurrence of cases of such infection in excess of what would normally be expected in a particular community, geographical area or season.” The phrase “would normally be expected” implies that this addresses exogenous infection endemic to the country. That cannot apply to COVID-19 in the UK. In medical terms,

COVID-19 is a new, highly infectious disease never previously seen, which presented acutely, quickly becoming widespread in the community, country and globally; but lacking an “expected occurrence of cases in a community, geographical area or season”. Although expert assessment is that in time COVID-19 is likely to become endemic in the UK, that is not the position presently.

37. The remainder of this note will be an overview of AFCS COVID-19 claims made to date, approximately 300 total, in light of the military clinical experience to date.

January 2022: claims update

38. As with many disorders, work-related COVID-19 is clinically indistinguishable from that arising in the general community, so to target benefit appropriately in this individual jurisdiction, awards are made when a causal link to service can be accepted, in line with the legislation. Claim determination is evidence based, on case-specific facts, contemporary medical understanding of causation and progress following an adequate course of best practice treatment. That can be particularly challenging where a potentially compensable disorder is: -

- a new, highly infectious disease, quickly becoming a pandemic
- a disorder which presented globally, in waves
- over time, from the first cases in the UK, successive claimants at different risk presented with illness due to virus variants of different infectivity and virulence
- associated with significant morbidity and high mortality; changing over time
- one for which there was and remains limited understanding, only emerging over time
- one for which preventive and protective interventions of varying effectiveness have been introduced in different UK locations at different dates

39. There are also other potential confounding factors for COVID-19 infection in UK military personnel. Several UK studies and surveys confirm the high risk of infection in the home especially where there are children, on public transport and at different phases of the pandemic and locations, as prevention measures of varying effectiveness were gradually introduced (19). Potential routes to virus acquisition in the military population include:

- travel to work including by public transport (note: injury or illness sustained during travel to work is generally excluded from occupational compensation schemes including AFCS)
- pockets of high incidence in military workplace, ship or service accommodation or training establishment (Such clusters of COVID-19 have been seen on board ship, at training establishments both in the UK and deployed locations).
- deployed overseas service
- military workplaces restricted in size, e.g., submarines, multi-engine aircraft with multiple crew, “bunker” style operations rooms with little opportunity for effective worker social distancing
- working in military clinical services involving face-to-face healthcare delivery
- DSHC clinicians working in NHS clinical services alongside NHS colleagues
- working in the general community in test and trace, immunisation etc activities involving face-to-face contact with infected asymptomatic and ill members of the public

40. Based on claims received to date, COVID claims under the AFCS divide into: -

- asymptomatic, minimal, or mildly symptomatic PCR-test positive cases
- acute COVID-19, with signs and/or symptoms for up to four weeks
- ongoing symptomatic COVID-19, with signs and/or symptoms for four to twelve weeks
- COVID-19 complications related to acute COVID-19
- post COVID-19 syndrome with signs and/or symptoms that develop during or after a COVID-19 infection, continue for more than twelve weeks and are not explained by an alternative diagnosis: this usually comprises clusters of symptoms often overlapping, which can fluctuate and change over time and affect any system in the body
- deaths from COVID-19

How to approach lawful decision making

41. Claims for asymptomatic COVID infection and minimal/mild short-lived symptoms with no adverse functional impact, and no recurrence within twelve weeks, do not meet the scheme compensation threshold and can be rejected. To determine causation in the other types of COVID claims, the case facts first have to be established and considered against the legislation. Information sources include the claim form, military service and medical records, and any other medical records. From these, confirmation of diagnosis, circumstance and dates of infection being acquired and symptom onset, the course of illness and its management, other cases in the vicinity, accommodation, training establishment or workplace, can be obtained, as well as details of immunisation, principal service occupation, deployment location, dates and duration, possible contacts, work place details including spaciousness, ventilation, numbers of colleagues, direct contact, working hours, availability of social distancing, personal hygiene, protection measures (including details of type and dates of and any supply problems with PPE), and test and trace or immunisation activities. There would also be enquiry about travel to work, details of, and numbers and generations in households, and medical employability grading before, at the date of infection and the date of claim.

