Australian Government

Repatriation Medical Authority

Repatriation Medical Authority
Guidelines for Researchers

Contents

Writing briefing papers 1
Main briefing paper 1
Current Statements of Principles 1
Background 1
Correspondence/submissions 1
Literature search 2
Definition of disease or injury 2
Introduction 2
Factors 2
Summary and conclusions 4
Referencing 5
Comparison Table 5
Consistency of factor wording and doses 6
Searching 7
Databases 7
Standard database searches 7
Checklist of common factors 7
Standard reference texts 8
Interactions and correspondence 8
Interactions with Professors 8
Preparation for initial planning discussion 8
Scoping document and discussions 9
Interactions with outside sources 9
Meeting and post-meeting procedures 9
Presentation of briefing papers at RMA meetings 9
Briefing papers 10
Appendix 1 Flowchart for SOP processing procedures 12
Appendix 2 Glossary/Abbreviations 13
Appendix 3 Standard wording for specified factors and definitions 14
1) Infectious disease SOPs and factors concerning infectious disease 14
Factors concerning infectious disease 15

2) Standard radiation factors 15
Cancer SOPs 15
Non-cancer SOPs 16
3) Genetic risk factors and genetic disorder SOPs 16
4) Smoking factors in SOPs 17
5) Obesity factors 18
Cancer SOPs 18
Non-cancer SOPs 18
6) Immunosuppression factors 19
7) Wording of transplantation factors and associated definitions in cancer SOPs 19
8) Chronic kidney disease and chronic renal failure 20
Chronic kidney disease 20
Chronic renal failure 21
9) Dietary factors 21
10) Harmonisation of ingredient names 21
11) Drug factors and lists 21
12) Periods of one month 24
13) Generic exposure factors 24

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.

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 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

    c) Draft SOPs setting out the phrasing of the contents of the proposed SOPs.

Main briefing paper

2. 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.

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

Current Statements of Principles

4. 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

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

Correspondence/submissions

6. The researcher lists 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.

7. Submissions may include an amount of material which is not peer-reviewed or not relevant. The researcher examines the material provided and obtains full articles that might be relevant or informative.

Literature search

8. See section on searching.

Definition of disease or injury

9. The current definition and ICD (International Classification of Disease) codes are 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

10. The purpose of the introduction is to provide a brief overview of the main facts about the condition. 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).

11. 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. A Google search is often useful. For definitions, useful references include *Dorland's Medical Dictionary*, DSM-5 and the ICD codebook.

Factors

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

13. 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.

14. 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.

15. 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.

16. 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.

17. 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 have been published more recently, or to obtain papers that are particularly influential or informative.

18. 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.

19. 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).

20. 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)
    - a dose-response effect

21. 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.

22. 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.

23. 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.

24. 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.

25. 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 *Veterans' Entitlements Act 1986*). 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.

26. 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 specific criteria should be applied. Details of these criteria can be found in Appendix 3 – Paragraph 11. *Drug factors and lists*.

Summary and conclusions

27. 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.

28. 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.

29. 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).

30. 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. Conversely, the evidence may have strengthened. In the absence of new information, the available SMSE should still be evaluated afresh against the grading system.

Referencing

31. 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".

32. 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. Make a note on the request if you require the abstract only.

33. You should allow 4 weeks to receive the requested articles. 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 (PMO) 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.

34. 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.

35. 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

36. 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.

37. 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.

38. The wording of the proposed 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).

39. 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.

40. Issues and reasons are recorded above the SOP definition and factors - issues in left hand column and reasons in the right hand column.

41. 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 "RMA Practices and Procedures" document in the Researcher Procedures Container 1303660 or on the RMA website.

Consistency of factor wording and doses

42. 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.

43. 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).

44. Documents in this container include tables of SOPs with common factors, such as smoking, mefloquine, dioxin and radiation.

45. 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 often useful to search by both methods, as one or other method may not be comprehensive.

46. 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.

