Morbidity of Vietnam veterans

Multiple sclerosis and motor neurone disease in Vietnam veterans

Supplementary report no. 3

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Supplementary report no. 3

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REPATRIATION COMMISSION

11 April 2001

The Hon Bruce Scott MP
Minister for Veterans' Affairs and
Minister Assisting the Minister for Defence
Parliament House
CANBERRA ACT 2600

Dear Minister

As Chairman of the Advisory Committee for the validation of the results of the Vietnam Veterans' Health Study, I am pleased to forward for your consideration the report entitled *"Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community: Multiple sclerosis and motor neurone disease in Vietnam veterans: Supplementary report no. 3."*

One of the recommendations from Volume 1 of the Vietnam Veterans' Health Study was that reported levels of multiple sclerosis and motor neurone disease in Vietnam veterans should be subject to validation. This report fulfils the commitment to implement that recommendation.

This report is supplementary to the wider validation study of veterans' conditions (Volume 3 of the Vietnam Veterans Health Study). The reason multiple sclerosis and motor neurone disease were not included in that Volume is that they are difficult to diagnose accurately. Validation involved obtaining clinical notes and having these assessed by an expert panel of neurologists against designated diagnostic criteria. The time required for this process would have delayed publication of the other validation results unnecessarily. Thus it was decided to publish the results for multiple sclerosis and motor neurone disease separately.

This report indicates that the levels of the two conditions in Vietnam veterans lie within the ranges that might be expected for the conditions in a group of the same size, age and sex in the general community. This accepted, I draw to your attention that portion of the Report's conclusion recommending caution in interpretation of the motor neurone disease result.

This is the final report of the study of the health of Vietnam veterans begun in 1997.

I wish to thank the Australian Institute of Health and Welfare and the Advisory Committee for the Health Study for their work in producing this report.

Yours sincerely

Paul Stevens

Paul Stevens
Chairman, Morbidity of Vietnam Veterans Study
Advisory Committee and
Commissioner, Repatriation

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Acknowledgments

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The AIHW would like to thank the members (listed below) of both the Study Advisory Committee and the Expert Neurologist Panel for their contribution to the study.

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Dr Paul Magnus (AIHW Medical Adviser)

Executive summary

This report forms an addendum to *Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community: Volume 3 Validation Study* (AIHW 1999), which validated a series of health conditions reported by Vietnam veterans in an earlier Morbidity Study (DVA 1998) about themselves and their children. During the conduct of this validation study, it was found that the time required to complete the validation of multiple sclerosis (MS) and motor neurone disease (MND) in veterans would have seriously delayed the release of the Validation Study report. Therefore it was recommended that the validation of these two conditions be undertaken as a subsequent study.

The aim of this study is to medically confirm self-reported cases of MS and MND among Vietnam veterans who participated in the Morbidity Study, and to compare the number of validated conditions with the number of expected conditions based on Australian community standards.

The Australian Institute of Health and Welfare (AIHW) conducted this Validation Study under the direction of a Study Advisory Committee that included ex-service representatives. An Expert Neurologist Panel convened by AIHW assisted the study.

The methodology used in this report to validate reported cases of MS and MND consisted of the following four stages:

- obtaining the veterans' permission to validate the condition(s) they reported in the Morbidity Study by contacting their relevant doctors;
- contacting the veterans' general practitioners for their opinions on the presence of MS or MND, and requesting the names of the veterans' neurologists;
- contacting the veterans' neurologists to request copies of clinical notes relevant to the diagnosis of MS or MND; and
- having these clinical notes assessed independently by the Expert Neurologist Panel according to internationally accepted diagnostic criteria: the Rose criteria for MS and the El Escorial criteria for MND. These criteria allow each case to be classified as either definite, probable, possible or 'does not have the condition'. Under the rules of the Rose and El Escorial criteria, only definite and probable cases are considered validated.

Response rates from veterans in this study were considered acceptable for statistical validity. In the original Morbidity Study 209 veterans reported that they had either MS or MND, and 145 (69.4%) replied to this follow-up study. The response from medical practitioners was excellent, with 98% of general practitioners and 96% of neurologists responding to requests for information about veterans' conditions.

After all reported cases of MS and MND were followed up and classified using the four stages outlined above, the number of validated conditions of MS and MND among veterans was substantially lower than the number reported in the Morbidity Study (Volume 1). This was believed to be due to misinterpretation of the terms MS and MND by veterans, particularly MND.

When the number of validated cases of MS and MND among veterans was compared with the expected number of conditions, based on the Australian community standard, no statistically significant difference was found between the prevalence of MS and MND in veterans and that of the general Australian community.

However, if reported cases of MND among deceased veterans are included as 'validated' where clinical notes were not available but MND is included as a cause of death on the death certificate,

the estimated number of cases among veterans is at the upper limit of the 95% confidence interval for the Australian community standard.

It is recommended that caution be used in the interpretation of the MND results. The estimated Australian community standard for MND used in this study is considered to be the most accurate estimate possible, but it should be understood that a number of assumptions were made in calculating this standard (Section 3.3, page 15). These assumptions introduce a level of uncertainty that cannot be measured statistically, but they were necessary because of the lack of prevalence data for MND in Australia. Any margin of error in these assumptions will affect the Australian community standard, and may have the potential to change the conclusion that there is no difference between the prevalence of MND in veterans compared with the Australian community standard.

In the case of MS, the number of validated conditions among veterans is well within the 95% confidence interval for the community standard. Therefore variations in the assumptions are unlikely to affect the conclusion of no statistically significant difference between the prevalence of MS for veterans and the Australian community standard.

1 Purpose, organisation and management

1.1 Introduction and background

This report forms an addendum to *Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community: Volume 3 Validation Study* (AIHW 1999). In the Validation Study, the Australian Institute of Health and Welfare (AIHW) was commissioned by the Department of Veterans' Affairs (DVA) to validate a range of conditions among veterans and their children reported in *Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community. Volume 1. Male Vietnam Veterans Survey Results* (DVA 1998).

Volume 1 of the Morbidity Study was a self-reported survey of Vietnam veterans regarding their own health and that of their partners and children. Findings from this study suggested that both veterans and their children may suffer from certain health conditions at a higher prevalence than that experienced by the overall Australian community. It was therefore recommended in this volume that some important conditions more prevalent amongst veterans and their children when compared to the Australian community standard be validated as a matter of urgency (DVA 1998). Thus the *Morbidity of Vietnam Veterans: A Study of the Health of Australia's Vietnam Veteran Community: Volume 3 Validation Study* was launched for these specified conditions (AIHW 1999). The validation of each condition was undertaken by seeking information from medical practitioners and community registers of medical information, such as death and cancer registrations. This process occurred only after obtaining the consent of relevant veterans and their children.

In the conduct of the Validation Study, it was found that the time required to complete the validation process for MS and MND in veterans would have seriously delayed the release of the validation report. Extra time was required to complete the validation of the MS and MND cases because they needed to be rigorously classified as either definite, probable or possible, using internationally recognised criteria. This meant having to obtain detailed clinical notes and then having these assessed by a panel of neurologists, rather than accepting a simple diagnosis as for the other conditions. It was therefore decided to delay the validation of these two conditions and present the findings in this subsequent report.

Objectives of the MS and MND study

- To medically confirm self-reported cases of MS and MND among Vietnam veterans who participated in the Morbidity Study and to classify validated cases into definite, probable or possible; and
- to compare the number of validated conditions with the number of expected conditions based on Australian community standards.

1.2 Study organisation and administration

This study was commissioned and funded by the Department of Veterans' Affairs. It was conducted by a project team at the Australian Institute of Health and Welfare under the *Australian Institute of Health and Welfare Act 1987*. The study was planned under the supervision of a Study Advisory Committee, gained ethical approval and was guided by the Expert Neurologist Panel.

Study Advisory Committee

The Study Advisory Committee, including representatives of Ex-Service Organisations, and staff from the DVA and AIHW were responsible for the conduct of this study. The committee provided an opportunity for debate on issues relating to the study methods, provided feedback from veterans, advised on modifications to the operational protocol, and assisted in promoting the study.

Ethics Committee

The protocol document for the MS and MND validation strategy was approved by the AIHW and the DVA Ethics Committees, and by the Expert Neurologist Panel (see below).

Expert Neurologist Panel

The Expert Neurologist Panel was established to review and assist with medical issues relating to this study, especially in the areas of diagnosis. Its terms of reference were to:

- assist the AIHW project team with issues and decisions that required technical medical knowledge;
- assist with the development of a suitable protocol for the study;
- define and apply criteria for multiple sclerosis and motor neurone disease;
- resolve areas of medical uncertainty relating to validation of individual cases; and
- help liaise with medical practitioners and independent experts for the purposes of the study.

Structure of the report

Chapter 2 provides information about MS and MND, including their epidemiology, signs, symptoms and diagnosis.

Chapter 3 presents a detailed account on the methodology used in this report.