42. If the evidence supports causation as predominantly service related, the next step is to decide the appropriate descriptor and award level. From Table 4 AFCS Order 2011. This will depend on severity, duration, and establishment of firm prognosis treatment outcome. Where an optimal steady state is established, the award is made final and notified, with reconsideration and appeal rights**.**

Conclusion and recommendations:

43. Quite apart from the changing clinical pattern of COVID-19 over the last two years, many of the early COVID studies were made available online without peer-review and with significant heterogeneity in study design, size, method of diagnosis of COVID-19, presence and suitability of controls, and virus variant. So, already at this date, early received wisdom on issues such as occupational risk factors, including varying risk at different times and locations since early 2020, were being revised. Occurring in a young, selected population, the military experience has been mainly of a mild-to-moderate illness,

responding well to supportive treatment and early rehabilitation, with developments such as prolonged disabling post covid syndrome being very rare (see para. 22 above). This is reflected in COVID AFCS claims. To date, AFCS has not identified any claim for a variant or complication of COVID-19 where the evidence supports AFCS service as the lawful predominant cause, the compensation threshold is met, and for which an award cannot be made under the present legislation. We have made reference above (para 7) to the changing clinical pattern of covid over time, in different occupations, parts of the UK and overseas, and similarly of different isolation, personal protection and immunisation practice. Against this background we recommend that claims determination should be based on case specific evidence of relevant factors. Where history is self-reported by claimants, corroboration should be sought, as far as practical.

44. To date, the most common COVID claim is for asymptomatic COVID positive lateral flow test cases with no functional compromise, pain, or suffering. Even if a predominant causal link to service can be accepted, no award is payable.

Recommendation:

IMEG recommends that MOD and Defence Business Services maintain overview of further developing understanding of COVID-19. Should a different definitive view of the disorder emerge, earlier decisions reflecting understanding at the date made, may be reviewed and revised.

Diversity and inclusivity

45. IMEG regards issues of equality and diversity as core values and aims to avoid unjustified discrimination on equality grounds whether age, disability, gender, gender reassignment, marriage and civil partnership, pregnancy, maternity, race, religion or belief and sexual orientation. During this updated review no diversity and equality issues emerged.

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The Fourth Nuclear Test Veteran Follow-up Study

Summary And Key Points

1. Between 1952 and final site clean-up in 1967, the UK conducted a series of atmospheric nuclear weapon tests and a weapons experimental programme in Australia and islands in the Pacific.

2. By the early 1980s, concern was growing about adverse health effects amongst participants, and in 1983 the MOD commissioned a longitudinal follow-up study into their health.

3. Approximately 20,000 military personnel who took part in the tests and a control group of similar size, age, rank and date of service entry, with service in tropical and sub-tropical areas around the same time but who were not present at the tests, was identified from MOD archives.

4. The subsequent data linkage study compared overall mortality, non-cancer and cancer mortality and incidence, regardless of the precise cause, in participants and controls.

5. Given the context, the study also considered whether the available recorded radiation exposures of test participants might be a possible source of any observed effects.

6. In the early tests, most participants were monitored, when the majority of the film badges recorded zero ionising radiation dose, and Defence policy was then changed to focus monitoring on personnel most at risk of radiation exposure. Twenty-three percent of the test veterans had film badges, with 64% of these showing zero dose, and 8% of the total cohort of participants a non-zero dose, average 9.9 mSv.

7. The first analysis gave follow-up to the end of 1988, the second to the end of 1993 and the third to the end of 1998. Each provided support, increasing with follow-up duration, that participation in the Tests had no detectable effect on expectation of life nor risk of developing most cancers.

8. To increase statistical power, the fourth follow-up study was commissioned, with the same aims, methods, measured outcomes, and statistical analyses as the first three, extending follow-up to the end of 2017, by when 56% of participants and controls had died.

9. The fourth follow-up study has now been published. Participant/control differences in risk of disorder incidence or mortality were usually only a few per cent, and risks were

not consistent over time, either in risk direction or size. Apparent difference in incidence and mortality values was often driven not by raised rates in test veterans, but by rather low rates in the military controls.