47. 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 or factor provides useful but non-essential information.

48. 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 spelt this way rather than changing to "Parkinson disease".

49. 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.

Searching

Databases

50. 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. Another public website, *PubChem* provides chemical synonyms and has sections on "Toxicity" and "Associated Diseases and Disorders" which are cross-referenced with articles in PubMed.

Standard database searches

51. 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.

52. 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.

53. After the initial search, additional specific searches for the condition and each factor of interest are conducted.

54. 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).

55. 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

56. 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.

57. Any mefloquine, passive smoking, benzene, radiation or dioxin-related factors should be brought to the attention of the administrative staff in case 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 factors are tagged.

Standard reference texts

58. Some standard references that should be checked if they are 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

59. 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.

Preparation for initial planning discussion

60. 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 any correspondence or submissions that have been received about the condition to see if any issues raised require attention

61. 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.

62. 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

63. In conjunction with the PMO and the legal team, a scoping document about the proposed investigation should be prepared. 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.

64. Once the scope is settled, additional discussions with the PMO and legal team 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. *First Draft – Final Papers*

65. There should be a discussion of the two briefing papers, the main briefing paper and the comparison paper, at the first draft stage with the lead Professor together with the PMO. The documents are updated following the discussion with the lead Professor.

66. Prior to that discussion, the comparison table with proposed factors and proposed definitions will be discussed with the PMO and the legal team.

Interactions with outside sources

67. Occasionally the RMA may consider that external 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

68. 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).

69. 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.

70. 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).

Briefing papers

71. 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.

72. 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 clear the exact wording that has been approved. Where a change to a proposed factor is significant or important, the reason should be documented in the table.

73. Normally the comparison table will only need to record one decision. If a factor is changed at multiple meetings, use a different coloured font to record the change for each meeting.

74. 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 in terms of words, doses, punctuation, differences between RH and BOP and use of onset and worsening factors.

75. 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.