Chapter 4 presents the results of the report, including the response rates achieved. A discussion of the results is also presented, along with the conclusion of the study.

The Appendixes contain samples of the various forms, letters and protocols used to support this study.

2 Multiple sclerosis and motor neurone disease

2.1 Multiple sclerosis

MS is one of the most common neurological causes of long-term disability. It is more than twice as common in females as males, and onset usually occurs between the ages of 20 and 50 years (AIHW 2000).

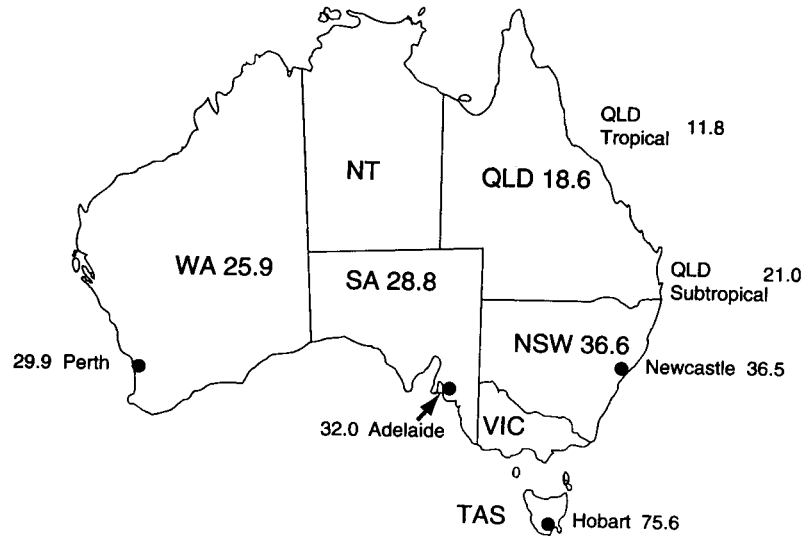
MS is a disorder of the central nervous system, which results in decreased nerve function. This is due to repeated episodes of inflammation of nervous tissue, which destroys the covering of the nerve fibres. This inflammation can occur in any area of the brain and spinal cord, leaving multiple areas of scar tissue (sclerosis). The condition is often of a remitting–relapsing nature, although it usually worsens over time, and the symptoms may vary in their pattern and duration during an active episode.

Epidemiology

MS in Australia has been well documented, with prevalence studies having been completed for Western Australia, Queensland, New South Wales, South Australia, and Tasmania.

According to McLeod et al. (1994), the prevalence of MS increases significantly with increasing south latitude in Australia. MS is about seven times more frequent in Hobart than in tropical Queensland (McLeod et al. 1994) (see Figure 2.1). This latitudinal difference is not explained by genetic factors, and is most likely the result of exposure to unknown environmental factors, possibly viruses. There has been a significant increase in the frequency of documented cases of MS between 1961 and 1981, although this may be due to better ascertainment and more awareness of MS. The clinical features of MS are similar in all parts of Australia. No cases of MS have been recorded in Aboriginal or Torres Strait Islander populations (McLeod et al. 1994).

Throughout the world, the frequency of MS tends to increase with increasing geographical latitude in both the northern and southern hemispheres. It also tends to be uncommon in the tropical and subtropical zones and relatively more prevalent in the temperate zones of Europe and North America. High prevalence rates of over 30 per 100,000 population occur in northern Europe, northern USA, southern Canada, southern Australia and New Zealand; moderate prevalence rates of between 5 and 25 per 100,000 population are found in southern USA, southern Europe and much of Australia, and the lowest prevalence is seen in Asia, Latin America, most of Africa and the Middle East (Lowis 1988).



Source: McLeod et al. 1994.

Figure 2.1: Age-standardised prevalence rates per 100,000 population for MS in Australia, persons 1981

Signs and symptoms

MS has a relapsing–remitting course in that clearly defined relapses occur with full recovery. Typically the symptoms of a MS attack evolve over days or weeks, remain stable for days or weeks, and then gradually resolve over days or weeks, although often incompletely. The symptoms and signs of the first attack usually recover within 1–3 months, and after a variable interval there may be a recurrence, in many cases within 2 years (Pender 2000). The most common signs and symptoms are shown in Box 2.1.

Diagnosis

The diagnosis of MS is a complex one to make. There are no reliable specific laboratory tests. Therefore the diagnosis remains a clinical one (i.e. physical examination), and so there is a need for clinical diagnostic criteria. It is also strongly recommended that the diagnosis of MS be established only by a competent neurologist (Poser et al. 1983).

Prior to the 1970s diagnosis of MS could only be derived from a pathological examination after death. However, it was believed at that time that 'by utilising the clinical observations made on patients who come to autopsy in the past, the diagnosis can be made during life with reasonable accuracy, and cases can be categorised on the basis of probability' (Rose et al. 1976).

Box 2.1: Common presentations of multiple sclerosis

- *Optic neuritis*
- *Visual difficulties due to visual loss and double vision*
- *Spinal cord lesion*
- *Weakness of limbs*
- *Pain or sensory loss of limbs or trunk*
- *Lhermitte's sign (electric shock radiating down back and triggered by neck flexion)*
- *Urinary urgency, and incontinence*
- *Brainstem lesion*
- *Pain or numbness of the face or tongue*
- *Vertigo and nystagmus (rhythmical oscillations of one or both eyes)*
- *Speech impairment due to dysarthria (weakness, slowness or incoordination of the muscles responsible for speech)*
- *Incoordination of limbs*
- *Unsteadiness*
- *Brain lesion(s)*
- *Impairment of concentration, memory loss and other cognitive processes*
- *Hemiparesis (paralysis on one side of the body)*
- *Hemisensory loss (loss of sensation on one side of the body)*
- *Visual field defect*
- *Severe fatigue*
- *Aggravated by heat and stress*

(Adapted from Pender 2000)

Over the years a number of criteria have been proposed for the diagnosis of MS, each with different types of categories, and different numbers of categories. Based on all these criteria, a group of neurologists from the UCLA School of Medicine and the Veteran Administration Wadsworth Hospital Centre designed their own set of criteria which has become universally accepted as the preferred form. This set of criteria is known as the Rose criteria, named after the major contributor.

The Rose criteria consists of three categories:

- clinically definite MS;
- clinically probable MS; and
- clinically possible MS.

These categories have been designed so that individual patients may be classified on the basis of clinical symptoms. After observation or time a patient can move from clinically possible to clinically probable to clinically definite or can be excluded altogether. Usually a diagnosis of clinically possible is excluded from research protocols and not included in prevalence counts (Poser at al. 1983). A description of the criteria can be found in Box 2.2.

The Australian community comparison for MS was derived from Australian prevalence rates as published by McLeod et al. (1994) (see Section 3.3). Here all patients for whom the

diagnosis of MS was considered to be correct were classified according to the diagnostic criteria of Rose et al. (1976) into clinically definite, probable and possible. Prevalence rates were then determined from those deemed clinically definite and clinically probable.

To make this Australian community standard comparable to the results of this veteran study, veterans' clinical records were assessed against the Rose criteria.

Box 2.2: The Rose criteria for MS

Clinically definite MS

- *Relapsing and remitting course with at least two bouts separated by no less than one month; or*
- *Slow or step-wise progressive course extending over at least six months.*
- *Documented neurologic signs attributable to more than one site of predominantly white matter central nervous system pathology.*
- *Onset of symptoms usually between ages 10 and 50.*
- *No better neurologic explanation.*

Probable MS

- *History of relapsing and remitting symptoms but without documentation of signs and presenting with only one neurologic sign commonly associated with multiple sclerosis; or*
- *A documented single bout of symptoms with signs of multifocal white matter disease with good recovery, and followed by variable symptoms and signs.*
- *No better neurologic explanation than MS.*

Possible MS

- *History of relapsing and remitting symptoms but without documentation of signs; or*
- *Objective neurologic signs insufficient to establish more than one site of central nervous system white matter pathology.*
- *No better neurologic explanation.*

(Adapted from Rose et al. 1976)

2.2 Motor neurone disease

MND occurs when motor neurones, the nerves that control muscles, fail to work normally. The motor neurones progressively deteriorate and, with no nerves to activate them, the muscles gradually weaken and waste. Early symptoms of MND are mild and may include stumbling, twitching, cramps and spasticity. As a result diagnosis is often clinically difficult in the early stages as MND can be confused with other conditions. Confirmation of a diagnosis must be made by a neurologist.

Epidemiology

The epidemiology of MND is not as well known as that of MS. According to the MND Association of Australia, there are about 1,400 people with MND in Australia (MNDAA 2000). Motor neurone disease is an adult disease, being extremely uncommon in people aged less than 30.

Estimated prevalence rates of MND in Australia for the period 1986 to 1994 (Lang 1996) show that the prevalence of MND in Australia has remained relatively stable over the 1986 to 1994 period at around four per 100,000 population (Table 2.1).