10. In scientific terms, the present conclusion must be cautious, and in the words of the authors of the study: -

“Taken overall, the current analysis indicates that the possibility that test participation has caused a small increased risk of leukaemia other than chronic lymphatic leukaemia (CLL) cannot be ruled out and that, whilst the evidence for any risk appears to have been greatest in the early years after the tests, a small risk might have persisted in more recent years, this long-term risk being particularly evident for chronic myeloid leukaemia, (CML).”

The explanation of this finding is unknown.

11. In relation to compensation under the War Pensions Scheme based on the scientific findings of the Fourth Report, IMEG would recommend no change.

Background

12. The 2017 Fourth IMEG report validated the science and medicine underpinning MOD war pensions no fault compensation policy for disorders claimed due to participation in the UK atmospheric nuclear weapons tests and experimental programmes (1). This policy was informed by the findings of the three National Radiological Protection Board (NRPB) analyses. A further (fourth) follow-up study has now been peer-reviewed and published. IMEG’s comments are based on its scientific and medical findings (2).

13. Between 1952 and final site clean-up in 1967, the UK conducted a series of atmospheric nuclear weapon tests and a weapons experimental programme, in Australia and islands in the Pacific Ocean. By the early 1980s, concern was growing about possible adverse health effects amongst participants and in 1983 the MOD commissioned a follow-up study into their health. Approximately 21,000 military personnel who took part in the tests - an estimated 85% of the total - and a control group of similar size, age, rank and date of service entry, who had deployed service in tropical and sub-tropical areas around the same time but were not present at the tests or experimental programme, was identified from MOD archives. The study aimed to detect any adverse health effects of test participation by comparing overall mortality, non-cancer and cancer mortality and incidence, regardless of the precise cause, in participants and controls. Given the context, and that radiation is a carcinogen, the study also considered whether the available recorded radiation exposures of test participants might be a possible source of any observed effects.

Ionising Radiation Exposures

14. In the early tests, the radiation exposures of most participants were monitored using personal film badges. The great majority of the badges recorded zero ionising radiation dose, and as a result, Defence policy was changed to focus further monitoring on those considered most at risk of radiation exposure. In total only 23% of the test veterans in the NRPB studies had film badges; of these, 64% had a zero recorded dose. Thus, only 8% of the total study population had a non-zero dose recorded, seriously limiting the power to detect adverse radiation health effects. Moreover, the average non-zero dose was 9.9 milliSieverts (mSv). The records show that fewer than 1000 of the total doses recorded, including for those deemed at "higher risk" (see below), were 1mSv or above: 81 study participants were exposed to a dose of 50 mSv or more, and 37 to more than 100 mSv.

15. Apart from its remoteness, a reason for location of the test sites in Australia and the South Pacific was the low background radiation level, typically 250 microSv (0.25 mSv) annually. This compares with an average UK annual natural background of 2.2 mSv, around 1000 times lower, with an additional 0.5 mSv average due to medical sources. The average age of nuclear test participants is now 81 years. Living in the UK to that age a person would, on average, be exposed to over 200 mSv ionising radiation. The average exposure for Hiroshima and Nagasaki survivors was 200 mSv, with a range up to 1000 mSv.

16. Some sub-groups of test veterans were identified as at "higher risk" of external radiation or radionuclide exposure, based on their location or particular role and, although numbers in these groups were small, their disorder incidence and mortality rates were analysed separately in the follow-up reports. These groups included: -

- RAF aircrews involved in sampling from airburst clouds (205 men) after the Mosaic, Totem, Buffalo, Antler, and Grapple tests
- RN personnel on HMS Diana when she sailed through the fallout at Operation Mosaic (282 men)
- the officers of the Buffalo Indoctrinee Force and Target response group who assembled to observe, at first hand, the effects of the detonation (249 men)
- those present at the Minor Trials at Vixen A and B and the subsequent clean-up operations
- others with recorded exposures greater than zero (1123 men)

The NRPB reports and a brief note on statistical concepts

17. The study follow-up reports use statistical analyses to test the hypothesis that presence at UK nuclear test sites and weapons trials was associated with adverse health effects. Some of the key concepts and terms may be unfamiliar and this brief note aims to aid accessibility.