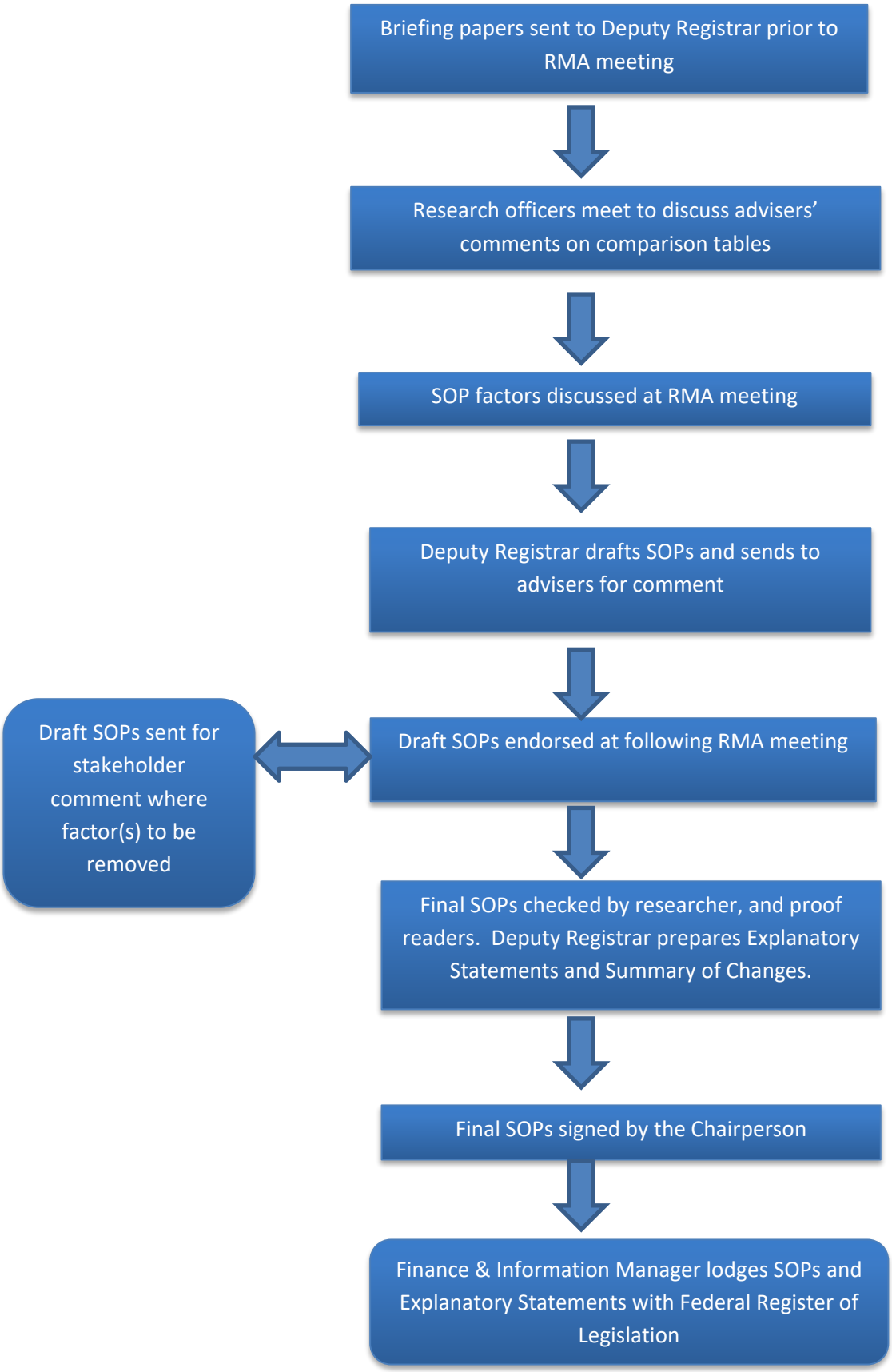
76. A separate bibliography should be prepared and stored in the appropriate HPE Content Manager container for that investigation. The administrative staff use the bibliography to check that all articles have been entered into the RMA database before preparing a reference list for that condition.

77. 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 andthe comparison table comprise the information that was available to the RMA.

78. 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 the RMA website for the most recent version and the variations of factors that may exist.

1) Infectious disease SOPs and factors concerning infectious disease
2) Standard radiation factors
3) Genetic risk factors and genetic disorder SOPs
4) Smoking factors in SOPs
5) Obesity factors
6) Immunosuppression factors
7) Wording of transplantation factors and associated definitions in cancer SOPs
8) Chronic kidney disease and chronic renal failure
9) Dietary factors
10) Harmonisation of ingredient names
11) Drug factors and lists
12) Periods of one month
13) Generic exposure factors

1) Infectious disease SOPs and factors concerning infectious disease

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 ca used by x; or
    b) Means an illness caused by infection with x, followed by the symptoms and signs which characterise the illness.
3. Factors in infectious disease SOPs are one of four categories:

(i) an exposure factor;
(ii) a proxy for exposure;
(iii) additional clinical onset factor;
(iv) clinical worsening.

Factors concerning infectious disease

Infectious disease factors included in SOPs should generally follow the standard wording "having infection with", although there will be variations in latency/cessation periods, or if the factor refers to a particular circumstance or specified list. Examples are given below.

Standard infection factor:

having infection with y virus before [within the z days/weeks/months before] the clinical onset/worsening of *disease x*;

Example:

having infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within the three months before the clinical onset of deep vein thrombosis;

Examples of varied wording of infectious disease factors included in SOPs:

having a *Streptococcus pyogenes* infection of the pharynx, tonsils or skin within the 30 days before the clinical onset of psoriasis;

having an infection from the specified list of infections before the clinical onset of spinal adhesive arachnoiditis;

Note: ***specified list of infections*** is defined in the Schedule 1 – Dictionary.

