Government of **Western Australia**
Department of **Health**

Guidelines for the Investigation of Cancer Clusters in Western Australia

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Abbreviations

ADGPH	Assistant Director General Public Health
CAAC	Cluster Assessment Advisory Committee
CAT	Cluster Assessment Team
CDC	Centers for Disease Control and Prevention, USA
DoH	Department of Heath, Western Australia
EA	Environmental Assessment
GP	General Practitioner
HRA	Health Risk Assessment
PE	Preliminary Evaluation
RE	Research Evaluation
SA1	Statistical Area 1
SA2	Statistical Area 2
SE	Secondary Evaluation
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
TE	Tertiary Evaluation
WA	Western Australia

Executive summary

A cancer cluster is the occurrence of a greater than expected number of cancer cases within a group of people in a geographical area over a period of time. Cluster assessment is a scientific process to determine if there is evidence of an increased number of cancer cases and a biologically plausible causal agent/s for the disease.

In the past decade, there were an increasing number of reported suspected cancer clusters from the communities and workplace in Western Australia. The investigation of such clusters was carried out by different parts of the health system such as Epidemiology Branch, Cancer Registry and population health units at health services. However, there were no Departmental procedures that could be followed to conduct systematical investigations and address community's concern; and the roles and responsibilities for each stakeholder were not clearly defined.

The purpose of these guidelines is to provide an efficient, coordinated, methodical and multidisciplinary approach to a response by officers of the Department of Health, Western Australia (DoH) after receiving concerns from the community, health professionals or others about potential cancer clusters. These guidelines outline a systematic process to follow in all circumstances and detailed methods/procedures required to assess a cancer cluster.

The development of the Guidelines was based on guidelines from other agencies such as the Centers for Disease Control (CDC), Queensland Health, Australian National Health and Medical Research Council, and European and other health authorities in developed countries.

The Guidelines propose the cancer cluster settings, key roles in cluster investigation, role of the DoH in cluster assessment, governance, four phases of evaluation and associated detailed procedures. The proposed four phases are primary evaluation (initial contact and response to an inquiry), secondary evaluation (epidemiologic assessment and health risk assessment), tertiary evaluation (detailed epidemiological and environmental health assessment) and an optional research evaluation (feasibility of conducting research study and ongoing surveillance). Depending on the assessment results, the investigation may end at any phase. Criteria for decision making for proceeding or ceasing a phase at conclusion of each phase are also described.

1.0 Introduction

1.1 Background

A cancer cluster is the occurrence of a greater than expected number of cancer cases within a group of people in a geographical area over a period of time[1,2]. The identification of a cluster using this definition does not necessarily mean there is a causal agent, because some cancer clusters occur simply by chance. In these situations, clusters are not the result of a single, external cause; instead, the cluster reflects coincidental grouping among individuals who have been diagnosed with cancer. It does, however, indicate the need to assess whether the cluster can be related to factors other than chance, including:

1. **Occupational and environmental exposures**: Although an identifiable cause may or may not be found, a suspected cancer cluster is more likely to be confirmed as a cluster rather than a coincidence, if the cluster involves the following three traits:
   - a large number of cases of one type of cancer
   - a rare type of cancer
   - a large number of cases of a type of cancer in an age group that is not usually affected by that cancer type.

2. **Better access to health care**: Residents from one geographic area may be more likely to be screened for cancer compared to residents from another area, so a cluster exists because more cases of cancer are being diagnosed earlier than in other areas, and so such cancer clusters do not reflect a truly elevated cancer risk in a geographic area.

3. **Clustering of lifestyle behaviours:** Tobacco use, lack of physical activity, diet and other behaviours strongly impact cancer risks, so a cluster may exist because of unhealthy lifestyle behaviours in the cluster setting compared to other settings.

Cluster assessment is a scientific process to determine if there is evidence of an increased number of cancer cases and a biologically plausible causal agent/s for the disease. Most suspected cancer clusters turn out, on detailed investigation, not to be true clusters. Occasionally, however, cluster investigations have led to the discovery of new exposure pathways related to cancer aetiology, such as with angiosarcoma, bladder cancer and vaginal

clear-cell adenocarcinoma. Most of these studies are related to occupational or pharmaceutical exposures, rather than exposures within a community setting.