18. For the study, the null hypothesis was that there were no differences in disorder incidence or mortality between the nuclear test veterans and the controls; the alternative hypothesis is that there were such differences. For statistical hypothesis testing the significance level, or "p-value," is generally set at 0.05. This means that there is a 5% chance that the alternative hypothesis will be accepted when the null hypothesis is actually true. The smaller the significance level, the greater the burden of evidence needed to reject the null hypothesis, and so support the alternative hypothesis.

19. "p-values" relate to significance level and measure the statistical strength of the evidence provided by the study data, on a scale between 0 and 1. The calculated "p-value" describes the probability of obtaining a sample statistic suggesting an adverse health effect, as less or more extreme than the significance level, by chance alone if the null hypothesis is true. If "p-value" = 0.01 this will happen 1 in 100 times by pure chance. In other words, such a result is unlikely to have happened by chance, compared with one with p=0.75, where 75 out of 100 times it will happen.

20. Confidence Intervals (CI) show the degree of uncertainty of the estimated factor, the 'interval' representing the range in which the true value lies. The wider the range, the less precise the estimate. 95% confidence intervals imply that the CIs for 19 out of 20 random samples would contain the true population value, while one would not.

21. The main focus of the NRPB analyses was detection of differences between the participant and military control groups, measured by relative risk (RR). Relative risk is calculated by dividing the disease rate among the veterans (study subjects) by the rate among the military controls. A RR greater than 1.00 indicates a higher risk among participants than controls; a value below 1.00 indicates a reduced risk. Since the main interest of the disease analyses was possible increases in mortality or cancer incidence in participants, a one-sided test with a 90% confidence interval was applied to the RRs.

22. The study also compared the findings for both military groups with those for the age matched general population of men in the UK. For these comparisons, Standardised Mortality Ratios (SMRs) and Standardised Incidence Ratios (SIRs) were calculated. An SMR is calculated by dividing the actual number of deaths observed in a study population by the number that would be expected if the study and reference populations had the same age (and gender) specific rates. This value is multiplied by 100 and applies to specific years. An SMR of 100 means death rates in both populations are the same; a value above 100 indicates that the death rate in the study population is higher than in the general community. As both increases and decreases in mortality or disease incidence in the military personnel (test veterans and controls), relative to the general population, might occur, two sided tests and 95% confidence intervals (CI) were used to assess the statistical significance of any deviation in SMR from 100. An SMR where the 95% CI encompasses 100 implies no statistically significant difference in rates between the comparator groups. In a similar fashion, an SIR is derived from measuring new cases (rather than deaths) of a disease; again, two sided statistical tests, with 95% CI were presented.

23. Military groups are selected populations, fitter than the general population, the so-called the "Healthy Soldier Effect". They have health screening pre-enlistment and at intervals during service to ensure appropriate fitness standards are met and maintained.

This may impact longevity and longer term development of other serious disorders, such as cancers and cardiovascular disease, compared with the general population. For this reason, both SMRs and SIRs for some diseases may be reduced (lower than 100).

24. The first three analyses of overall mortality, cancer incidence and mortality have been published in the peer-reviewed literature (3,4,5,6,7,8), the first with follow-up to the end of 1988, the second to the end of 1993 and the third to the end of 1998. These reports describe in detail the efforts made to ensure sample completeness and to control bias; study limitations are also acknowledged and discussed, and the report conclusions are reasoned and restrained. Together, they provided support, increasing with follow-up duration, that participation in the Tests had no detectable effect on participants' expectation of life nor risk of developing most cancers. The first report did suggest a raised risk of leukaemias (other than chronic lymphatic leukaemia, CLL, which is not considered radiogenic), in test veterans, and also of multiple myeloma. The leukaemia finding, although weakening over time, was still present in the second and third report analyses, but the early finding of a higher rate of multiple myeloma in test veterans was not confirmed in the second and third analyses and can be assumed to be a chance finding.

25. Follow-up in the third study went only to the end of 1998, and to increase statistical power and the study's capacity to detect small adverse health effects due to presence at the tests, in 2018 the now published fourth follow-up study was commissioned with the same aims, methods, measured outcomes, and statistical analyses as the first three (2). The fourth study extended follow-up of the original 21357 test participants and 22312 controls, to the end of 2017. By that date, follow-up for the earliest surviving participants was 65 years, and 56% of participants and controls had died.

