Australian Government
Repatriation Medical Authority

# Repatriation Medical Authority Guidelines for Researchers

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This document sets out the current standards for processes and procedures used by researchers when undertaking investigations for the purposes of assisting the consideration of sound medical-scientific evidence (SMSE) by the Repatriation Medical Authority (RMA). It is endorsed by the RMA and reviewed regularly.

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**WRITING BRIEFING PAPERS**

1. The assistance provided to the RMA by the medical researchers is focussed on identifying and evaluating the sound medical-scientific evidence (SMSE) relevant to the disease or injury under consideration. The suite of decision support papers includes:

    a) The main briefing paper summarising the SMSE relevant to the disease or injury under consideration;

    b) A summary of studies table or Forest plot, where relevant;

    c) A comparison table (a working document, comprising the suggested revisions to a Statement of Principles (SoP) with the content of the current SoP and suggestions for change and reasons for changes; or suggested factors and definitions for a new SoP); and

    d) Draft SoPs setting out the phrasing of the contents of the proposed SoPs.

2. There are standard templates for each of these documents and these must be used without variation of structure or alteration of formatting. Briefing templates are available in HPE Content Manager container 1605769.

3. There are also documents which provide standardised wording for factors and definitions. These documents are available in HPE Content Manager container 1302948 (hitherto referred to as the Standard Definitions and Factors container).

**Main briefing paper**

4. The purpose of the main briefing paper is to provide the information needed to make a decision as to whether there is evidence to support the inclusion of a factor for that condition, and if so at what standard. There may also be issues of dose and latency to decide.

5. The following standard subheadings are utilised in the main briefing paper:

***Current Statements of Principles***

6. The number/date of the current SoPs is stated, with a list of current factors. It is not necessary to copy the full wording of the factors in the current SoPs. The differences between the reasonable hypothesis (RH) and balance of probabilities (BoP) SoPs are highlighted in a table.

***Background***

7. This section summarises the reason for carrying out the investigation.

***Correspondence/submissions***

8. The researcher should list all submissions. This includes letters, requests for investigation and submissions. If the investigation is being undertaken because of a request from an eligible person or organisation, it is included in the section entitled “background”, and any subsequent correspondence or submissions are summarised here. For privacy reasons the name of the correspondent is not given; instead use initials or the term "a veteran" or "a widow" as appropriate.

9. Submissions may include an amount of material which is not peer-reviewed or not relevant. The researcher should examine the material provided and obtain full articles that appear as if they might be relevant or informative. The rationale for not obtaining information should be explained.

***Literature search***

10. See section on searching.

***Definition of disease or injury***

11. The current definition and ICD codes should be listed. Relevant definitions are provided from authoritative sources and adapted as necessary. The suggested definition is written in the comparison table rather than in the main briefing paper. ICD codes are included in the suggested definition if they correspond closely to the word definition. If there is poor correspondence between the ICD codes and the word definition, then their inclusion may cause confusion and it is preferable to omit them. If there is uncertainty about the use of ICD codes this can be discussed at the RMA meeting.

***Introduction***

12. The purpose of the introduction is to provide a *brief* overview of the main facts about the condition (usually no more than two pages). Some more detail may be required if it impacts on relevant decisions. For example, the definition may not be clear cut, or there may be factors that might be relevant to only some forms of the condition (for example, a certain histological subtype of a cancer).

13. Resources which are useful for giving good background information include *Harrison's Principles of Internal Medicine*, *UpToDate* and the *Oxford Textbook of Psychiatry*. There are various textbooks relevant to particular specialty areas in the RMA library. A Google search is often useful. For definitions, useful references include *Dorland's Medical Dictionary*, DSM-5 and the ICD codes.

***Factors***

14. If there is a current factor for a particular exposure, the wording of the factor and any associated definition should be included.

15. Where relevant and useful, there should be an indication or "sign-posting" of the major issues and the conclusions pertaining to each factor at the beginning of the presentation of evidence (without repeating all the evidence) in the Summary of Important Issues section. "Sign-posting" helps the reader understand where to direct the focus of his or her attention. For example, the researcher could state something like "While there is little disputation about the factor being causally related to disease x, there is considerable uncertainty in the literature about the dose/exposure required". Where a factor is complex, there may need to be a brief background explanation of what the factor is about, or difficulties with classification and measurement (e.g., what is meant by the term "organochlorines", how the term "sedentary" is defined and measured). Where there has been a request for review into the particular factor, this should be stated here.

16. In this section the papers that have been identified as relevant from your search are analysed separately, then the information from all the studies is synthesized in the

summary. The papers should be discussed in order of study type, from the highest quality to the lowest quality:

- Meta-analyses, systematic reviews
- Cohort studies (prospective studies first)
- Case-control studies
- Cross-sectional studies
- Case series, case reports.

17. General (non-systematic) reviews are of varying quality, but may be included before the other studies if they help to give an overview of the evidence or highlight important issues.

18. In the interests of efficiency, you should in the first instance obtain information from systematic reviews, meta-analyses, International Agency for Research on Cancer (IARC) monographs, Health and Medicine Division reports, Veterans and Agent Orange updates, UpToDate or other relevant reviews, where such information exists and provided that it is of good quality and from a reputable source. Further information may be necessary if such reviews are not recent, or if more detailed information about dose, latency or cessation periods is needed to formulate a factor. Information from case-control studies or cross-sectional studies may not be needed if there are a reasonable number of good quality cohort studies.

19. Some systematic reviews are very recent and comprehensive, and in that case there is no need to separately analyse the papers that were included in the review. However, there may be a need to separately obtain papers that were published since the review came out if it is not recent, or to obtain papers that were particularly influential or informative.