2) 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 5 years [BOP 10 years] before the clinical onset of malignant neoplasm of the *organ/site*;

Note: ***cumulative equivalent dose*** is defined in the Schedule 1 – Dictionary.

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.

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 1 year [BOP 2 years] before the clinical onset of *leukaemia x*;

Note: ***cumulative equivalent dose*** is defined in the Schedule 1 – Dictionary.

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*;

Note: ***cumulative equivalent dose*** is defined in the Schedule 1 – Dictionary.

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 is required, 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.

3) Genetic risk factors and genetic disorder SOPs

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 below criteria would also apply to determining SOPs for 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.

4) Smoking factors in SOPs

To maintain consistency of wording and doses in factors in cancer SOPs, the researcher should refer to the smoking relativities table (1374913R) and include the table with the briefing papers. When determining doses for new smoking factors, refer to doses in 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.

The standard smoking factor in all SOPs should include the dose, and where the evidence is available, should also include a latency period and a cessation period. The dose may be expressed in pack-years or the equivalent thereof in other tobacco products. Additional wording may be added with regard to whether the person is a current smoker.

Examples of smoking factors and associated definitions as finalised in April 2021 are given below.

Example of standard smoking factor with dose expressed as pack-years:

having smoked at least y pack-years of tobacco products before the clinical onset/worsening of *disease x*;

having smoked tobacco products:

(a) in an amount of at least x pack-years before the clinical onset/worsening of *disease x*; and
(b) commencing at least y years before the clinical onset/worsening of *disease x*; and

if smoking has ceased before the clinical onset/worsening of *disease x*, then that onset/worsening occurred within z years of cessation;

Note: ***one pack-year*** is defined in the Schedule 1 - Dictionary.

one pack-year means the amount of tobacco consumed in smoking 20 cigarettes per day for a period of 1 year, or an equivalent amount of tobacco products.

Note 1: An equivalent amount of tobacco products is 7,300 grams of smoking tobacco by weight, either in cigarettes, pipe tobacco or cigars, or a combination of same. For pipe tobacco, cigars or combinations of multiple tobacco types, 1 gram of tobacco is considered to be equal to one cigarette.

Note 2: Pack-years are calculated by dividing the number of cigarettes smoked per day by 20 and multiplying this number by the number of years the person has smoked. For example, smoking 10 cigarettes per day for 10 years is equal to 5 pack-years, and smoking 40 cigarettes per day for 10 years is equal to 20 pack-years.

Example including dose expressed as cigarettes per day:

having smoked tobacco products:

(a) in an amount of at least 10 cigarettes per day or the equivalent thereof in other tobacco products; and
(b) commencing at least y years before the clinical onset/worsening of *disease x*; and

if smoking has ceased before the clinical onset/worsening of *disease x*, then that onset/worsening occurred within z years of cessation;

Note: ***cigarettes per day or the equivalent thereof in other tobacco products*** is defined in the Schedule 1 - Dictionary.

cigarettes per day or the equivalent thereof in other tobacco products means:

(a) cigarettes, pipe tobacco or cigars, alone or in any combination; and

(b) 1 gram of cigar, pipe or other smoking tobacco (including roll your own smoking tobacco) is equivalent to one tailor made cigarette.

5) 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. Waist circumference can be added to the definition of being overweight or obese if the evidence supports it.

being obese for at least five years [ten years BOP] within the 20 years before the clinical onset of malignant neoplasm of the *organ/site*;

Note: ***being obese*** is defined in the Schedule 1 – Dictionary.

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.

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. Waist circumference can be added to the definition of being overweight or obese if the evidence supports it.

<u>For factors where mechanical effects are likely to be the predominant mechanism</u>:

being obese at the time of the clinical onset of *condition y*;

Note: ***being obese*** is defined in the Schedule 1 – Dictionary.

<u>For factors where systemic effects are likely to be the predominant mechanism</u>:

being obese for at least 5 years [no difference RH and BOP] within the x years before the clinical onset of *condition y*;

Note: ***being obese*** is defined in the Schedule 1 – Dictionary.