26. For the majority of cancer types and many individual cases, presenting clinically, medically the precise cause is never established. There is no evidence that low dose radiation (less than 100 mSv) can directly cause cancer in humans. The US National Academy of Science's Biological Effects of Ionising Radiation (BEIR) VII report in 2006 (9) states "On average, assuming a sex and age distribution similar to that of the entire U.S. population, the BEIR VII lifetime risk model predicts that approximately one individual in 100 persons would be expected to develop cancer (solid cancer or leukaemia) from a dose of 100 mSv, while approximately 42 of the 100 individuals would be expected to develop solid cancer or leukaemia from other causes. Lower doses would produce proportionally lower risks." Cigarette smoking, diet, obesity, alcohol are today increasingly considered much more potent causal influences in development of many cancer types and individual cases (10).

27. The remainder of this note provides brief IMEG comment on the key scientific and medical findings of the fourth NPRB report. The context is war pensions no fault compensation policy. As with AFCS, entitlement for claimed disorders is given when a causal link to service can be accepted. For war pensions the relevant service is before 6 April 2005 and the standard of proof is not "balance of probabilities" but "reasonable doubt". Decisions are medically certified, evidence-based on individual case specific facts, reflecting contemporary medical understanding and the relevant scheme's standard of proof. For nuclear test participant claims, Article 41 of the Service Pensions Order applies. This means that the onus is on the claimant to raise a reasonable doubt by reliable evidence that the claimed disablement is attributable to service. Although higher court

case law has provided clarification/guidance on the meaning of “reasonable doubt”, the term has never been defined quantitatively and there remains a significant element of personal judgement in the interpretation of evidence in the individual case.

28. Successive governments have held that in matters of public compensation, regard must be paid to contemporary medical and scientific understanding of causation and progress of disorders. In assessing any new approach in science, the evidence must always be considered and weighed relative to the existing body of published peer-reviewed evidence on the subject, with account taken of the robustness and authority of new studies. This includes attention to the study design and methods, sample size, participant selection, statistical validity, repeatability of findings, approach to bias and possible confounding. These matters are further discussed in the Policy Statement on Claims for Ionising Radiation Related Conditions included in the December 2017 IMEG report (1).

29. The NPRB study reports, continued in the recent paper, test the hypothesis that presence at UK nuclear test sites and weapons trials was associated with adverse health effects. Data on overall mortality from all causes, non-cancer causes, for example accidents and violence and intentional self-harm, and cancer mortality and incidence, were collected and analysed for nuclear test veterans and controls. Using International Classification of Diseases (ILD) classifications (11), the studies considered a large number of diagnoses. Some of the ICD codes are high level and general, e.g., non-melanoma skin cancer, respiratory cancers, liver cancers, brain and central nervous system cancers, cancer of the mouth and pharynx, accidents and violence, and information on specific diagnoses/pathologies included in the ICD categories or study populations, was not always available. In general, participant/control differences in risk of incidence or mortality for the disorder categories were small, usually only a few per cent difference. In addition, risks were not necessarily consistent over time, either in risk direction or size. In numerous cases, apparent difference in RR values for both incidence and mortality were a reflection not of raised rates in test veterans but of rather low rates in the military controls. Reference has already been made to the role of chance in a study of this design, duration and numbers of disorder categories considered and the generally small case numbers of individual diagnoses. Lastly, the lack of information on potentially confounding differences in and between the study groups, limits explanations for any differences observed between the veterans, controls, and the general population.

Findings of the Fourth Nuclear Test Veteran Study

Overall mortality:

30. Overall mortality of both the participants and controls was lower than in men of the same ages in England and Wales over the whole follow-up period, 1952-2017 (SMRs of 90 and 88, respectively, $p<0.001$). When participants were compared with controls their all-cause mortality rate was 2% higher than for controls. (RR=1.02,90% CI. 1.00-1.05, $p=0.04$.)

Cancer mortality

31. For all cancers combined, there was a 3% increase in deaths in participants compared with controls, but this was not statistically significant (RR -1.03, CI 1.00-1.07 p=0.07).

32. Compared with the general population up to 1998, the “all cancer” mortality rates for both military groups was lower than general population, but in the final period of follow-up, 1999-2017, SMRs in both participants and controls increased so that for participants it was the same as the general population level (SMR=100) , and for controls just below the national level (SMR 96).