20. There are sometimes studies which don't fit the above categories. If the study design is distinctive, you may wish to include a separate heading, e.g., record linkage studies, case-cohort studies, nested case-control studies, case-time-control studies, genetic studies. On reading a paper it sometimes becomes apparent that the authors have categorised their study incorrectly. You should place it where you think it belongs and explain why.

21. Randomised controlled trials (RCTs) are seldom available in the field of causation, but can add to the coherence of an argument for or against causation. For example, if RCTs of vitamin D supplementation do not consistently increase bone mineral density, it can go against an argument for a causal association between vitamin D and osteoporosis (bearing in mind mechanism of action, adequacy of dosage and adherence to treatment).

22. Case reports can provide evidence for causation when a combination of the criteria below are met.

- a close temporal link between exposure and effect
- reversibility
- recurrence of symptoms or pathology on repeat exposure
- absence of likely alternative explanations

- multiple case reports (usually at least three, though one or two reports may be enough if they are convincing using the other criteria)
- a likely mechanism for the effect is known (biological plausibility)
- dose-response effect

23. Information in textbooks needs to be treated with caution, as it is often out of date by the time it is published, and broad lists of factors may be perpetuated without reference to the original research, or without consideration of the quality of the source.

24. PhD, Masters and Honours' theses are sometimes submitted by applicants. These documents are subject to a peer review process and published by universities, therefore the Authority considers them to be SMSE. The usual requirement for critical evaluation of the quality of the evidence applies. However, researchers are not required to search for and obtain these types of theses when conducting investigations.

25. Nearly all SoPs have a factor for "inability to obtain appropriate clinical management". However, this factor is not automatic. The management of the condition needs to be briefly documented, and consideration given as to whether such management would prevent worsening of the condition, or delay death from the condition.

26. Consider whether or not or any of the factors should be differentiated by gender. Different doses for males and females should be specified where there is sufficient evidence to do so.

27. In general, the RMA considers that exposures which can cause a condition may also permanently worsen that condition or increase the rate of progression beyond that normally expected. Some exceptions are cancers and infectious diseases, in which some causes logically only relate to the onset of the condition. Before any exposure can be included as a worsening factor, it is necessary to be satisfied that the exposure is able to be related to service after the onset of that condition (as per s196B VEA). For example, a chronic disease could not logically worsen an infectious disease of acute onset because it would have to occur after the onset of the infectious disease.

28. Drug factors require special consideration in situations where there is uncertainty about inclusion of a drug as a possible or probable cause of the disease under investigation. At its April 2018 meeting, the RMA agreed that in those situations the following criteria will be applied.

    *Basic criteria (first 3 plus 4 or 5) for limited association (RH)*

    (1) Plausible/reasonable temporal association- onset precedes effect within reasonable time frame for that particular drug-disease association; and
    (2) Dechallenge - recovery occurs on drug cessation; and
    (3) At least two independent reports (where no additional criteria are met); and
    (4) Other aetiologies possible but not likely (e.g., other diseases or other drugs); or
    (5) Plausible biological mechanism.

*Additional criteria (one or more) for suggestive or convincing association (RH and BoP)*

(6) Rechallenge - response recurs on repeat administration (may be to the same drug or the same class of drug).
(7) Recovery on administration of an antagonist (e.g., anticholinergics after organophosphate poisoning).
(8) Proven biological mechanism in that patient (e.g., drug dependent antibodies, positive hypersensitivity testing).
(9) A significant association is demonstrated in adequately powered epidemiological studies or randomised controlled trials.
(10) Other aetiologies excluded or highly unlikely.
(11) Characteristics of the patient are linked to the metabolism of the drug (e.g., presence of a relevant genetic polymorphism, renal or liver impairment).
(12) Dose-response effect (not always present, there may be a threshold for toxicity or an idiosyncratic reaction).
(13) Commonality of reports across different reviews (unless there is an indication of perpetuation of single case reports or the reviews are based on loose criteria).
(14) A large number (usually at least 10) of independent reports.
(15) The drug is not common and the effect is not common (so that the association is less likely to be coincidental).
(16) Length of time the drug has been on the market - all but rare adverse effects are likely to be known for older drugs, previously unreported effects may plausibly occur for newer drugs once they are marketed to a wider population.
(17) The drug is in the same class as a drug which has a probable association.

***Summary and conclusions***

29. The amount of information in this section will clearly depend on the number of studies available, and whether or not the conclusions are obvious. Where there are a number of studies and the outcome is not immediately evident, an assessment of the evidence in terms of the Bradford Hill criteria is usually the most useful method of summarising and weighing the material before you.

30. For example, you would summarise the number of cohort studies, and how many were significantly positive and how many were null. Then you would do the same with case-control studies, etc. You would comment on the strength of the effect in positive studies, and whether or not there were concerns with bias and confounding. You might comment whether studies showing lack of effect were underpowered. You would look for studies that measured a dose-response effect, and state how many showed such an effect. You would briefly describe the proposed biological mechanisms, or the lack of knowledge thereof. If it is difficult to judge the consistency of the evidence, you might make a Forest plot or a summary of studies table.

31. At the end of the summary you should state the conclusions in terms of the levels of evidence, including assigning a grade (e.g., the evidence for that particular association supports a judgement of a convincing/suggestive/possible causal association, or the evidence is too limited/inadequate/insufficient to suggest a causal association).

32. You should carefully consider at each review whether or not factors should be retained in either the RH or BoP SoPs. New evidence may alter the balance of the total body of SMSE, such that it may not reach the threshold for an RH or BoP factor. In the absence of new information, the available SMSE should still be evaluated afresh against the grading system.

***Referencing***

33. All material should be referenced. The standard referencing style in the body of briefing paper is numerical footnoting. In the summary and conclusions use author/date citations to support your statements (no need to footnote again). In general the full article is obtained, but if only the abstract is used in an investigation (.e.g., foreign language articles) then the reference must state “abstract only”.