A suspected cancer cluster can be reported to a state or local health department and may be suspected when an individual (the *informant*) reports that several family members, friends, neighbours, or co-workers have been diagnosed with cancer. Following the report of a suspected cluster, public health officials evaluate the situation and may initiate a response (*cluster investigation*). A perceived clustering of health events and in particular cancer is usually associated with a great deal of anxiety and stress from involved communities (the *study community* as well as the *wider community*), so these investigations continue to be a very important and necessary public health responsibility, with good risk communication being an essential component. It is recommended that a *cluster assessment team* (CAT) maintain communication and an ongoing collaborative relationship with the informant and the study community throughout the process.

The documentation and implementation of established guidelines provide a resource that can instruct the conduct of cluster investigations undertaken by DoH and guide stakeholders involved in the investigation. The guidelines can also facilitate collaboration between public health officials, support agencies, media and the general public. Many public health agencies worldwide have published guidelines and protocols for investigating clusters of non-communicable health diseases. While development of these guidelines has been informed by those established by other agencies (such as the Centers for Disease Control (CDC) and Queensland Health), they are not specific to Western Australia (WA) in terms of data access, data quality, or state-specific communication needs. Establishing guidelines for WA will standardise the investigation process, and promote efficient and informed communication among all stakeholders, as well as the community. In addition, the guidelines will help instruct, support and educate individuals completing surveillance or analytic work required in such investigations.

The need for these guidelines arises from the increasing number of clusters being referred for investigation to DoH, and increasing community concern about the relationship between environmental contamination, or occupational exposures, and cancer.

1.2 Methods

A detailed literature review including peer-reviewed journal publications related to cancer cluster investigations was performed. This included a review of guidelines and protocols that have been published by public health agencies such as the internationally recognised CDC[2,3], and in countries including Canada[4], New Zealand[5], also Europe[6], and some states of the United States[7-13] and Queensland[14]. Each document outlined the region specific protocol followed in the event of a suspected cluster of non-communicable health events. We have also reviewed and considered discussions and recommendations regarding statistical analyses required for small numbers of cases, methodological issues as well as risk communication strategies[15-37].

1.3 Overview of the Guidelines

The purpose of these guidelines is to provide an efficient, coordinated, methodical and multidisciplinary approach to a response by DoH officers after receiving concerns from the community, health professionals or others about potential cancer clusters. These guidelines outline a systematic process to follow in all circumstances with documents in Appendices to support the methods required to assess a cluster.

Cluster assessment includes two main components: epidemiological assessment and environmental (public) health assessment to inform cluster management. These two main components will be done through four phases of evaluations including primary, secondary, tertiary and research evaluations as described in these guidelines. More evidence and greater validation is gained as the investigation progresses through the phases, as necessary.

Cluster management is defined as the process of identifying and evaluating appropriate actions, and implementing them in response to cluster assessments and related matters. To inform decision making for cluster management, the assessment process must also include community concerns, context and surrounding issues. Cluster management is led by the Cluster Manager (a representative from the setting of the cluster or the study agency/community). DoH is rarely the cluster manager, except when DoH facilities (eg, public hospitals) are involved.

Cluster assessment informs cluster management (cluster manager) by providing clear and objective information (including assumptions and uncertainties) relating to the assessment. Cluster assessment and cluster management are interdependent, both processes should

commence simultaneously and may have different objectives. Guidelines for cluster management are beyond the scope of this document.

The four phases of evaluations in the cluster assessment are designed to optimise resource use and provide a response to the informant in a timely and empathetic manner based on the best available evidence.

Definitions of terms used are provided in a Glossary in Appendix 1.

1.3.1 Cancer cluster settings

In these guidelines, there are two main settings for cancer clusters: occupational and community settings.

An occupational cluster is defined as a suspected cluster occurring in a workplace. Three types of occupational settings are defined to allocate management responsibilities and involvement of DoH. The types are defined as:

- within a DoH workplace
- within a WA Government (non - DoH) workplace
- within other occupational settings (private workplaces).

Community setting cluster assessments are defined as a suspected cluster occurring outside of the workplace. This includes, but is not limited to, suspected clusters occurring in geographical areas (suburbs) or in institutions (schools).