Non-cancer mortality

33. Mortality rates for all non-cancers were lower in both participants and controls compared with age-matched men in England and Wales (SMR=85 and 83 respectively, p=0.001) suggesting a stronger “healthy soldier effect” than for cancer mortality. Rates of cirrhosis of the liver were raised in both participant and control groups relative to the national population. This probably reflects the long-standing observation of higher alcohol consumption by service personnel compared with the general population. Deaths from accidents, road traffic accidents and intentional self-harm in both participants and controls were higher than in the general population but not significantly different comparing participants and controls for the period to 31 December 1998. For the second period to 31 December 2017, deaths in both participants and controls for accidents and violence and accidents decreased and were lower than for the general population but comparing the two study groups, deaths in participants relative to controls, based on 21 deaths showed a non-significant increase. In comparisons of participants and controls, there was some evidence that overall non-cancer mortality was slightly higher, by two percent, among participants driven by a higher number of cerebrovascular deaths (RR=1.12, 90% CI 1.03-1.21, p=0.01). This excess risk of cerebrovascular disease has only become evident during the latest follow-up period.

Specific cancers

34. Cancers of the stomach, bladder and prostate, respiratory cancers and leukaemias excluding chronic lymphatic leukaemia (CLL), all showed evidence of higher overall mortality or incidence rates in participants compared with controls.

Stomach cancer

35. Raised rates of stomach cancer were observed in participants relative to the controls but both groups had lower rates than the national population, especially so in the control group. There was no evidence of raised rates in subgroups identified to be most likely to be radiation exposed.

Bladder cancer

36. Although neither bladder cancer mortality nor incidence was increased in participants compared with the general population, raised mortality and incidence rates were observed in participants relative to the controls. This was marked in the first period of follow-up to the end of 1998 and again related to lower mortality and incidence in controls (for participants, SMR=81,P=0.09, compared with control bladder cancer mortality

SMR=56). In the second period to 2017, SMR in participants was 92, and increased to 93 in controls. Incidence in test veterans was similar to the general population for the whole follow-up period (SIR=102). For controls for the whole study period, SIR was 91 and RR 1.14 (1.01-1.27, p=0.033). Again there was no evidence that bladder cancer risk was elevated in groups identified as most likely to have been radiation exposed. Cigarette smoking and occupational exposure to aromatic amines are also known risk factors for bladder cancer but no details of exposure in participants or controls are available and it seems unlikely that such exposures would not impact both on both study groups. The overall findings could well be due to chance.

Prostate cancer

37. There was some evidence over the whole period of follow-up that the rate of mortality from prostate cancer was higher in the veterans (SMR 102) than controls, but mortality in controls was again low (SMR 89). There was no evidence for an overall difference in incidence between test veterans and controls or with either group compared with the national population. There was additional evidence for raised incidence rates among men in the special test veteran groups most liable to exposure to radiation, in particular the HMS Diana crew and those identified as most likely to be exposed to any internal radiation.

Respiratory cancer

38. In the earlier follow-up studies the lung cancer rates were higher in controls compared with test participants. Follow-up now shows small and statistically non-significant increases in both incidence (RR=1.04) and mortality (RR=1.06) in “respiratory cancer” in participants relative to the controls over the whole follow-up period. This is due to higher participant lung cancer rates in the most recent period (SMR=110, p=0.02; SIR=111, p=0.004). Rates in the control group (SMR=96, SIR=102) were in line with the national population.

39. Notable challenges in interpretation of the findings in the studies, including the fourth follow-up, are the small differences between participant and control groups and, the frequent absence of any plausible explanation for the differences. The observed small, raised risks could well be due to chance rather than a real adverse effect associated with the tests. Examples from findings from the earlier reports accepted as “real” at the time of publication, but requiring review and revision with more evidence, include the raised liver cancer incidence in participants compared with controls. This was not seen in the fourth follow-up, suggesting a chance finding. Similarly, the raised rate of multiple myeloma in the first study was not confirmed in the second and third reports or over the full period of follow-up. The fourth report provided no evidence of raised multiple myeloma among test participants, relative either to national mortality or incidence rate (SMR=85, SIR=96), or in comparison with controls for neither mortality (RR 0.93, 90% CI 0.70-1.24, p=0.34) nor incidence (RR 0.98, 90% CI 0.78-1.23, p=0.45). This strongly supports the conclusion that the raised risk seen in the first analysis was a chance finding. Similarly, early evidence of raised rates of primary polycythaemia (the red blood cell equivalent of the leukaemias types) is not supported by the fourth report.