34. Articles may be obtained by yourself online or by the administrative staff. They can use a printout of a search, or a printout of an abstract, or you can email them a list of requested articles. Let them know your name, the name of the condition and the date requested. Specific request forms are available if you prefer to use them. Make a note on the request if you require the abstract only.

35. You should allow 4 weeks to receive the requested articles, so to maintain a flow of work it is advisable to start searching for articles for a new investigation while completing a current investigation. In some circumstances articles may be needed more urgently and you should discuss this with the Principal Medical Officer or administrative staff. Such a circumstance might include follow up of a request from the RMA at a meeting for more information, or the need to finalise a briefing paper in time for an RMA meeting.

36. The reference to any material obtained from the internet must be entered by the administrative staff into the RMA Database and the relevant HPE Content Manager container, including the date the information was accessed. Therefore, if you download an article or internet page yourself, you must provide a pdf version of the document to the administrative staff.

37. A bibliography for each investigation should be compiled and added to the finalised briefing paper. This is most easily accomplished by transforming the footnotes. Ensure that the reference style in the footnotes matches the standard reference style. The bibliography is included in the briefing paper and saved in the appropriate investigation container so that the administrative staff can check the references against the database.

**Comparison Table**

38. A working document referred to as the comparison table is used during the RMA's consideration of an investigation. The document succinctly records the implications and recommendations arising from the main briefing paper and associated tables. This document is also used to record your grading of the evidence, summarise the reasons for changes, highlight issues for discussion and document directions given at RMA meetings.

39. For reviews of existing conditions, the comparison table lists the current condition definition, current factors and current factor definitions in the left hand column, and the proposed definition, factors and factor definitions in the middle column. The right hand column provides the grade. The comparison table also lists all factors for which

the evidence was examined but no risk factors were proposed, as well as any factors which are being removed on the basis of new evidence.

40. In the left hand column, indicate whether current factors are included in RH and BoP, and onset and worsening, and whether there are doses/time frame differences between RH and BoP.

41. In the middle column, indicate the following in a bolded heading: no change or a change to wording or dose, RH and BoP or RH only. If the factor is for onset only or worsening only, also specify this in the heading. The wording of the factor should provide doses/timeframes for each standard of proof, where such parameters are relevant. Proposed factors and definitions must be discussed with the supervising professor before the RMA meeting (see Interactions with Professors).

42. For a new condition the left hand column lists only the contended factor (e.g., smoking) and the middle column is used to list the proposed factors and definitions as usual.

43. Issues and reasons are recorded above the SoP definition and factors - issues in left hand column and reasons in the right hand column. The progress of the investigation is updated by the Deputy Registrar at the beginning of the table.

44. In the third column of the table you should record your assessment of the level or grade of evidence next to the proposed factor, after discussion with and approval by the lead Professor. Grades are assigned by the researchers after a critical appraisal and assessment of the available evidence pertaining to each contended risk factor. They serve as a guide to RMA members in determining whether factors should be included in the RH instrument, both instruments or neither instrument. The grades, and the basis for each grade, can be found in the "levels of evidence" document in the Researcher Procedures container 1303660.

***Consistency of factor wording and doses***

45. To ensure consistency across SoPs, factors and definitions should be written in the same style and format as that of previous similar factors and definitions, unless the evidence requires that the factor be updated or differentiated.

46. Documents describing standard factors and standard definitions are kept up to date and can be found in the Standard Definitions and Factors container (HPE content manager container 1302948).

47. Documents in this container include tables of SoPs with common factors, such as smoking, mefloquine, dioxin and radiation. So that these tables are kept up to date, you should alert the Deputy Registrar of any changes or additions which affect factors in the tables whenever an investigation is finalised.

48. It is also important to search previous SoPs for similar factors, paying particular attention to the wording of more recent SoPs. SoPs can be searched by two methods: a factor search on the RMA website, or a word or phrase search in the HPE Content Manager container entitled “All operative SoPs for searching”. It is usually best to search by both methods, as one or other method may not be comprehensive.

49. Some commonly used factors and definitions have been the subject of discussion at RMA meetings and a standard form of words has been endorsed. These factors are

listed in Appendix 3 of these guidelines and should be used unless the evidence suggests otherwise.

50. Advice was provided at the December 2016 RMA meeting concerning the use of notes. Notes have legal standing and are to be used when a part of a definition provides useful but non-essential information. This applies to both disease definitions and factor definitions. Guidance on the application of notes may be sought from the Principal Medical Officer, the Deputy Registrar or the Registrar.

51. When referring to eponymous conditions in factors, the possessive apostrophe 's' should be omitted, unless there are SoPs which use the possessive form. For example, there is a SoP for "Parkinson's disease", so factors should continue to be spelled this way rather than changing to "Parkinson disease".

52. The two standards of proof allow for different doses in RH and BoP, but the amount and quality of available evidence may affect the ability to differentiate between the suggested factors. Where there is detailed information concerning the relationship between the exposure dose and the condition, it may be possible to accurately determine a dose consistent with the reasonable hypothesis standard, i.e., which is associated with a small but measurable increase in risk. When such information is absent, the lowest dose in the range can be applied to the reasonable hypothesis standard. For risk factors with less information, a reliable distinction between the doses for the two standards is harder to make based on empirical evidence and it may not be possible to make a differentiation between the doses suggested in the RH and BoP standards.

**Summary of studies table**

53. A summary of studies table is sometimes useful, but is time consuming to construct and not necessary for every investigation. It may be useful where the information is complex and inconsistent, making it difficult to get a clear picture of the weight of the evidence in relation to a particular factor. The column layout allows the study design, study numbers, control for confounding and main results to be presented in a clear and simplified way.

**Forest plots**

54. These may be useful when the evidence is complex and inconsistent and a visual representation of the data would assist understanding of consistency. Results should be grouped by exposure type, study design, or in whatever grouping best enhances the meaning of the data. The Researcher Procedures container 1303660 has an example of how to make a Forest plot in Excel using the chart wizard and the standard stock plots.