These prevalence rates were derived from mortality rates, based on the relationship between incidence (the number of new cases in a year), and the average duration between diagnosis and death. Mortality rates were used as a proxy for incidence rates, and these were multiplied by the average duration between diagnosis and death, estimated to be 27 months, to estimate the prevalence of MND in Australia.

Table 2.1: Prevalence and mortality rates of MND in Australia, 1986–1994

Year	Prevalence rate[(a)] (per 100,000 population)	Mortality rate (per 100,000 population)
1986	3.4	1.5
1987	3.7	1.7
1988	4.0	1.8
1989	4.4	1.9
1990	4.0	1.8
1991	3.6	1.6
1992	4.1	1.8
1993	4.1	1.8
1994	4.3	1.9
Average	**4.0**	**1.8**

(a) Prevalence rates are estimated from mortality and average duration between diagnosis and death.

Source: Lang 1996.

Signs and symptoms

MND is a progressive disorder, and affects middle-aged and elderly people. There is a clear preponderance of males, as a male excess is found almost universally in both morbidity and mortality data (Kurtze 1991).

The onset of MND is gradual and in the early stages of the disease the symptoms are slight. The weakness of MND often starts in the hands or feet, and because MND is a progressive disease, the muscle weakness becomes worse with time, leading to loss of function of limbs and wasting of the muscles of the trunk and neck. The person may therefore become immobile and require help in performing daily activities. Common symptoms are shown in Box 2.3.

MND affects each individual differently with respect to initial symptoms and the rate and progression of the illness. There is no remission during the course of the condition, but people may experience a 'plateau' lasting weeks or months while no deterioration occurs. MND is incurable and leads to death within 1–5 years of diagnosis. Death is most commonly due to respiratory muscle weakness or breathing failure.

Diagnosis

As with MS, the diagnosis of MND is also a complex one to make, again because there are no reliable laboratory tests. However, clinical criteria for diagnosis have not always been available for MND, as they have for MS. Similar to MS though, the diagnosis must be made by a competent neurologist.

Due to the lack of agreed clinical criteria for MND, a 3-day workshop on 'The Clinical Limits of MND' was convened in El Escorial, Spain, in May 1990 by the World Federation of Neurology Subcommittee of Motor Neurone Disease. The purpose of the workshop was 'to develop diagnostic criteria for MND which are workable, internationally acceptable, and provide an algorithm which will enhance clinical studies, therapeutic trials and molecular genetics research studies' (World Federation of Neurology Research Group on Neuromuscular Diseases 1994).

Box 2.3: Common presentations of motor neurone disease

- *Degeneration of anterior horn cells in the spinal cord*
- *Skeletal muscles wasting and fasciculation*
- *Reduced muscle tone and stretch reflexes*
- *Weakness of the facial jaw and bulbar muscles*
- *Degeneration in corticobulbar and corticospinal pathways*
- *Spastic weakness of cranial and bulbar muscles*
- *Spastic weakness of limb and truncal muscles*
- *Exaggerated jaw, gag and cough reflexes plus emotional lability*
- *Exaggerated limb stretch reflexes and extensor plantar responses*
- *Emotional reactions may be affected, causing inappropriate laughing or crying, which can be distressing for both the person with MND and their family.*
- *Respiratory difficulties occur if the muscles involved in breathing are affected and in a few cases this may be the predominant feature of the disease*

(Adapted from Motor Neurone Disease Association of Australia 2000)

The criteria that were developed as a result of this workshop are known as the World Federation of Neurology in El Escorial criteria (El Escorial criteria, for short) and enables the classification of cases into the following categories:

- clinically definite MND;
- clinically probable MND;
- clinically possible MND; and
- clinically suspected MND.

As with MS, these categories have been designed so that individual patients may be classified on the basis of clinical symptoms. After observation or time a patient can move from clinically possible to clinically probable to clinically definite or can be excluded altogether. Usually a diagnosis of possible or suspected is excluded from research protocols and not included in prevalence calculations (Poser et al. 1983). A description of the criteria is provided in Box 2.4 below.

The Australian community standard for MND in this study has been derived based on a diagnosis made with the El Escorial criteria (Section 3.3). The methodology used for validating veterans' conditions in this study is comparable to this standard as it is also based on the El Escorial criteria (see Chapter 3).

Box 2.4: The El Escorial criteria for MND

Clinically definite MND

- *The presence of upper motor neurone (UMN) degeneration, as well as lower motor neurone (LMN) degeneration signs in three regions*

Probable MND

- *The presence of UMN degeneration, as well as LMN degeneration in at least two regions with some UMN signs necessarily rostral to (above) the LMN degeneration signs*

Possible MND

- *UMN and LMN clinical signs in only one region; or*
- *UMN signs found alone in two or more regions; or*
- *LMN signs found rostral to UMN signs; and*
- *Other (i.e. non-MND) causes excluded*

(Adapted from World Federation of Neurology Research Group on Neuromuscular Diseases 1994)

3 Study design

In summary, the MS and MND study design sought to:

- obtain the veterans' permission to validate the condition they reported in the Morbidity Study;
- contact medical practitioners to obtain their opinion on the presence of the reported condition and to provide the name of the veterans' neurologist;
- contact neurologists to request copies of clinical notes relevant to the reported condition;
- have these clinical notes assessed by the Expert Neurologist Panel to determine the validation status of the veterans; and
- compare the number of validated conditions with the number expected, based on Australian community standards.

The study design aimed to ensure:

- the comparability of the results with population-based estimates of disease in the community;
- high participation rates from veterans, their doctors and neurologists while minimising the impact of the study upon them; and
- the confidentiality of personal information used in this study.

In establishing this study design it was crucial to define the criteria by which the conditions would be accepted as valid. These are discussed in the following section.

3.1 Study population

The study population of this report is derived from the 1997 Morbidity Study. All the veterans who indicated in this study that they had been diagnosed with either MND (126) or MS (83) have been included.

Veterans who died between the time of the Morbidity Study and the completion of the MS and MND Study have been identified by matching the Morbidity Study population with the AIHW National Death Index (NDI). The NDI documents the names and causes of death of all Australians who have died since 1980. The deceased veterans are considered respondents and, where possible, their details have been followed up.

'New veterans' and 'new conditions'

During the course of the study, a number of veterans who had not participated in the Morbidity Study survey came forward to offer their information. Additional survey forms were forwarded to these veterans, and, for the purpose of this study, they were termed 'new veterans'.

In some instances, veterans who participated in the Morbidity Study reported conditions that they had developed since that study. These are referred to as 'new conditions'.

Data provided regarding 'new veterans' and 'new conditions' have been recorded in the study data systems, and have undergone the same validation process. However, they have been treated separately in the results to prevent any bias. Bias would be introduced into the

results because conditions reported by 'new veterans' are not considered representative of the total veterans' population. 'New veterans' could only be included in the results if all living veterans not in the Morbidity Study were included in the calculation of the prevalence rate. Similarly, 'new conditions' could be included in the analysis only if 'new conditions' were obtained from all living veterans, rather than only the Validation Study population.

Results of the validation process for 'new veterans' and 'new conditions' have therefore been excluded from the main results, and are shown separately in Table 4.6.

3.2 Survey methods

Veterans, doctors and neurologists were surveyed using questionnaires. The questionnaires and accompanying information (Appendixes 1–3) were designed by the study team with the guidance of the Expert Neurologist Panel. They were all personally addressed.

The survey methodology comprised four major steps:

- survey of veterans reporting MS and MND;
- survey of general practitioners and hospitals;
- survey of neurologists; and
- classification of clinical notes.

Survey of veterans

The initial survey of the veterans who reported MS and MND was completed as part of the overall Validation Study conducted between 1998 and 2000. The veterans were asked to provide permission to validate their condition and the name of their doctor. The survey consisted of introductory letters from the AIHW and the Repatriation Commissioner, one or more survey forms to the veteran, an information sheet about the study and a reply-paid envelope (Appendix 1). This information was sent in October 1998, and a response time of three weeks was allowed for the respondents.

In November 1998 a reminder package was sent to those veterans who had not yet responded and included a letter of encouragement from the Minister for Veterans' Affairs and veterans' representatives. A second reminder mail-out was sent in January 1999, which included a reissue of the entire survey package. The Study Advisory Committee and AIHW Ethics Committee approved telephone prompting for those veterans who had reported MS and MND in the Morbidity Study, as the response rates for both conditions were not at an acceptable level for statistical validity. This took place in the period of 16–26 February 1999.

Another survey package was sent to the non-respondents in March 2000 after the Study Advisory Committee recommended that they be given one final chance to participate in the study.

Survey of general practitioners and hospitals

As previously mentioned, the diagnosis of MS and MND is quite complex and requires the expertise of a neurologist. Therefore if medical practitioners provided by veterans as a validation source were not neurologists, they were used as an initial screening device.