All leukaemias excluding chronic lymphatic, referred to as non-CLL

40. It is generally accepted from atomic bomb and high dose medical treatment studies that there is a causal link between ionising radiation exposure and leukaemias, other than chronic lymphatic leukaemia (CLL). Echoing this, the fourth follow-up report showed no evidence of increased risk for participants relative to controls for either CLL mortality (RR 0.78, 90% CI 0.47-1.29, p=0.794) or incidence (RR 0.98, 90% CI 0.75-1.27, p=0.557). Over the full study follow-up period, 1952-2017, the rate of non-CLL mortality among participants was consistent with national rates, whilst among the controls it was significantly lower than expected, (SMRs of 102 and 79 respectively). There was some limited evidence of a raised risk of non-CLL mortality among test participants relative to controls (RR 1.26, 90% CI 0.98-1.62, p=0.07). For non-CLL incidence, both the participant and control rates were consistent with the national levels (SIRs of 116 and 83 respectively) although participants continued to have higher non-CLL rates than the controls (RR 1.38, 90% CI 1.10-1.75, p=0.01).

41. The earlier NRPB analyses recorded that overall non-CLL leukaemia risk increased early after the tests and that over time the size of the effect was diminishing. A similar pattern continues in the present analysis. Up to 1998, both non-CLL mortality (RR 1.82, 90% CI 1.18-2.82, p=0.01) and incidence (RR 1.49, 90% CI 1.01-2.18, p=0.04) rates were raised in participants relative to controls. Over the 19 years of additional follow-up in the current analysis, non-CLL mortality and incidence rates among test participants were much closer to those observed among the controls (for mortality RR 1.04, 90% CI 0.76-1.42, p=0.42; for incidence RR 1.32, 90% CI 0.99-1.78, p=0.06).

42. For all leukaemias, the mortality rate among participants was consistent with national levels (SMR 93, p=0.45) while for the control group, rates were lower than in men of the general reference population (SMR 79, p=0.02). Comparing participants with controls, the RR for all leukaemia mortality was 1.14 (90% CI 0.91–1.43, p=0.16), i.e., there was only weak evidence of a difference between the two groups. For leukaemia, excluding chronic lymphatic (non-CLL), the participants' mortality rate was consistent with the national level (SMR 102), while the controls' rate, although increased from earlier periods, remained below the national rate (SMR 79, p=0.04). The excess RR for non-CLL was slightly higher than for all leukaemia (26% compared to 14%), with rates in participants compared to controls, at most, of borderline significance (RR = 1.26, 90% CI 0.98–1.61, p=0.06).

43. The position with chronic myeloid leukaemia (CML) is different, and higher incidence rates have persisted with increased follow-up. CML incidence rates to 1998, relative to the national population (SIR=151, p=0.03) and the control group (RR 2.43, 90% CI 1.43-4.13, p=0.003), when followed to 2017 showed SIR further increased to 167, p=0.04 with a similar increase in RR compared with controls (RR 2.78, 90% CI 1.40-5.52, p=0.007). These data, over the whole study, refer to 32 CML cases in participants and 14 among the controls, with in 21 participants and eight controls, clinical onset post 1998.

44. In 1955, a study of mortality from leukaemias and other cancers in over 14000 patients irradiated for ankylosing spondylitis between 1935 and 1954, followed patients to 1960. Mortality due to all leukaemias and ratios of cases "observed" to "expected" were calculated from start of treatment and shown to increase over time to a peak ratio of "observed" to "expected "leukaemia deaths 3-5 years after the start of treatment with, thereafter, a decline to very low levels (12). This is similar to the pattern seen in nuclear

test veterans, in the first three reports and the fourth report, apart from for chronic myeloid leukaemia (CML). It is difficult to explain the finding on CML in the fourth report by presence at the tests.