55. It is inherent in these graphs that much qualitative information is not represented. It may be useful to add additional relevant information in text windows or in the author-date label on the x-axis.

56. The final plot or plots must be copied into the main briefing paper.

## SEARCHING

### *Databases*

57. The databases most commonly used are *PubMed*, *Ovid Medline* and *PsycInfo*. The latter two are available via the DVA intranet. ToxNet is a public website which may be useful when researching toxic substances.

### *Standard database searches*

58. The standard Medline search for doing an initial "sweep" of the literature is "condition/ epidemiology, aetiology, chemically induced." It is often useful to limit your initial search to systematic reviews and meta-analyses, as a way of scoping the information. The initial search is usually limited to humans and English language, but you may choose not to have these limits if you need to consider animal studies or foreign language abstracts/articles.

59. For a new condition generally do a ten year search. For reviews of existing conditions generally do a search from the year before the existing SoPs were determined to the present. For both new conditions and reviews, your research may indicate that older articles are important and require consideration.

60. After the initial search, additional specific searches for the condition and each factor of interest are conducted. Searches should be updated if your initial search was not conducted in the last month.

61. Check the HPE Content Manager articles container for the condition you are researching for any recent, relevant articles that may have been added since the last investigation (key papers may have been saved there for later review).

62. Printouts of search results do not need to be retained, but your search strategy should be clearly described, especially if it varies from the standard method.

### *Checklist of common factors*

63. There are a number of factors which are of particular interest to veteran and military groups. These should be routinely considered, depending on the type of condition you are investigating. They include: alcohol, smoking, dioxin/herbicides, pesticides, solvents, fuels, benzene, asbestos, stressors, mefloquine/antimalarials, firefighting, per- and poly-fluoroalkyl substances (PFAS), repetitive trauma, ionising radiation and non-ionising radiation.

64. Any mefloquine, passive smoking, benzene, radiation or dioxin-related factors should be brought to the attention of the administrative staff if they are worded in such a way that they need to be tagged so that they will be identified on a factor search on the RMA website. For example, a search for the term mefloquine will not identify factors for "quinoline derivatives" unless these SoPs are tagged.

### *Standard reference texts*

65. Some standard references which should be checked where relevant to the condition are listed below. Most are available in the RMA library or on the internet.

- IARC Monographs on causes of cancer;
- ATSDR (Agency for Toxic Substances and Disease Registry) toxicological profiles for toxic substances;

- The latest update of the US VAO (Veterans and Agent Orange) review of the literature concerning the health effects of exposure to dioxin-contaminated herbicides and dioxin;
- UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) for the health effects of ionising radiation;
- The Australian Study of Health Outcomes in Aircraft Maintenance Workers (SHOAMP) for solvents;
- The US Institute of Medicine's Gulf War and Health series of literature reviews of the health effects of fuels, infectious diseases, stress, depleted uranium, pyridostigmine bromide, sarin, vaccines, traumatic brain injury and other Gulf War related exposures;
- The World Cancer Research Fund/American Institute of Cancer Research and IARC Handbooks of Cancer Prevention for cancer risks related to diet, obesity and physical activity;
- The US Surgeon General's reports on the health consequences of exposure to tobacco smoke and environmental tobacco smoke.

**INTERACTIONS AND CORRESPONDENCE**

## Interactions with Professors

66. One of the RMA members is designated the "lead Professor" for each investigation. The lead professor-researcher arrangement enables the detailed review and epidemiological analysis of the SMSE with respect to the disease or injury in question to proceed in a timely and effective manner.

67. An initial planning discussion with the lead Professor should occur in order to scope the investigation before the detailed investigation is commenced.

***Preparation for initial planning discussion***

68. If the condition has a current SoP the researcher should prepare for the initial discussion by:

    -reviewing the previous comparison tables and the previous briefing paper;
    -conducting a standard database search of the condition to identify any contentious issues that may have arisen since the previous investigation; and
    -reviewing the correspondence that has been received about the condition to see if any issues raised require attention (peruse the Investigation container including the *Correspondence – Destruction permitted* folder).

69. If the condition is non-SoP the researcher should conduct initial standard database searches and review standard texts to gain an understanding of the condition and any potential contentious issues.

70. The researcher should consider developments in the literature which may bear on nomenclature, status as a SoP condition, relationship to other SoPs and whether the RMA has varied current factors in other SoPs in a relevant manner. The RMA may have already flagged these issues in its decision to investigate.

***Scoping document and discussions***

71. In conjunction with the Principal Medical Officer (PMO), a scoping document about the proposed investigation should be prepared and circulated to the lead Professor. The scoping document should be in the form of a draft comparison table and should include the established factors, the likely contentious issues and the new issues arising in the literature which may require greater focus.

72. The purpose of the scoping paper is to identify where most effort should be spent in evaluating the literature and writing up the findings. Little effort should be spent on the reinvestigation of established factors, unless the scoping search throws up unexpected information about the factor, its dose or some other relevant matter. Most effort needs to be spent on investigating and writing up possible new factors and proposed variations of existing factors.

73. Once the scope is settled, additional discussions with the lead Professor and PMO may occur in the course of the investigation as required. In particular during the investigation the nature of the issues requiring investigation and the focus of the investigation may change. This may lead to variation of the delivery date and overall work plan. When such becomes apparent further discussion should be held with the PMO and the lead Professor and the Registrar notified so that the work plan can be amended.

***First Draft – Final Papers***

74. There should be a discussion of the two briefing papers at the first draft stage with the lead Professor.

75. Initially, the comparison table with proposed factors and proposed definitions will be given to the PMO and Deputy Registrar for review and to the Registrar for drafting approval.