These doctors were contacted and asked to provide their opinion on the presence of MS or MND. If they believed the patient did have the condition they were asked to provide the

name of the neurologist who attended the patient, so the neurologist could be followed up for details. If they stated that the patient did not have the condition, the patient was not followed up further and was deemed 'not validated'.

The survey package sent to doctors consisted of a letter explaining the study, a form for them to specify whether or not they thought the veteran might have the condition and to provide the name of the neurologist, and a copy of the veteran's consent form (Appendix 2). These were sent out in March 2000, with follow-up telephone prompting in April 2000. A reminder package was sent to the non-responding doctors in July 2000, consisting of a reminder letter as well as the survey form and the veteran's consent form. The AIHW Medical Adviser contacted the few non-responding doctors again in November 2000 to prompt them a final time.

Survey of neurologists

The survey of neurologists consisted of a letter and a copy of the veteran's consent form. The letter requested copies of clinical notes that would help in the classification of MS and MND. The letter was approved by the Expert Neurologist Panel and was signed by the panel chair, Professor JG McLeod (Appendix 3). The initial survey packages were sent in July 2000, followed by reminder letters and telephone prompting in August and September. In November 2000, Professor McLeod contacted the six neurologists who had not responded by this time, requesting their assistance.

Classification of clinical notes

The clinical notes from the veterans' neurologists were initially sent to the study team at AIHW, who then forwarded them to the members of the Expert Neurologist Panel in August 2000. The panel members individually assessed each veteran's clinical notes against the Rose criteria for MS cases or the El Escorial criteria for MND cases. This assessment was recorded on a form containing a series of Yes/No tick boxes reflecting the El Escorial and Rose criteria (Appendix 4). Completed forms were then returned to the AIHW where the study team collated the results.

Further clinical notes, as a result of the final effort to prompt doctors and neurologists, were sent to the panel throughout October and November. These were all returned by February 2001 when the final results were collated.

The final classification result for each veteran was based on a clear majority decision between the five neurologists on the panel. Where there was not a clear majority, these cases were put aside for a face-to-face meeting of the panel. Some hypothetical illustrations of this majority rule are shown in Table 3.1.

Table 3.1: Illustrations of outcomes based on Expert Neurologist Panel individual classifications

	Classification category derived from Expert Neurologist Panel					
Example	**Neurologist 1**	**Neurologist 2**	**Neurologist 3**	**Neurologist 4**	**Neurologist 5**	**Outcome**
1	Definite	Definite	Probable	Definite	Definite	Definite
2	Definite	Probable	Probable	Probable	Definite	Probable
3	Definite	Possible	Possible	Possible	Not	Possible
4	Possible	Not	Possible	Not	Not	Not
5	Definite	Probable	Possible	Probable	Definite	For meeting
6	Unable	Possible	Unable	Not	Unable	For meeting

Note: These illustrations are hypothetical examples, not real cases.

For each veteran where a definitive classification could not be made (illustrations 5 and 6 above), the veteran's clinical notes were assessed at a face-to-face meeting of the panel on 3 February 2001. At this meeting 16 cases were considered. Each criterion was discussed for every veteran, with evidence in the notes consulted where necessary. Once consensus was reached on these criteria, the AIHW study team determined the overall classification for each veteran. This classification was considered to be the final result.

From this meeting 13 of the cases were classified, with the remaining three being followed up for further information with the veterans' neurologists. The overall classification process was considered to be highly rigorous, as each veteran's notes were carefully assessed by five neurologists independently, and then by the group if classification was difficult.

Deaths of veterans

Veterans who had died in the period between the Morbidity Study (1998) and the completion of this study were identified by matching the Morbidity Study population with the National Death Index (NDI). The NDI contains identifiable information for all deaths occurring in Australia from 1980. The identifying details of the study population were regularly checked against the NDI using automated matching algorithms or by manual search. These algorithms looked for the level of match between the complete name, dates of birth, sex and place of diagnosis.

The cause of death recorded on the NDI is the 'underlying' (i.e. the primary) cause of death from the death certificate. However, other 'associated' causes of death recorded on the death certificate are also accessible from 1997.

Where a death registration was identified, the cause of death, date of death and place of death were ascertained from the NDI. If the underlying cause of death on the NDI was not MS or MND, then the associated causes of death were investigated.

The veterans who had died were not counted as validated conditions unless clinical notes could be obtained. This is because the classification process had to be identical to the strict criteria-based approach used to calculate the community prevalence, and to classify the living veterans reporting MS and MND. However, veterans with a cause of death indicating MS or MND, for whom their clinical notes could not be obtained, were not excluded from the analysis altogether. Table 4.4 in the results section examines the effect on the validation results if these cases are included as validated.

Three of the veterans who had died had made claims to DVA for their conditions, and therefore had relevant clinical notes available. These were obtained from their DVA file,

enabling the veterans' conditions to be classified by the Expert Neurologist Panel. Another five veterans who had died did not have clinical notes on DVA files, but had the name of their treating doctor on their file. These doctors were followed up in the same way as the living veterans. Overall, clinical notes were obtained for six veterans who had died since the Morbidity Study, and these were able to be assessed by the Expert Neurologist Panel.

For the remaining four veterans who had died, information was not available. These cases have been designated 'not able to be validated'.

3.3 Validation methodology

Recalculation of Australian community standards

Multiple sclerosis

The Australian community standard for MS used in the Vietnam Veterans Morbidity Study (Volume 1) was based on a study completed by Hammond et al. (1988b), which estimated the prevalence of MS in three Australian cities: Perth, Newcastle and Hobart. In a later study by the same authors, the prevalence of all of Australia was studied and it 'confirmed the presence of a clear relationship between increasing MS prevalence and increasing south latitude' (McLeod et al. 1994). In other words, the further south in Australia you go, the higher the rates of MS, with the age-standardised rates increasing about sevenfold between subtropical Queensland and the statistical division of Hobart.

Since this relationship exists with latitude and more veterans live in Queensland than any other Australian State or Territory, it is not appropriate to use rates from only Perth, Newcastle and Hobart, all in the southern part of Australia. Therefore the Study Advisory Committee asked the AIHW to derive a new Australian community standard for MS based on the prevalence data from each State. Age-specific prevalence rates were devised for each State and Territory and the weighted sum of these (weighted by the number of veterans living in each State) became the revised Australian community standard (Table 3.2).

Data were not available for each State and Territory. Only New South Wales, South Australia, Queensland and Western Australia had data available for the whole State. For the other States and Territories, the rates for similar latitudes were substituted (McLeod et al. 1994, Hammond et al. 1987, Hammond et al. 1988b). Thus for Victoria, the New South Wales rates were used, for Northern Territory the Queensland rates were used, while for Tasmania the Hobart rates were used.

Based on these calculations, the expected number of cases of MS in the veteran population is 17, with a confidence interval of 9–26 (Table 3.2). This compares with the 1997 Morbidity Study expected number of cases of 19 and confidence interval of 17–22, which was based only on Perth, Newcastle and Hobart data.

Table 3.2: Multiple sclerosis prevalence rates, Australia, 1981

State	Crude prevalence rate of MS (per 100,000 male population)	Veteran population as reported in Morbidity Study	Expected no. of cases of MS in veteran population (confidence interval)
NSW (ACT included)	22.6	12,739	6.0
Qld	11.0	10,705	3.4
Vic	22.6	7,178	3.4
WA	12.0	4,397	1.4
SA	17.8	3,426	1.5
TAS	52.0	1,186	1.2
NT	11.0	399	0.1
Total	**—**	**40,030**	**17 (9–26)**

Motor neurone disease

An investigation into the method used to calculate the Australian community standard for MND, as used in the Morbidity Study (Volume 1), revealed an inconsistency with the El Escorial criteria based validation methodology for MND. This inconsistency is caused by the Volume 1 standard being derived from prevalence rates which were based on reported cases of MND, rather than cases classified according to the stricter El Escorial classification. Given that the El Escorial criteria are used to validate reported cases of MND among Vietnam veterans, the Australian community standard must also be estimated according to the El Escorial criteria for any comparisons to be valid.

The Study Advisory Committee therefore asked the AIHW to recalculate the Australian community standard for MND based on estimated prevalence rates in Australia, adjusted for the effect of applying the El Escorial criteria.

As reported prevalence rates for MND in Australia are not available, the Australian community standard for MND was calculated from mortality rates and average life expectancy from MND. Because of the relationship between these, male 5-year age-specific prevalence rates were able to be estimated by multiplying the average annual age-specific mortality rates over this period by the average life expectancy from diagnosis for MND of 27 months (Sach 1995, Lang 1996).

However, since 1997 multiple cause of death information has been available from the death certificate (associated causes as well as the underlying cause of death). For the 3 years 1997–1999 there were 635 male deaths in Australia where MND was listed as the underlying cause of death and an additional 170 male deaths where MND was listed as an associated cause of death. Therefore the mortality rates obtained above, which were based only on underlying cause of data information, were adjusted upwards by a factor of 1.27 (805/635) to allow for deaths where MND was listed as an associated cause rather than an underlying cause.