Definition of being obese

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.

6) 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) having a haematological or solid organ malignancy;
(b) having chronic renal failure;
(c) having infection with human immunodeficiency virus;
(d) having severe malnutrition;
(e) taking an immunosuppressive drug; 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).

7) Wording of transplantation factors and associated definitions in cancer SOPs

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

Transplantation factors in cancer SOPs should include the explicit mention of the use of immunosuppressive drugs if there is evidence that immunosuppression is the main mechanism. For example:

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

Note: ***organ or tissue transplantation*** and ***taking an immunosuppressive drug*** are defined in the Schedule 1 – Dictionary.

organ or tissue transplantation means the transplantation of:

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

The definition of taking 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) if that exposure has ceased before the clinical onset of malignant neoplasm of *organ/site*, then that onset 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.

Where immunosuppression is not the main mechanism, the transplantation factor should be worded as follows:

undergoing organ or tissue transplantation, excluding corneal transplant, before the clinical onset of malignant neoplasm of the organ/site;

Note: ***organ or tissue transplantation*** is defined in the Schedule 1 – Dictionary.

organ or tissue transplantation means the transplantation of:

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

8) 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 disease. The factor and definition of chronic renal failure will progressively replace current factors for end-stage renal disease.

At its meeting in December 2021, the RMA revised the factor and definition concerning chronic kidney disease.

Chronic kidney disease

having chronic kidney disease at the time of the clinical onset of *disease x*;

chronic kidney disease means:

(a) having a glomerular filtration rate of less than 60 mL/min/1.73 m^2 for at least 3 months; or
(b) having albuminuria for at least 3 months; or
(c) having kidney damage, as evidenced by renal biopsy, imaging studies, urinary sediment abnormalities or other markers of abnormal renal function; or
(d) having had a kidney transplant.

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

albuminuria means an albumin to creatinine ratio of at least 3 milligrams/millimole.

Chronic renal failure

having chronic renal failure at the time of the clinical onset of disease x;

Note: ***chronic renal failure*** is defined in the Schedule 1 - Dictionary.

chronic renal failure means:

(a) having a glomerular filtration rate of less than 15 mL/min/1.73 m^2 for a period of at least 3 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.

9) Dietary factors

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

For protective factors:

inability to consume an average of at least x grams per day of any combination of fruit and vegetables, for at least 5 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 5 consecutive years within the 20 years before the clinical onset of *disease x*;

10) 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

11) Drug factors and lists

At its April 2018 meeting, the RMA agreed that in situations where there is uncertainty about inclusion of a drug as a possible or probable cause of the disease under investigation, 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.

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. Generally, three examples of common drugs used within a class may be included following the class name.

All drug factors should start with "taking a drug", along with the relevant time frames, with no requirement to mention 'class of drugs' if these are included in the list. The drugs, either classes or individual drugs, are included in a specified list of drugs. Where drug lists are long (> 20), a table of drugs will be formatted during the drafting process and included in a Schedule 2 – Drugs. The drug factor may also relate to a specific drug or a specific class of drugs.

There is a standard generic drug factor for idiosyncratic drug reactions, although there are variations depending on the particular condition. Examples are given below.

taking hydroxyurea for at least the x months before the clinical onset/worsening of *disease x*;

taking an immune checkpoint inhibitor or interferon alfa within the x years before the clinical onset/worsening of *disease x*;

taking a drug from the specified list of drugs within the y days before the clinical onset/worsening of *disease x*;

Note: ***specified list of drugs*** is defined in the Schedule 1 – Dictionary.

specified list of drugs means:

(a) alpha-adrenoceptor agonists;
(b) alprazolam;
(c) amantadine;
(d) amphetamines including methamphetamine and 3,4-methylenedioxymethamphetamine; or
(e) anabolic-androgenic steroids.