76. Following approval, the comparison table should be delivered to the lead Professor with the main briefing paper for consideration. These papers should be available on HPE Content Manager.

77. Following discussions with the lead Professor as necessary and endorsement, the two briefing papers are tabled at the RMA meeting. Those discussions may include further discussions with the PMO and the Registrar as necessary.

***Meetings***

78. It is the responsibility of the researcher to arrange any meetings with the lead Professor, which are usually by teleconference or videoconference but may occur in the course of meeting days. Additional discussions or email clarification may be necessary between the initial RMA meeting and subsequent RMA meetings. The outcome of any discussion may be reflected in changes to the comparison table or a file note, depending on the circumstances.

79. In addition, the researcher may seek guidance from the PMO or the Registrar.

**Interactions with outside sources**

80. Occasionally the RMA may consider that expert advice is necessary to clarify a technical issue, or to seek current clinical opinion. The information request should be

filed, as should any responses. A summary of the advice should be recorded in the main briefing paper.

## MEETING AND POST-MEETING PROCEDURES

### Presentation of briefing papers at RMA meetings

81. The researcher and supervising Professor give a brief introduction which could include the following: reason for the investigation, plus any defining features of the condition that need to be highlighted (e.g., particular problems with the quality of the evidence, or issues with defining the condition or a major change in thinking about the nature or causes of the condition).

82. The researcher goes through the comparison table, starting with the definition, then current factors, then new factors, then factors that were investigated but not proposed. There is no need to discuss in detail the factors that are not changing. There is no need to read out the factor or go through the evidence in detail unless it is something you are seeking clarification about.

83. Factors “investigated but not proposed" are listed at the end of the table. You need not go through each factor, but you should highlight any contentious factors (e.g., factors which were reviewed as part of a request).

84. Look to the Chair to signal that the discussion of the factor/issue/SoP is complete or for any final directions.

### Briefing papers

85. Briefing papers should be sent to the Deputy Registrar on the Monday which occurs two weeks before the RMA meeting is scheduled, to allow time for the material to be distributed and considered by all of the RMA members. An electronic version and the HPE Content Manager version of each document should be sent. Discussions with Professors should occur well before this deadline so that no late papers are presented.

86. Feedback from advisers on operational issues is usually received in the week before the RMA meeting and discussed by researchers as a group during that week. Each researcher should give consideration to the comments pertaining to his or her investigation prior to the researcher and RMA meetings. Following the view concluded at the researcher meeting, the Deputy Registrar will draw up a document incorporating the stakeholder view and the Secretariat's response for consideration by the Authority members. Further discussion with your lead Professor may be required before the meeting if changes have been proposed following the discussion. The content of those discussions will inform what is included in the Deputy Registrar's document.

87. At the RMA meeting the relevant researcher is responsible for recording the decisions that have been taken with regard to a particular condition. The decisions are documented in the comparison table in a different coloured font, using the subheading “month meeting” to indicate the words that were agreed to, whether or not the factors are in RH only, RH and BoP or neither, and whether or not the factor is for both onset and worsening. If there are any changes to the factor or definition, then the whole factor and definition should be copied below the proposed factor. This makes the exact wording that has been approved clear for the Professors and drafters. The templates for comparison tables provide the correct format for

documenting meeting decisions (see container 1605769). Where a change to a proposed factor is significant or important, the reason should be documented in the table.

88. Normally the comparison table will only need to record one decision. If there are multiple decisions over several meetings, copy the original factor so that it is opposite the latest agreed factor. This is so that the comparison between the old factor and the new factor can be easily made.

89. The final row of the post-meeting comparison table should state which factors or sub-parts of factors have been removed. If a factor has been removed but subsumed by another factor, then this should be stated. The post-meeting comparison table is sent to the Deputy Registrar for drafting the SoPs for that condition, which will appear at the next RMA meeting. The Deputy Registrar drafts the SoPs presented to the RMA meeting for second mention and approval by the Authority. These drafts are based on the updated comparison table. The responsible Medical Researcher will be asked to check and affirm that the draft is accurate.