The next adjustment that needed to be made to these rates was that of the El Escorial factor. The only study that could be found which compares medically reported cases of MND against El Escorial confirmed cases was a Welsh study conducted in 1992 (James et al. 1994). In this study the El Escorial criteria were applied to 56 patients identified as having MND in the Welsh counties of South Glamorgan, Mid Glamorgan and Gwent (a combined population of 1,394,400 persons). When each of the 56 patients was classified according to the El Escorial criteria, the number of cases reduced from 56 (a prevalence of 4.02 per 100,000 population) to 38 (a prevalence of 2.73 per 100,000 population). Therefore, an adjustment El

Escorial factor of 0.68 (2.73/4.02), reflecting this study, was applied to each age-specific prevalence rate, resulting in El Escorial based prevalence rates.

Using the El Escorial based prevalence rates, the Australian community standard for MND was then calculated by multiplying the age-specific prevalence rates by the Vietnam veteran population in each age group (Table 3.3).

Table 3.3: Derivation of Australian community standard for motor neurone disease

Age group	El Escorial criteria based prevalence rate of MND (per 100,000 population)	Veteran population as reported in Morbidity Study	Expected no. of cases of MND in veteran population (confidence interval)
35–39	0.40	7	0
40–44	0.69	563	0
45–49	1.24	13,161	0.16
50–54	2.35	16,513	0.39
55–59	3.54	4,354	0.15
60–64	6.52	2,459	0.16
65–69	8.21	1,729	0.14
70 and over	12.32	1,244	0.15
Total	**—**	**40,030**	**1.2 (0–3.3)**

Given the limited data available on MND in Australia, this community standard is considered to be the most accurate estimate possible. However, it should be noted that the accuracy of this standard is dependent upon the accuracy of the recorded deaths data for MND, the appropriateness of the El Escorial factor based on the Welsh study, and the accuracy of the assumed interval between diagnosis with MND and death. Each of these introduces a level of uncertainty that cannot be measured statistically.

Based on these calculations the expected number of cases of MND among the veteran population (or Australian community standard) is 1.2, with a 95% confidence interval of 0–3.3 (Table 3.3).

Misallocation of conditions

The major reason why self-reported cases of MS and MND were not validated was the misinterpretation of these conditions by veterans, particularly in relation to MND. Examples of alternative conditions that veterans may have misinterpreted as MS or MND are listed in Table 3.4.

In some cases the veteran's doctor indicated on the survey form that they had suggested a possible diagnosis of MS or MND for veterans presenting with symptoms of a nervous disorder, such as a twitch or a tingling, numbness or a sore back. As a result the veteran answered in the positive for MS and MND because it had at one time been a possibility.

Table 3.4: Self-reported conditions misallocated to study conditions

Study condition	Alternative conditions misallocated
Motor neurone disease	Post traumatic stress syndrome (PTSD), Guillain–Barré syndrome, progressive supranuclear palsy (PSP), Reiter's disease, peripheral and autonomic neuropathy (diabetes related), malformations of the spinal cord
Multiple sclerosis	Sleep disorder, retrobulbar neuritis, spastic paraparesis, scoliosis, Devic's disease, Kearns-Sayre syndrome

Allocation of non-respondents and not able to be validated responses

In the validation process, responses from veterans and their children were classified as validated, not validated, not able to be validated, or non-responding (AIHW 1999). Five models have been used to illustrate the effect of including some of the not able to be validated and non-responding responses into the validated category. The five models decrease in their level of strictness for the validation of responses. Model 3 (see below) was adopted for the Validation Study, and therefore has been adopted for the MS and MND Study.

The components included to determine the estimated number of validated responses for each model are:

Model 1

(a) counting only positively validated responses; but

(b) excluding non-respondents.

Model 2

(a) counting positively validated responses; and

(b) including a prorated component of those responses not able to be validated due to a non-response from the clinician, or a clinician indicating there was insuffient information to confirm the condition—prorated according to the ratio of validated to not validated responses; but

(c) excluding non-respondents.

Model 3

(a) counting positively validated responses; and

(b) including a prorated component of those responses not able to be validated regardless of reason—prorated according to the ratio of validated to not validated responses; but

(c) excluding non-respondents.

Model 4

(a) counting positively validated responses; and

(b) including a prorated component of those responses not able to be validated due to a non-response from the clinician, or a clinician indicating there was insufficient information to confirm the condition—prorated according to the ratio of validated to not validated responses; and

(c) redistributing cases from non-responding veterans between validated, not validated and not able to be validated responses.

Model 5

(a) counting positively validated responses; and

(b) including a prorated component of those responses not able to be validated regardless of reason—prorated according to the ratio of validated to not validated responses; and

(c) including a prorated component of non responses—prorated according to the ratio of validated to not validated responses.

The assumption behind component (b) is that respondents have provided information available to them for validation in a manner confident of a likely positive response. However, the information has been insufficient for the Validation Study to validate the condition through its validation sources. It is therefore assumed that these responses can be counted as validated. Component (c) takes the same assumption but does not distinguish between the reasons for the inability to validate the condition.

Conditions whose estimated incidence is higher than expected from community rates when using Models 1 to 3 have a greater level of confidence associated with them than those only becoming statistically significant in Models 4 and 5, where there may be some doubt about the redistribution of the non-respondents. While it would be of great benefit to the Validation Study to have a greater response rate or further opportunity to seek alternative validation sources for those conditions not able to be validated, the redistribution of these conditions is reasonable but based on limited evidence.

Therefore, the number of expected cases of MS and MND in the study are based on Model 3, where the not able to be validated cases have been distributed proportionally between the validated and not validated cases.

4 Results

4.1 Survey response

An important part of the study is the level of response to the survey. To provide sufficient confidence in the results, the response rates must be high enough to produce statistically valid estimates, the data quality must be high and biases minimised or eliminated.

Considerable resources were allocated to achieve satisfactory response rates. These involved a series of mail-outs and telephone reminders which prompted veterans, their doctors and their neurologists.

Veterans

The initial mail-out of survey forms to veterans in the Validation Study in October 1998 resulted in a response rate of 41%, which was below that needed to produce statistically reliable estimates for all conditions. Consequently, two reminder mail-outs were conducted on 23 November 1998 and 9 February 1999. These mail-outs proved successful in lifting the response rates for all conditions excluding MS and MND. To increase the response rates for these two conditions, telephone calls were made over the period of 16–26 February 1999 to those veterans who had reported MS and MND, but who had not responded to the Validation Study. This lifted the overall response rate to 72%.

During the course of the Validation Study, it was decided to validate MS and MND in a separate study, after the Validation Study was released. When the MS and MND study was recommenced in March 2000, a further reminder mail-out was sent to those veterans who had reported MS or MND but who had not yet responded to the Validation Study. This final mail-out received few responses and so it was deemed by the Study Advisory Committee that no further follow-up of these veterans was warranted.

The final response rate (Table 4.1) was higher for MS than MND, but overall the response rates for both conditions were considered acceptable for statistical validity.

Table 4.1: Response rates for veterans' specific conditions

Condition	Number of conditions reported in Morbidity Study[(a)]	Number of responses received	Response rate (%)
MS	83	65	78.3
MND	126	80	63.5
Total	**209**	**145**	**69.4**

(a) The number of conditions reported here are derived from the electronic version of the Morbidity Study and vary slightly from the published results.

Doctors

Where the veteran had nominated that his validation source was a general practitioner or a hospital, a survey package was sent to this validation source, seeking the name of the veteran's neurologist if the source believed the veteran did or might have MS or MND. The

initial response to this survey was high, especially as a telephone call was made to each doctor a couple of days after the survey package had been sent. Only 10 doctors needed to be sent a reminder package, with most responding. One final reminder was made in November 2000 by the AIHW Medical Adviser. This resulted in all but one doctor responding, pushing the final response rate to 98%.

Neurologists

Fifty-one neurologists were sent a letter in June 2000, requesting copies of clinical notes regarding each veteran's diagnosis of MS or MND. This approach was well received and the response rate was excellent. The overall response rate was 80.4% after one reminder letter and two telephone prompts. One final prompt was made by the Chair of the Expert Neurologist Panel, Professor McLeod, resulting in a final response rate of 96%.

4.2 Validation of conditions

Panel classification results

The first objective of this study was to classify MS and MND into the three categories of clinically definite, clinically probable or clinically possible according to the Rose and El Escorial criteria. This classification was based on a review of the clinical notes by the Expert Neurologist Panel, but not every veteran who reported MS or MND was classified by the panel. Those veterans who were designated not validated (106 cases), either by themselves (43%), or their doctor/neurologist (57%), were excluded from the panel review. The high number of conditions not validated is due to misclassification and misinterpretation of the conditions in the Morbidity Study (see Section 3.3, page 16). Veterans for whom clinical notes could not be obtained were also excluded from panel review.