Generic drug factor

taking a drug which is associated in the individual with the development/worsening of *disease x* during drug therapy and either:

(a) the improvement of *disease x* within y months of discontinuing or tapering drug therapy; or
(b) the redevelopment/worsening of *disease x* on rechallenge with the same drug; and

where taking the drug continued for at least the z days before the clinical onset/worsening of *disease x*;

Continuity of drug use

For non-malignant diseases, drugs can be one of 3 categories:

1. triggers for disease (don't need to be continually taken);
2. causes of injury (don't need to be continually taken); or
3. pharmacological causes of disease (need to be taken continually as condition is reversible).

With regard to the reversible effect of a drug, since the RMA cannot make factors for temporary departure from the physiological normal (except where it causes death), the factor should have a caveat such as taking a drug which cannot be ceased or substituted.

The standard generic drug factor for idiosyncratic drug reactions can be modified in this circumstance, although there are variations depending on the particular condition (see the Standard Factors file (HPE CM 1374905R) for additional options).

Examples of factors where the drug effect is reversible are given below:

taking a drug specified in the Schedule 2 - Drugs of this Instrument, that cannot be ceased or substituted, for at least the X days before the clinical onset of *disease x*;

Modified generic drug factor

taking a drug that cannot be ceased or substituted and which is associated in the individual with:

(a) the development of *disease x* within X days of first taking the drug; and
(b) the redevelopment of *disease x* on rechallenge with the same drug;

taking a drug that cannot be ceased or substituted and which is associated in the individual with the development/worsening of *disease x* during drug therapy and either:

(a) the improvement of *disease x* within y months of discontinuing or tapering drug therapy; or
(b) the redevelopment/worsening of *disease x* on rechallenge with the same drug; and

where taking the drug continued for at least the z days before the clinical onset/worsening of *disease x*;

Malignant disease

Drug factors can be complex as there are many variables that can be included, particularly for malignant conditions. Factors concerning taking a drug for a malignant condition may include:

1. dose (related to duration of taking the drug or the pharmaceutical dose);
2. proximity to the onset of the condition; and
3. latency;

if the relevant data can be obtained from the sound medical-scientific literature. Drug taking may be continuous or cumulative. The wording of the factor will depend on the evidence that is available. Specific examples are provided as follows:

taking an acid-suppressing drug from the specified list of acid-suppressing drugs for a cumulative period of at least 1 year within the 5 years before the clinial onset of malignant neoplasm of the stomach, and where the last dose of the drug was taken at least 1 year [latency] before the clinical onset of malignant neoplasm of the stomach;

taking a combined oral contraceptive pill for a continuous period of at least 3 years, commencing at least 5 years before the clinical onset of malignant neoplasm of the organ/site, and if taking the drug has ceased before the clinical onset of malignant neoplasm of the organ/site, then that onset occurred within 15 years of cessation;

taking a non-topical non-steroidal anti-inflammatory drug, excluding aspirin, on at least 15 days per month for at least 10 years before the clinical onset of malignant neoplasm of the kidney;

12) 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 4 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;

13) Generic exposure factors

With the refinement of the smoking factors in 2021, the wording of factors for other exposures (e.g., chemical agents) should be expressed and formatted in the same way where there is evidence for dose, and latency with or without cessation. Examples are given below:

inhaling, ingesting or having cutaneous contact with *chemical agent:*

(a) for a cumulative period of at least x hours, within a consecutive period of y years before the clinical onset/worsening of *disease x*; and
(b) commencing at least z years before the clinical onset/worsening of *disease x;* and

if that exposure has ceased before the clinical onset/worsening of *disease x*, then that onset/worsening occurred within x years of cessation;

<u>If no cessation period</u>

inhaling, ingesting or having cutaneous contact with a chemical agent:

(a) for a cumulative period of at least x hours, within a consecutive period of x years, before the clinical onset/worsening of *disease x*; and
(b) commencing at least x years before the clinical onset/worsening of *disease x*;