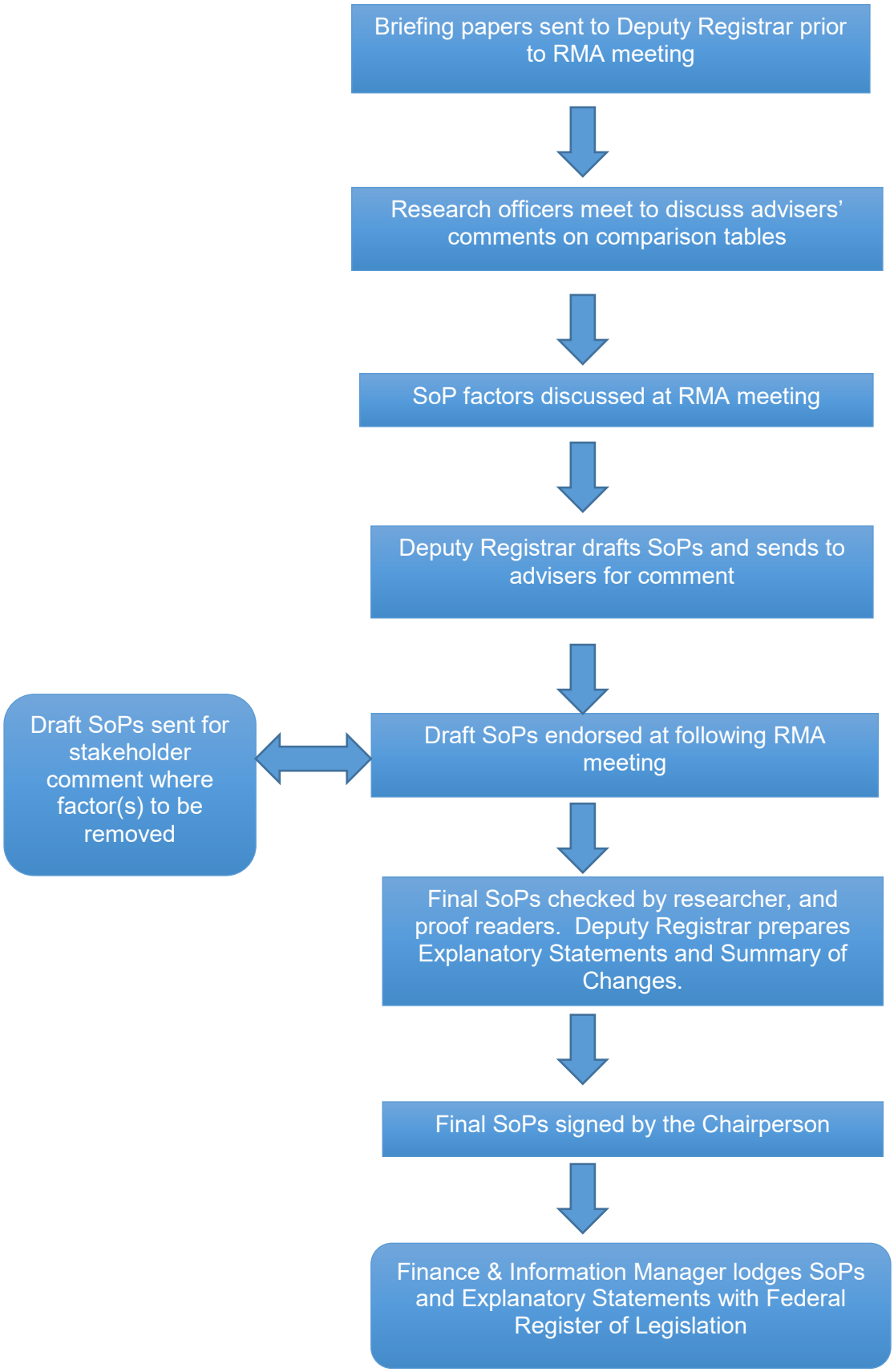
90. The briefing paper and comparison table, should be updated and finalised and sent to the Deputy Registrar well before the meeting at which the draft SoPs are considered (ideally within a week of the meeting at which they were considered). If the grading of a factor has been changed at the direction of the RMA, the change should be reflected in the briefing papers. If a draft SOP has gone out for stakeholder consultation due to the removal of an existing factor, it is the Medical Researcher's responsibility to ensure that the briefing papers and the amended comparison table are updated and provided to the Deputy Registrar well before the meeting at which the SoPs will be determined.

91. A separate bibliography should be prepared and stored in the appropriate HPE Content Manager container for that investigation. The administrative staff use the bibliography to check that all articles have been entered into the RMA database before preparing a reference list for that condition.

92. The finalised versions of the papers are available to the Authority members at the meeting at which the SoPs are determined by the RMA. For the purposes of reviews by the SMRC, the main briefing paper, the comparison table and, if completed, a summary of studies table comprise the information that was available to the RMA.

93. In preparing all documentation, researchers should be mindful that any document may potentially be subject to public scrutiny or may be the subject of legal consideration. It is important that the writing is of a high standard and that attention is paid to professional-looking formatting in the finalised documents, including correction of errors, removal of template prompts and unnecessary spaces, updating of footers, and inclusion of the bibliography. If an additional briefing paper has been developed and presented subsequent to the main briefing paper, it must be incorporated into one finalised briefing paper.

## APPENDIX 1 FLOWCHART FOR SOP PROCESSING PROCEDURES



## APPENDIX 2 GLOSSARY/ABBREVIATIONS

| | |
|---|---|
| BoP | balance of probabilities |
| CI | confidence interval |
| DVA | Department of Veterans' Affairs |
| ESO | Ex-Service Organisation |
| IARC | International Agency for Research on Cancer |
| ICD | International Classification of Diseases |
| OR | odds ratio |
| RH | reasonable hypothesis |
| RMA | Repatriation Medical Authority |
| RR | relative risk |
| SMRC | Specialist Medical Review Council |
| SMSE | sound medical-scientific evidence |
| SoP | Statement of Principles |

## APPENDIX 3 STANDARD WORDING FOR SPECIFIED FACTORS AND DEFINITIONS

There are standard forms of words for some factors and definitions. Over the course of the year these may change, so always check the standard definitions and factors documents (HPE Content Manager reference 1374904R and 1374905R) for the most recent version.

- Infectious disease SoPs
- Standard radiation factors
- Genetic risk factors and genetic disorders
- Smoking factors in cancer SoPs
- Obesity factors
- Immunosuppression factors
- Periods of one month
- Chronic kidney disease and chronic renal failure
- Dietary factors
- Harmonisation of ingredient names
- Drug lists
- Wording of transplantation factors and immunosuppressive drug definitions in cancer SoPs

### Infectious disease SoPs

A standard approach for infectious disease SoPs was agreed at the February 2020 RMA meeting as listed below. The following recommendations are to be implemented for infectious diseases SOPs whenever a new SOP is created, or an existing SOP is revised. The recommendations do not apply to diseases which are defined as having an infectious aetiology but for which there is not a requirement in the definition to specify a particular organism, such as osteomyelitis.

There should be good documentation in the underlying Briefing Paper of the evidence and reasoning to support the inclusion of an additional clinical onset factor. The clinical worsening factors should be checked to ensure that they are not already covered by the generic inability to obtain appropriate clinical management factor.

1. The title of an infectious disease SOP should always include the term infection. For example, hepatitis A would become hepatitis A infection. An exception to this rule may occur when the infection is widely known by a commonly used name, such as malaria.
2. The definition of diseases specific to an organism should use one of two types of wording, in which x is the name of the organism:
    a) Means an infection caused by x; or
    b) Means an illness caused by infection with x, followed by the symptoms and signs which characterise the illness.
3. The definition should not require specific types of testing, unless there are particular reasons to do so.