Table 4.2 shows the results for the 39 veterans whose review by the Expert Neurologist Panel led to classifications of clinically definite, probable or possible. Six of these 39 are veterans who have died and these are further discussed in the next section.

Table 4.2: Number of conditions classified by Expert Neurologist Panel by category

Condition	Clinically definite	Clinically probable	Clinically possible	Not validated	Not able to be validated	Total
MS	12	2	3	8	2	27
MND	2	—	—	10	—	12

Note: Both clinically definite and clinically probable are deemed to be validated.

Veterans' deaths since 1997

Of the 209 veterans who reported in the Morbidity Study that they had MS or MND, ten have since died. The methods used to assess these veterans differed depending on the information obtained for them. The process used is shown in Figure 4.1 and is discussed below.

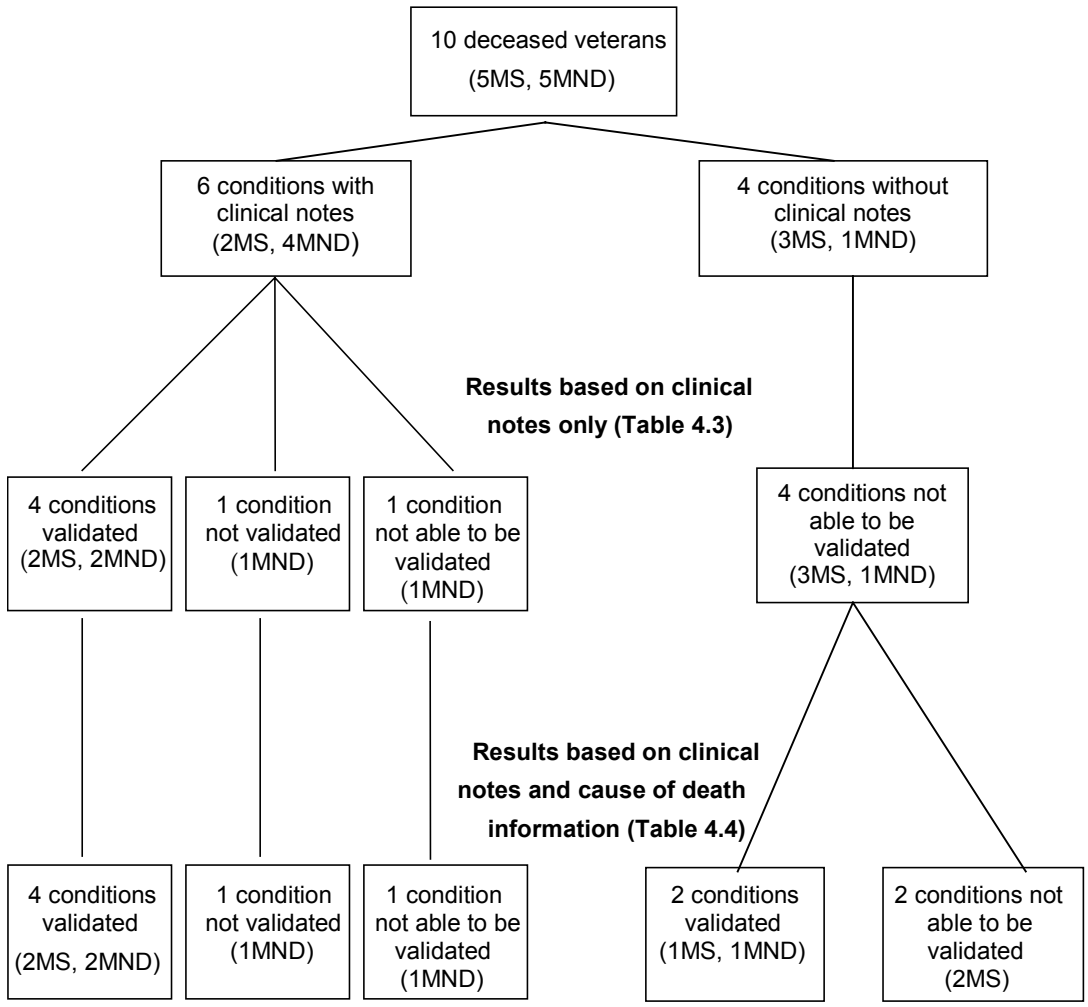


Figure 4.1: Flow diagram showing the validation process for veterans who have died since the 1997 Morbidity Study

In order for the veterans who have died to be considered validated according to the Rose or El Escorial criteria, their case must undergo the same process as the living veterans, i.e. their clinical notes must be obtained and assessed by the Expert Neurologist Panel. Therefore, where medical practitioners' names had been provided to the study by these veterans prior to their death, they were followed up in the same way as the living veterans. Where the names of medical practitioners had not been provided by the veterans prior to their death, medical records for these veterans were sought from DVA. As a result of these approaches to medical practitioners and DVA, clinical notes were obtained for six veterans who had died, but notes were not available for the remaining four veterans (Figure 4.1). Details for the six veterans with clinical notes available were assessed by the Expert Neurologist Panel. Four of them were deemed 'validated', one 'not validated' and one 'not able to be validated' (Figure 4.1). Since the clinical notes of these veterans underwent the assessment process they are included in the results based on clinical notes in Table 4.3.

The four veterans for whom clinical notes were not available are considered not able to be validated in the results based on clinical notes (Table 4.3). However, according to the National Death Index (NDI), two of these veterans had either MS or MND as the underlying

cause of death on their death certificate. Although these veterans were not assessed by the Rose or El Escorial criteria, the fact that they had MS or MND on their death certificate suggests that their doctors believed they had the reported condition. Therefore an additional result table has been produced which includes these two veterans as validated (Table 4.4). In these additional results, the deceased veterans with clinical notes (from above) are still included as four validated, one not validated and one not able to be validated. The deceased veterans without clinical notes are included in the additional results as two validated, with the other two remaining not able to be validated (Figure 4.1).

Validation of MS and MND in veterans

The purpose of this Validation Study was to compare the prevalence of MS and MND in Vietnam veterans with that of the Australian community standard. In estimating the number of veterans with MS and MND it is inappropriate to only count the number of validated responses as this does not take into account the responses that were not able to be validated, among which some valid conditions may exist. Therefore an adjustment has been made to account for this in the results, and is referred to as the 'estimated validated conditions'. The method of adjustment is described in Section 3.3 (Model 3).

The expected number of conditions, based on the Australian community standard, includes a 95% confidence interval. For the validated conditions to be considered statistically significantly higher or lower than the expected number at the 95% confidence level, the validated conditions should be outside the bounds of the confidence interval.

Results based on clinical notes only

A comparison of the number of validated conditions with the expected number of conditions, based on the Australian community standard and using the results from clinical notes only, found no significant difference between the prevalence of MS and MND in veterans and the Australian community (Table 4.3).

Table 4.3: Number of conditions reported by veterans, by validation status, based on clinical notes only

Condition	Validated[(a)]	Not validated[(b)]	Not able to be validated	No response	Estimated validated conditions	Expected no. of conditions (confidence interval)
MS	14	36	15	18	18	17 (9–26)
MND	2	70	8	46	2	1.2 (0–3.3)[(c)]

(a) Includes two cases of MS and two cases of MND where the veteran has died (Figure 4.1).

(b) Includes cases where the veteran, or the veteran's doctor or neurologist reported that the veteran did not have the condition.

(c) Due to the small numbers, the expected number of conditions includes one decimal place.

Results based on clinical notes and cause of death information

If deaths where the underlying cause of death on the death certificate are included as validated cases, there is still no statistically significant difference between the number of estimated validated conditions of multiple sclerosis and motor neurone disease for veterans and the Australian community standard (Table 4.4).

Table 4.4: Number of conditions reported by veterans, by validation status, based on clinical notes and cause of death information

Condition	Validated	Not validated	Not able to be validated	No response	Estimated validated conditions	Expected no. of conditions (confidence interval)
MS	15	36	14	18	20	17 (9–26)
MND	3	70	7	46	3	1.2 (0–3.3)[(a)]

(a) Due to the small numbers, the expected number of conditions includes one decimal place.

Impact of method of allocation of non-respondents and not able to be validated responses

In the validation process, responses from veterans and their children were classified as validated, not validated, not able to be validated, or non-responding (AIHW 1999). Five models have been used to illustrate the effect of including some of the not able to be validated and non-responding responses into the validated category (Section 3.3). The five models decrease in their level of strictness for the validation of responses. Model 3 was adopted for the Validation Study, and for the results shown above.

Regardless of the model used (Table 4.5), there is no significant difference for MS between the number of estimated validated conditions for veterans and the Australian community standard for the results based on clinical notes only. For MND, the difference between the number of estimated validated conditions for veterans and the Australian community standard for the results based on clinical notes only becomes significant in model 5. For models 1 to 4, there is no statistically significant difference (Table 4.5).