DoH involvement in a cluster assessment will occur when:

- the reported cluster occurs in a community setting e.g. a street, suburb or town
- the reported cluster relates to a WA Government workplace
- there is a specific need for DoH expertise that is not available elsewhere.

Accordingly, DoH may not be involved in a cluster assessment when another party has clear responsibility for the cluster assessment such as private workplaces.

The settings for clusters are defined to assist in evaluating the role of DoH in cluster assessment. Different settings will affect the definition of the population, stakeholders involved in the assessment and allocation of members to the assessment teams.

1.3.2 Key roles in cluster investigation (Cluster Assessment Team)

There are several key roles in any cluster investigation. In the case of a primary evaluation the first responder should seek initial support from the Principal Epidemiologist, Epidemiology Branch, DoH. The appointment of a Cluster Manager is necessary to take the lead for other evaluation phases (Secondary, Tertiary and Research evaluations). If deemed necessary by the Assistant Director General, Public Health (ADGPH), a Cluster Assessment Advisory Committee (CAAC) should be formed and required resources identified for the investigation.

Cluster Manager: The cluster manager will be the representative from the agency/community of the cluster setting. While in a community setting the cluster manager may be a representative from the Health Service responsible for the setting, in an occupational setting the cluster manager will come from the workplace. The investigation will be led by the cluster manager who should engage a Cluster Assessment Team (CAT) including an epidemiologic assessor and an environmental assessor through consultation with DoH to assist with:

- initial response to the informant
- evaluation of environmental and other factors contributing to observations, including characteristics of population (age, diet, smoking and socioeconomic status)
- evaluation of sensitivities, history of local population and key informants
- public education and coordination of local educational events
- communication with the WA Cancer Registry or other agencies, as needed.

Epidemiologic Assessor: The roles of the epidemiologic assessor include:

- to undertake literature reviews, collect the required information, conduct statistical analyses, surveillance, and research for the cancer cluster investigation
- to identify whether a statistical excess of cases has occurred, using various statistical techniques including comparing observed numbers of cases to expected number of cases for calculating Standardised Incidence Ratio (SIR) and/or Standardised Mortality Ratio (SMR), and to derive other statistics from analytical measures
- to provide epidemiological advice and technical support to stakeholders
- to provide recommendations to management at the cluster site, partners and other stakeholders on epidemiology and research.

Environmental Health Assessor: The role of the environmental health assessor is to:

- identify the relevant existing environmental data, historical and current, for the setting
- identify the possibility of exposure to an environmental agent
- assess the presence, past or current, of a suspected etiologic agent, rather than an open-ended inquiry to identify potential contaminants in a community
- provide advice on environmental testing
- conduct a health risk assessment (HRA, including exposure and toxicity assessment).

A Cluster Assessment Team (CAT) should be formed for all phases of the investigation which would generally include but not be limited to an epidemiologist, a toxicologist or other environmental health professional, a public communication officer, a representative from the WA Cancer Registry and a representative from the agency of the setting (usually the cluster manager).

Other agencies involved in cluster investigations will vary depending on the setting of the cluster and the phase of the investigation. While it is possible a staff member of these agencies may be the first responder, any assessment involving DoH should follow these guidelines.