4. Factors are one of four categories:
   (i) an exposure factor;
   (ii) a proxy for exposure;
   (iii) additional clinical onset factor;
   (iv) clinical worsening.

**Standard radiation factors**

Standing rules for radiation factors were agreed upon by the RMA in 2011 and modified at the October 2016 RMA meeting in respect of therapeutic radiation factors. Revisions to the definition of cumulative equivalent dose were accepted at the August 2017 RMA meeting. There is a set of rules for radiation factors in cancer SoPs and another set of rules for radiation factors in non-cancer SoPs.

***Cancer SoPs***

*Solid cancer factor*

*having received a cumulative equivalent dose of at least 0.1 [BOP 0.5] sievert of ionising radiation to the [affected organ/region] at least five years [BOP ten years] before the clinical onset of malignant neoplasm x;*

*Leukaemia factor*

*having received a cumulative equivalent dose of at least 0.01 [BOP 0.05] sievert of ionising radiation to the bone marrow at least one year [BOP two years] before the clinical onset of leukaemia x;*

***cumulative equivalent dose** means the total dose of ionising radiation received by the particular organ or tissue from external exposure, internal exposure or both, apart from normal background radiation exposure in Australia, calculated in accordance with the methodology set out in Guide to calculation of 'cumulative equivalent dose' for the purpose of applying ionising radiation factors contained in Statements of Principles determined under Part XIA of the Veterans' Entitlements Act 1986 (Cth), Australian Radiation Protection and Nuclear Safety Agency, as in force on 2 August 2017.*

Note 1: Examples of circumstances that might lead to exposure to ionising radiation include being present during or subsequent to the testing or use of nuclear weapons, undergoing diagnostic or therapeutic medical procedures involving ionising radiation, and being a member of an aircrew, leading to increased levels of exposure to cosmic radiation.

Note 2: For the purpose of dose reconstruction, dose is calculated as an average over the mass of a specific tissue or organ. If a tissue is exposed to multiple sources of ionising radiation, the various dose estimates for each type of radiation must be combined.

***Non-cancer SoPs***

*Circulatory disease*

Two factors, one quantitative and one qualitative.

*having received a cumulative equivalent dose of at least 0.5 sievert [1 sievert BoP] of ionising radiation to the affected organ [latency] before the clinical onset/worsening of disease x;*

*undergoing a course of therapeutic radiation for cancer, where the affected organ was in the field of radiation, [latency] before the clinical onset/worsening of disease x;*

*Non-circulatory disease*

Only a qualitative factor, unless there is evidence for a quantitative factor as well.

*undergoing a course of therapeutic radiation for cancer, where the affected organ was in the field of radiation, [latency] before the clinical onset/worsening of disease x;*

Generally no latency period, on the grounds that effects could be prompt if an organ was directly exposed to high doses. However, if the mechanism was by fibrosis then a latency period of 1 to 2 years might be appropriate. Depending on the evidence for a particular condition, a longer latency period might be warranted.

**Genetic risk factors and genetic disorders**

It was agreed at the April 2011 RMA meeting that genetic risk factors would be included if they met the tests listed below. It was further agreed at the December 2012 RMA meeting that the above criteria would also apply to genetic disorders.

(i) the condition would not preclude entry to service; *and*

(ii) the condition could be worsened by some service-related factor; *or*

(iii) the condition could be worsened by inability to obtain appropriate clinical management.

**Smoking factors in cancer SoPs**

To maintain consistency of wording and doses in factors, the researcher should refer to the smoking relativities table and include the table with the briefing papers. When determining doses for new smoking factors, refer to doses for other factors in the table to ensure that dose relativities are consistent with other conditions with similar relative risks.

A consistent approach is taken to the assessment of cessation periods for smoking factors. Studies which assess cessation will report the number of years it takes for the relative risk to return to null, compared to never smokers. Where there is more than one study, there may be a category which is common to most studies. There is usually some uncertainty about number of years because of the size of the categories (which can range from 5 to 20 years).

In general:

(i) the cessation period for the BoP standard should reflect the majority of the evidence; and

(ii) the cessation period for the RH standard can be relaxed by five years in most cases (possibly ten years in some cases), to allow for uncertainty in the data.

## Obesity factors

### *Cancer SoPs*

It was agreed at the October 2014 RMA meeting that a standard form of words be used for obesity factors in cancer SoPs, unless the evidence suggests otherwise. An overweight factor might be considered if there is strong evidence to suggest effects at this level.

*being obese for at least five years [ten years BoP] within the 20 years before the clinical onset of malignant neoplasm of x;*

### *Non-cancer SoPs*

It was agreed at the February 2015 RMA meeting that a standard form of words be used for obesity factors in non-cancer SoPs, unless the evidence suggests otherwise. It was also agreed that the definition of being obese or overweight should be amended to remove reference to "an increase in body weight by way of fat accumulation. Any latency periods should reflect the evidence.

(i) for factors where mechanical effects are likely to be the predominant mechanism:
*being obese at the time of the clinical onset of condition y;*

(ii) for factors where systemic effects are likely to be the predominant mechanism:
*being obese for at least five years [no difference RH and BoP] within the x years before the clinical onset of condition y;*

(iii) For all obesity factors, the definition of being obese is as below. Waist circumference may be added to the definition of being obese if the evidence supports it.

***being obese*** *means having a Body Mass Index (BMI) of 30 or greater.*

*Note:* ***BMI*** *is also defined in the Schedule 1 - Dictionary.*

***BMI*** *means* $W/H^2$ *where:*

*(a) W is the person's weight in kilograms; and*

*(b) H is the person's height in metres.*

## Immunosuppression factors

The following factor and definitions were adopted at the December 2014 RMA meeting and modified slightly at the February 2015 RMA meeting. They should be used unless the evidence suggests a different wording.