Table 4.5: Validation results using selected reallocation models and their significance level

Condition	Model 1	Model 2	Model 3	Model 4	Model 5	Expected no. of conditions
MS	14	16	18	21	23	17 (9–26)
MS including deaths	15	18	20	22	24	17 (9–26)
MND	2	2	2	3	4	1.2 (0–3.3)
MND including deaths	3	3	3	5	5	1.2 (0–3.3)
MS	—	—	—	—	—	
MS including deaths	—	—	—	—	—	
MND	—	—	—	—	High	
MND including deaths	—	—	—	High	High	

Notes

1. High–The estimated validated conditions are statistically significantly higher than the Australian community standard at the 95% confidence level.
2. Dashes indicate no statistically significant differences from the Australian community standard.
3. The report results use Model 5.

When the cause of death information is included, there is still no significant difference for MS between the number of estimated validated conditions for veterans and the Australian community standard for all five models. For MND, the difference between the number of estimated validated conditions for veterans and the Australian community standard is not significant for models 1 to 3, but becomes significant for models 4 and 5.

'New veterans' and 'new conditions'

'New veterans' are those who did not participate in the Morbidity Study, but sought to participate in this study. These 'new veterans' were accepted up until the end of the study in January 2001. 'New conditions' are conditions that have developed since the Morbidity Study in veterans who did participate in the Morbidity Study.

'New veterans' and 'new conditions' were not included in the results above, as this would have introduced selection bias (see Section 3.1). Instead their results are shown separately in the following table.

Table 4.6: Number of conditions of 'new veterans' and 'new conditions' by validation status

Condition	Validated	Not validated	Not able to be validated	Total
MS	4	0	0	4
MND	1	1	1	3

4.3 Conclusion

After all reported cases of MS and MND were followed up and classified, the number of validated conditions of MS and MND among veterans was substantially lower than the number reported in the Morbidity Study (Volume 1). This was believed to be due to misinterpretation of the terms MS and MND by veterans, particularly MND.

When the number of validated cases of MS and MND among veterans was compared with the expected number of conditions, based on the Australian community standard, no statistically significant difference was found between the prevalence of MS and MND in veterans and that of the general Australian community.

However, if reported cases of MND among deceased veterans are included as 'validated' where clinical notes were not available but MND is included as a cause of death on the death certificate, the estimated number of cases among veterans is at the upper limit of the 95% confidence interval for the Australian community standard.

It is recommended that caution be used in the interpretation of the MND results. The estimated Australian community standard for MND used in this study is considered to be the most accurate estimate possible, but it should be understood that a number of assumptions were made in calculating this standard (Section 3.3, page 15). These assumptions introduce a level of uncertainty that cannot be measured statistically, but they were necessary because of the lack of prevalence data for MND in Australia. Any margin of error in these assumptions will affect the Australian community standard, and may have the potential to change the conclusion that there is no difference between the prevalence of MND in veterans compared with the Australian community standard.

In the case of MS, the number of validated conditions among veterans is well within the 95% confidence interval for the community standard. Therefore, variations in the assumptions are unlikely to affect the conclusion of no statistical significance between the prevalence of MS for veterans and the Australian community standard.

Appendixes

Appendix 1 Veterans form
Appendix 2 Survey package to doctors
Appendix 3 Letter to neurologists
Appendix 4 Form sent to Expert Neurologist Panel
Appendix 5 Classification criteria checklists

Appendix 1 Veterans form

This form was sent in the survey package to veterans, seeking permission to validate their reported condition, and the name of the medical practitioner/practice/hospital treating their condition. The completed form was included in the doctor and neurologist packages to verify the veteran's consent to contact the veteran's medical practitioner.

VIETNAM VETERANS VALIDATION STUDY
IMPORTANT: PLEASE READ THE INFORMATION SHEET FIRST

1. Our records show that in the initial study you indicated that you have been diagnosed with the following medical condition:

Please indicate the year and place this condition was first diagnosed 19……. in (State/Territory) ……

If unsure of the exact year, please indicate an approximate period ……..

2a. To enable us to conform this condition through medical records, will you give us permission to obtain medical information (relating to this condition only) from a medical practitioner or hospital or consult disease registers?: **(Please tick)**

YES ☐ **If Yes, go to 3**

NO ☐ **If No, go to 2b**

2b. If **No**, would you prefer to contact the doctor yourself? In this case we will send you the medical from which you will need to either send or take to an appropriate doctor as soon as possible. **(Please tick)**

YES ☐ **If Yes, go to 4**

NO ☐ **If No, go to 4**

3. Please indicate an appropriate medical practitioner/practice/hospital with information about your condition.

(Note: if you cannot give us these details, please give any information that may help our follow-up)

PLEASE PRINT CLEARLY

Doctor's name ….……

Doctor's phone number ( )…….

Doctor's address Street …….

Suburb…… State ……Postcode……

If you have any documentation which may assist us in this study, it would be helpful if you enclose a copy with your reply.

PLEASE DO NOT SEND ORIGINALS

4. Your date of birth ……/……/19…..
Day Month Year

5. Can we contact you again if we need more details from you for this study **(please tick)** **YES** ☐ **NO** ☐

If Yes, what is your phone number ( ) ……..Home / Work **If No, go to 6**

Other contact details (e.g. fax, E-mail) ……

6. Your name and address:

Please correct the above details where necessary. If any information is missing, please write this in the space above including given names and any other names by which you are known. This will allow us to identify your relevant medical records more easily. **PLEASE PRINT CLEARLY**

7. **Signed** ……

Date ……./……./1998
Day Month Year

HELPLINE 1800 236 166

PLEASE SEND THIS FORM IN THE REPLY PAID ENVELOPE BY MARCH 26 TO:

REPLY PAID 1297
VIETNAM VETERAN VALIDATION STUDY
AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE
LOCKED BAG 8550
CANBERRA ACT 2601
The Institute will treat your answers with strict confidentiality

THANK YOU FOR YOUR PARTICIPATION.

AIHW
AUSTRALIAN INSTITUTE OF HEALTH & WELFARE

Appendix 2 Survey package to doctors

This package was sent to all doctors who were not neurologists, that is, general practitioners, other specialists and hospital medical record departments. The package included:

- Doctor letter
- Doctor form

Dear Doctor,

Vietnam Veterans Validation Study

Patient

Veteran

Self–reported condition

Motor neurone disease/multiple sclerosis

I am writing to you as part of the **Vietnam Veterans Validation Study**. This study aims to validate self reported conditions in Vietnam veterans. The AIHW has completed the main part of this validation study, which was released in November 1999. One of the recommendations of this study was to undertake a validation of multiple sclerosis and motor neurone disease in veterans. This was unable to be completed in the main body of the study due to the complexity of diagnosing these two conditions.

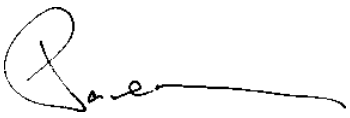
The veteran mentioned above has provided your name and their permission to approach you to help us validate their condition above. A signed patient consent form is attached. To this end could you please complete the enclosed form and return it by fax or mail by **April 14**.

Reimbursement of costs you incur in completing the survey can be made, including the cost of any consultation with the patient in relation to this study. We may contact you in the next few days to follow up this request. For further information on the study please contact the Helpline on 1800 236 166.

We should stress that any information you or your patients provide is collected under the strict confidentiality provisions of the Australian Institute of Health and Welfare Act (1987) and will not be used in a way that could identify individual patients, doctors or hospitals. It is important to note that this personalised information will not be released to the Department of Veterans' Affairs or any claims authority.

Your input into this landmark Australian study is vital in shaping policies for the best health care of veterans. Thank you for you cooperation.

Yours sincerely,



Dr Paul Magnus
Medical Adviser
28 March 2000

AUSTRALIAN INSTITUTE OF HEALTH & WELFARE

For health and welfare statistics and information

6A Traeger Court
Fern Hill Park
Bruce ACT

GPO Box 570
Canberra ACT 2601

Phone 02 6244 1000
Fax 02 6244 1299
http://www.aihw.gov.au

VIETNAM VETERANS VALIDATION STUDY
MEDICAL VALIDATION FORM–CONFIDENTIAL

To: Validation Source

Please correct any of these details if necessary

AIHW
AUSTRALIAN INSTITUTE OF HEALTH & WELFARE

1. DETAILS OF THE PATIENT OR FORMER PATIENT

Patient's name: **Address:**
Date of birth:
Study ID number:

2. VALIDATION

Diagnosis
According to our records this patient has reportedly been diagnosed with
Diagnosed condition

Year of diagnosis (approx): Place of Diagnosis:

From your own knowledge or medical records please complete (tick) the statements below.