45. CML is one of the best understood cancers; it has a simpler aetiology than most cancers and its time course is comparatively easy to monitor in the clinic. It is characterized by Ph+ cells which have a Philadelphia (BCR-ABL) chromosome translocation. Mathematical models of CML cell population dynamics are being developed to improve understanding and treatment of the disease. The generally accepted understanding has been that the latency time, from CML initiation to diagnosis, is less than 10 years (13). Recent radiobiologic estimates, based on Japanese atomic bomb survivor data, indicate a substantially longer latent period with evidence that sporadic chromosome translocation incidence increases with age during adulthood (13). This might make some contribution to the observed CML pattern, present in both groups although more marked in participants, but more study is needed.

Conclusion

46. In terms of radiation exposure at test sites, the overall clinical findings on disorder incidence and mortality support the available records of generally very low radiation exposures in participants, making it unlikely that any observed adverse health effect will have been caused by radiation exposure. The small size of the differences in mortality and incidence rates, limited study and control matching, and long follow-up makes heterogeneity in the background characteristics unaccounted for in the analysis (e.g., smoking habits, diet), between participants and the control group, a possible cause.

47. In scientific terms, the present conclusion must be constrained, and that of the authors: -

“Taken overall, the current analysis indicates that the possibility that test participation has caused a small increased risk of leukaemia other than CLL cannot be ruled out and that, whilst the evidence for any risk appears to have been greatest in the early years after the tests, a small risk might have persisted in more recent years, this long-term risk being particularly evident for CML.”

Based on present evidence, the basis of this finding is simply unknown.

Compensation Issues

48. Based on the scientific and medical findings of the first (1988) NRPB report, the Secretary of State’s normal policy became to award war pension for claims for leukaemia (other than chronic lymphatic leukaemia) and multiple myeloma in those present at test sites. The policy also included awards for primary polycythaemia, the red blood cell equivalent of leukaemia.

49. In the light of the 1993 report, the Secretary of State's normal policy was revised. Since then, on the basis of presence at atmospheric nuclear test sites, new claims for multiple myeloma are rejected but awards continue to be made for leukaemia (other than chronic lymphatic leukaemia) and primary polycythaemia having clinical onset within 25 years of first presence at the test sites.

50. Following the 2003 report, the Secretary of State's current normal policy remained unchanged from that in 1993.

51. The Secretary of State was, and remains of the opinion, that the first three reports do not provide reliable evidence sufficient to raise a reasonable doubt that generally other cancers (e.g. primary liver and urinary bladder) might be attributable to service in the Armed Forces because of presence at the nuclear test sites. It is presently his normal policy that entitlement for solid cancers, causing disablement or death, may not be presumed, i.e., accepted solely on the basis of presence at atmospheric nuclear test detonations, weapons tests or clean-up operations.

52. Entitlement may be certified for cancer or other radiogenic disorders in any case where, on the case specific facts, there is reliable evidence of service exposure to a sufficient level of ionising radiation and there is a recognised causal link between the claimed condition or cause of death and such accepted exposure.

53. The earlier war pensions policy decision to accept Polycythaemia Rubra Vera (PRV) on a presumptive basis as for the analogous leukaemia (other than CLL) diagnosed within 25 years of presence at the tests was based on a single claim and a small US case study suggesting an excess of cases in a population who had taken part in a nuclear test (14). This finding and its interpretation was challenged at the time (15) and has not been replicated in any other population. There are also issues as to the soundness of the histological diagnosis in the cases in the study. As a result, from 5 December 2017, publication date of the current Policy statement for claims for ionising radiation related conditions, PRV (now primary polycythaemia) is not accepted on the basis of presumption amongst nuclear test and weapons programme participants.

54. As discussed in this IMEG report the scientific findings of the 2022 fourth analysis contain much uncertainty and require cautious interpretation. We recommend they provide no scientific or medical basis for change to present war pensions policy. Awards continue to be made based on presumption for leukaemia (other than chronic lymphatic leukaemia) having clinical onset within 25 years of first presence at the test sites. Otherwise, entitlement may be certified for cancer or other radiogenic disorders in any case where, on the case specific facts, there is reliable evidence of service exposure to a sufficient level of ionising radiation or other exposure, and there is a recognised causal link between the claimed condition or cause of death and such accepted exposure.

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