*being in an immunocompromised state as specified at the time of the clinical onset/worsening of disease x;*

***immunocompromised state as specified*** means *a condition of substantially lowered immune function, such as would occur in the following conditions or circumstances:*

*(a) being treated with an immunosuppressive drug;*
*(b) having a haematological or solid organ malignancy;*
*(c) having chronic renal failure;*
*(d) having infection with human immunodeficiency virus;*
*(e) having severe malnutrition; or*
*(f) undergoing solid organ, stem cell or bone marrow transplantation.*

Note: ***chronic renal failure*** and ***immunosuppressive drug*** are also defined in the Schedule -1 Dictionary.

*immunosuppressive drug* means a drug or an agent which results in substantial suppression of immune responses.

*Note: Examples of an immunosuppressive drug include:*
*(a) chemotherapeutic agents used for the treatment of cancer;*
*(b) corticosteroids, other than inhaled or topical corticosteroids;*
*(c) drugs used to prevent transplant rejection; and*
*(d) tumour necrosis factor-α inhibitors.*

***chronic renal failure*** *means (see updated definition below).*

### Periods of one month

A standard way to express periods of one month was agreed at the June 2015 RMA meeting. Where duration of exposure is concerned, the factor should be expressed as 4 weeks. Where the exposure must have occurred within a certain time period, the factor should be expressed as 30 days. Examples are given below:

*living or working in a hostile or life-threatening environment for a period of at least four weeks before the clinical onset of posttraumatic stress disorder;*

*having a cerebrovascular accident involving the brainstem within the 30 days before the clinical onset of trigeminal neuropathy;*

### Chronic kidney disease and chronic renal failure

The RMA agreed to adopt standard factors and definitions in future SoPs at its February 2016 meeting. The factor and definition of chronic kidney disease will progressively replace current factors for chronic renal failure. The factor and definition of chronic renal failure will progressively replace current factors for end-stage renal disease.

***Chronic kidney disease***

*having chronic kidney disease before the clinical onset of disease x;*

***chronic kidney disease*** *means an abnormality of kidney structure or function that has been present for at least three months.*

*Note:* ***an abnormality of kidney structure or function*** *is also defined in the Schedule -1 Dictionary.*

***an abnormality of kidney structure or fu**nction means:*

*(a) having a glomerular filtration rate of less than 60 mL/min/1.73 $m^2$; or*
*(b) having kidney damage, as evidenced by renal biopsy, imaging studies, albuminuria, urinary sediment abnormalities or other markers of abnormal renal function; or*
*(c) having had a kidney transplant.*

***Chronic renal failure***

*having chronic renal failure before the clinical onset of disease x;*

***chronic renal failure** means:*

*(a) having a glomerular filtration rate of less than 15 mL/min/1.73 m2 for a period of at least three months; or*
*(b) a need for renal replacement therapy (dialysis or transplantation) for treatment of complications of decreased glomerular filtration rate which would otherwise increase the risk of morbidity and mortality; or*
*(c) undergoing chronic dialysis.*

**Dietary factors**

The RMA agreed to adopt standard wording for dietary factors at its February 2016 meeting.

For protective factors:

*an inability to consume an average of at least x grams per day of any combination of fruit and vegetables, for at least five consecutive years within the 20 years before the clinical onset of disease x;*

For risk factors:

*consuming an average of at least x grams per day of processed meat product, for at least five consecutive years within the 20 years before the clinical onset of disease x;*

**Harmonisation of ingredient names**

From April 2016 the Therapeutics Goods Administration (TGA) will be updating some medicine ingredient names used in Australia to align with names used internationally. The RMA is adopting the same policy for drug factors, to be applied progressively to SoPs from April 2016. A list of affected ingredients is available on the TGA website at https://www.tga.gov.au/updating-medicine-ingredient-names-list-affected-ingredients

**Drug lists**

At the February 2020 RMA meeting, it was agreed that drugs should be listed separately in drug lists, unless there is evidence that the entire class of drugs is causally associated with the condition under investigation. Examples of common drugs used within a class may be given in brackets.

**Wording of transplantation factors and immunosuppressive drug definitions in cancer SoPs**

The RMA agreed at its February 2020 meeting to adopt a generic transplantation factor and immunosuppressive drug definition in cancer SoPs.

Transplantation factors in cancer SOPs should include the explicit mention of the use of immunosuppressive drugs. For example:

*taking an immunosuppressive drug for organ or tissue transplantation before the clinical onset of malignant neoplasm of the organ/site.*

***organ or tissue transplantation*** *means:*

*(a) the transplantation of all or part of an organ or tissue; or*
*(b) the transplantation of a substance obtained from an organ or tissue.*

The definition of being treated with an immunosuppressive drug (whether or not the drugs are being used in relation to transplantation) should include temporal duration, proximity and latency, provided the relevant data can be obtained from the sound medical-scientific literature. Where this information is available, the preferred format would be as follows:

***taking an immunosuppressive drug*** *means taking a drug or agent which results in substantial suppression of immune responses:*

*(a) for a cumulative period of least x months [duration] before the clinical onset of malignant neoplasm of the organ/site; and*
*(b) where the first treatment occurred at least y months before [latency] the clinical onset of malignant neoplasm of the organ/site; and*
*(c) where that exposure has ceased, the clinical onset of malignant neoplasm of organ/site has occurred within z years of cessation [proximity].*

*Note: Examples of an immunosuppressive drug include:*

*(a) chemotherapeutic agents used for the treatment of cancer;*
*(b) corticosteroids, other than inhaled or topical corticosteroids;*
*(c) drugs used to prevent transplant rejection; and*
*(d) tumour necrosis factor-α inhibitors.*

In any event these three issues should be specifically addressed in the Briefing Paper.