1. This person has had **Diagnosed condition**

YES ☐ NO ☐ Not able to say ☐

If the person has not had **Diagnosed condition** but has had a similar condition or one that may be confused with it, please specify the condition……

Has your patient been assessed by a **neurologist**? YES ☐ NO ☐

If your patient has been referred to a neurologist, would you please provide their name and enough information to contact them below:

Name:……..……..… Address:……..……..……..……..……

Phone:……. ……..

State:……... Postcode: ……...

4. COMPLETING DOCTOR'S SIGNATURE AND OTHER INFORMATION

Name ……...
(if not the same as above)

Signature …….. Address ……..…

Date …../…../……. State …… Post code …..…….

FREECALL HELPLINE 1800 236 166
Dr Paul Magnus, Mr Phil Trickett
PLEASE RETURN AS SOON AS POSSIBLE TO THE REPLY PAID ADDRESS OR VIA FAX (02) 6244 1166

REPLY PAID 1297
LOCKED BAG 8550
AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE
CANBERRA ACT 2601

Appendix 3 Letter to neurologists

This letter was sent to all the neurologists provided by the veteran or their general practitioner, and requests copies of clinical notes to enable the Expert Neurologist Panel to validate the veteran's reported condition.

Dear Neurologist

Vietnam Veterans Validation Study

Patient

Veteran

Self–reported condition

Diagnosed condition

We write to you to seek your support as part of the Vietnam Veterans Validation Study. This study aims to validate selected self reported conditions from a 1997 survey of all Vietnam veterans. The Australian Institute of Health and Welfare (AIHW) has published the main part of this validation study and is now turning to the more difficult task of validating multiple sclerosis and motor neurone disease reported by veterans.

Because of the complexity of these two disorders the AIHW has formed an expert advisory panel of independent neurologists, of which one of us (Jim McLeod) is the Chair. The agreed standardised approach to validation is for the panel to classify all cases from clinical details supplied by neurologists who have seen the veterans. To classify MS we are using the Rose criteria and for MND, the World Federation of Neurology El Escorial criteria.

To this end we would much appreciate your sending us copies of any consultation reports or clinical notes that you feel would give us sufficient information to classify your patient named above. He or his General Practitioner has provided your name, and the veteran has provided his permission for us to approach you (see the attached patient consent form). **We would greatly appreciate it if you could send copies of relevant clinical notes in the envelope provided by 4 August. Reimbursement of costs you incur in doing this can be made.**

We would like to stress that this exercise is solely for the purpose of measuring the prevalence of multiple sclerosis and motor neurone disease among Vietnam veterans. Any information that you provide is collected under the strict confidentiality provisions of the Australian Institute of Health and Welfare Act (1987), and will not be reported in a way that could identify individual patients, doctors or hospitals. It is important to note that no personalised information will be released to the Department of Veterans' Affairs or any claims authority. The results of our classification will be returned to you and it is your decision as to whether you wish to pass this onto the veteran.

The study team may contact you in the next few weeks to follow up this request. For further information on the study please contact the Helpline on 1800 236 166 or myself (Jim McLeod) on (02) 9531 3385.

Yours sincerely,

Prof JG McLeod
FRCP, FRACP

Dr Paul Magnus
Medical Advisor (AIHW)

AIHW
AUSTRALIAN INSTITUTE OF HEALTH & WELFARE

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Appendix 4 Form sent to Expert Neurologist Panel

This form was used by the Expert Neurologist Panel to apply the Rose and El Escorial criteria to classify each of the veterans' conditions against the clinical notes provided by the veterans' neurologists.

VIETNAM VETERANS VALIDATION STUDY
MEDICAL VALIDATION FORM–CONFIDENTIAL

1. DETAILS OF THE PATIENT

Patient's name: **Study ID number:**

2. VALIDATION

Diagnosis

According to our records this patient has reportedly been diagnosed with

MULTIPLE SCLEROSIS

Year of diagnosis (approx): Last consultation date (approx):

3. CHECKLIST

	Yes	No	Cannot say
1. Both UMN and LMN signs in *three* regions	☐	☐	☐
2. Both UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs	☐	☐	☐
3. UMN *and* LMN clinical signs in only one region	☐	☐	☐
4. UMN-only clinical signs in two or more regions	☐	☐	☐
5. LMN clinical signs found rostral to UMN signs	☐	☐	☐
6. UMN-only clinical signs in one region	☐	☐	☐
7. LMN signs, defined by EMG criteria, in at least two limbs	☐	☐	☐
8. Other (ie non-MND) causes excluded by proper use of neuro-imaging and clinical laboratory protocols	☐	☐	☐

4. DIAGNOSIS

Based on the clinical notes, what is the diagnosis of the veteran?

DEFINITE MND ☐ NOT MND ☐

POSSIBLE MND ☐ UNABLE TO SAY/OTHER ☐

PROBABLE MND ☐

If UNABLE TO SAY/OTHER, do you suggest:

More information from the veterans neurologist ☐

A fresh clinical appraisal ☐

5. PANEL MEMBER'S SIGNATURE

Signature …….

Date …../…../…….

AIHW
AUSTRALIAN INSTITUTE OF HEALTH & WELFARE

VIETNAM VETERANS VALIDATION STUDY
MEDICAL VALIDATION FORM–CONFIDENTIAL

1. DETAILS OF THE PATIENT

Patient's name: **Study ID number:**

2. VALIDATION

Diagnosis

According to our records this patient has reportedly been diagnosed with

MOTOR NEURONE DISEASE

Year of diagnosis (approx): Last consultation date (approx):

3. CHECKLIST

	Yes	No	Cannot say
1. Relapsing and remitting course with at least two bouts separated by no less than 1 month	☐	☐	☐
2. Slow or step-wise progressive course extending over at least 6 months	☐	☐	☐
3. Documented neurological signs to accompany history	☐	☐	☐
4. Documented neurological signs attributable to more than one site of predominantly white matter CNS pathology	☐	☐	☐
5. Onset of symptoms between ages of 10 and 50	☐	☐	☐
6. Presents with only one neurologic sign commonly associated with MS	☐	☐	☐
7. Documented single bout of symptoms with signs of multifocal white matter disease with good recovery	☐	☐	☐
8. Objective neurologic signs insufficient to establish more than one site of CNS white matter pathology	☐	☐	☐
9. No better neurologic explanation than MS (possible/ probable/definite)	☐	☐	☐

4. DIAGNOSIS

Based on the clinical notes, what is the diagnosis of the veteran?

DEFINITE MS ☐
POSSIBLE MS ☐
PROBABLE MS ☐
NOT MS ☐
UNABLE TO SAY/OTHER ☐

If UNABLE TO SAY/OTHER, do you suggest:

More information from the veterans neurologist ☐
A fresh clinical appraisal ☐

5. PANEL MEMBER'S SIGNATURE

Signature …….

Date …../…../…….

AIHW
AUSTRALIAN INSTITUTE OF HEALTH & WELFARE

Appendix 5 Classification criteria checklists

These checklists were used by the Expert Neurologist Panel to classify each veteran's condition according to the Rose and El Escorial criteria.

El Escorial criteria

	YES	NO
1) Both UMN and LMN signs in *three* regions	☐	☐
2) Both UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs	☐	☐
3) UMN *and* LMN clinical signs in only one region	☐	☐
4) UMN-only clinical signs in two or more regions	☐	☐
5) LMN clinical signs found rostral to UMN signs	☐	☐
6) UMN-only clinical signs in one region	☐	☐
7) LMN signs, defined by EMG criteria, in at least two limbs	☐	☐
8) Other (i.e. non-MND) causes excluded by proper use of neuro-imaging and clinical laboratory protocols	☐	☐

Note: all boxes must be filled either yes or no

Definite: yes to 1 (regardless of other answers)

Clinically probable: no to 1 and yes to 2 (regardless of rest)

Laboratory supported: yes to 3, 7 and 8 **or** yes to 6, 7 and 8

Possible: yes to 3 and 8 and no to 7 or yes to 4 and 8 and not to 7 or yes to 5 and 8 and no to 7

Rose criteria

	Yes	No
1. Relapsing and remitting course with at least two bouts separated by no less than 1 month	☐	☐
2. Slow or step-wise progressive course extending over at least 6 months	☐	☐
3. Documented neurological signs to accompany history	☐	☐
4. Documented neurological signs attributable to more than one site of predominantly white matter CNS pathology	☐	☐
5. Onset of symptoms between ages of 10 and 50	☐	☐
6. Presents with only one neurologic sign commonly associated with MS	☐	☐
7. Documented single bout of symptoms with signs of multifocal white matter disease with good recovery	☐	☐
8. Objective neurologic signs insufficient to establish more than one site of CNS white matter pathology	☐	☐
9. No better neurologic explanation than MS (possible/probable/definite)	☐	☐

Note: all boxes must be filled either yes or no

Definite: yes to 1,3,4,5 and 9 **or** to 2,3,4,5 and 9

Probable: yes to 1,6 and 9 **or** to 7 and 9

Possible: yes to 1 and 9 **or** to 8 and 9

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