1.3.3 Role of the DoH in cluster assessment

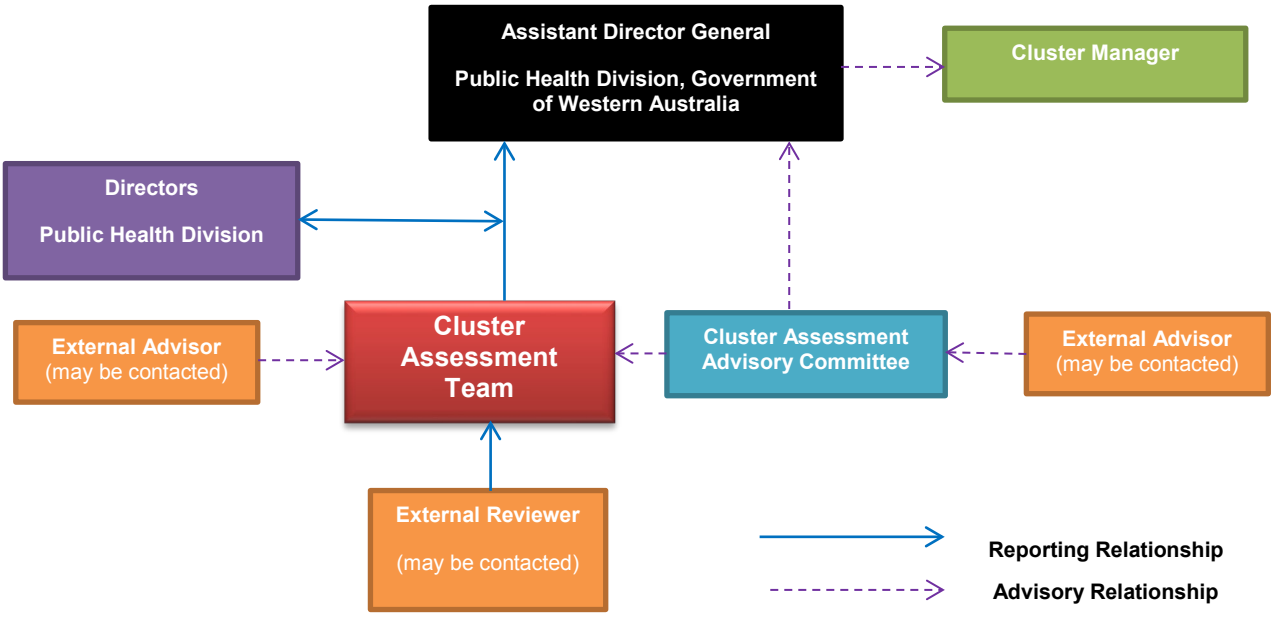
In any cluster assessment with the potential for DoH involvement, the role of the Department must be clarified as soon as possible, prior to commencement of any assessment.

If DoH is not the cluster manager, it is important to determine if it has any role in the assessment. It may have a limited role determined by the scope, duration, and/or reporting procedures.

For cluster assessments in which DoH has a role, the role and responsibilities of team members and agency/agencies responsible for each component of the assessment and responsibility for the management of the assessment must be identified and agreed by all parties as soon as possible. The management of the assessment is usually conducted by the agency/agencies of the setting.

1.3.4 Governance: Cluster assessment by DoH is conducted using established reporting and advisory pathways (Figure 1).

Figure 1: Reporting and Advisory Relationships of Cluster Assessment



1.3.5 Structure of the guidelines

This guideline describes four phases of evaluations including primary, secondary, tertiary and research evaluations for the process of evaluating suspected clusters. Figure 2 provides an overview of the entire cluster evaluation process. Each phase begins with identifying the issues of concern of the informant and community, followed by assembly of the assessment team for each evaluation, defining roles and responsibilities, determining individual steps in each phase of evaluation and developing a communications plan (Appendix 2).

Certain criteria must be met in order to proceed to the next phase, otherwise the investigation ceases at that point (Tables 2, 4, and 6). This format is essential to ensure standardised assessment of a complex process and the best possible allocation of resources. These phases are not prescriptive – sometimes two or more phases will be performed in unison, or phases may be skipped. Of course, the resource implications need to be considered and appropriate approvals granted to proceed with further analysis.

Whatever the decision at the end of each phase, a standard set of actions should be considered and/or completed before ceasing the assessment or proceeding to the next phase. More details for each phase of the assessment are provided in Figures 3 to 6.

1. **Phase 1 Primary evaluation (PE) - initial contact and response to an enquiry.**

   The aims of primary evaluation are to establish an open communication with the person or organisation reporting a suspected cancer cluster and to collect their information to determine the likely scope of the investigation. The person or organisation reporting the cluster is the informant, who could be, for example, a member of the public or a concerned health care provider. All cancer cluster investigations should begin with this evaluation.

2. **Phase 2 Secondary evaluation (SE) - epidemiologic assessment and health risk assessment.**

   This phase is pursued if the data gathered from primary investigations suggest the need for further evaluation. The primary purpose of this evaluation is to determine whether there is a statistically significant excess of cases within the suspected cancer cluster. Calculating a standardised incidence/mortality ratio and conducting other statistical analyses are recommended at this step. This step also includes a preliminary health risk assessment, including identifying possible exposures to environmental agents.

3. **Phase 3 Tertiary evaluation (TE) - Detailed epidemiological and environmental health assessment**.

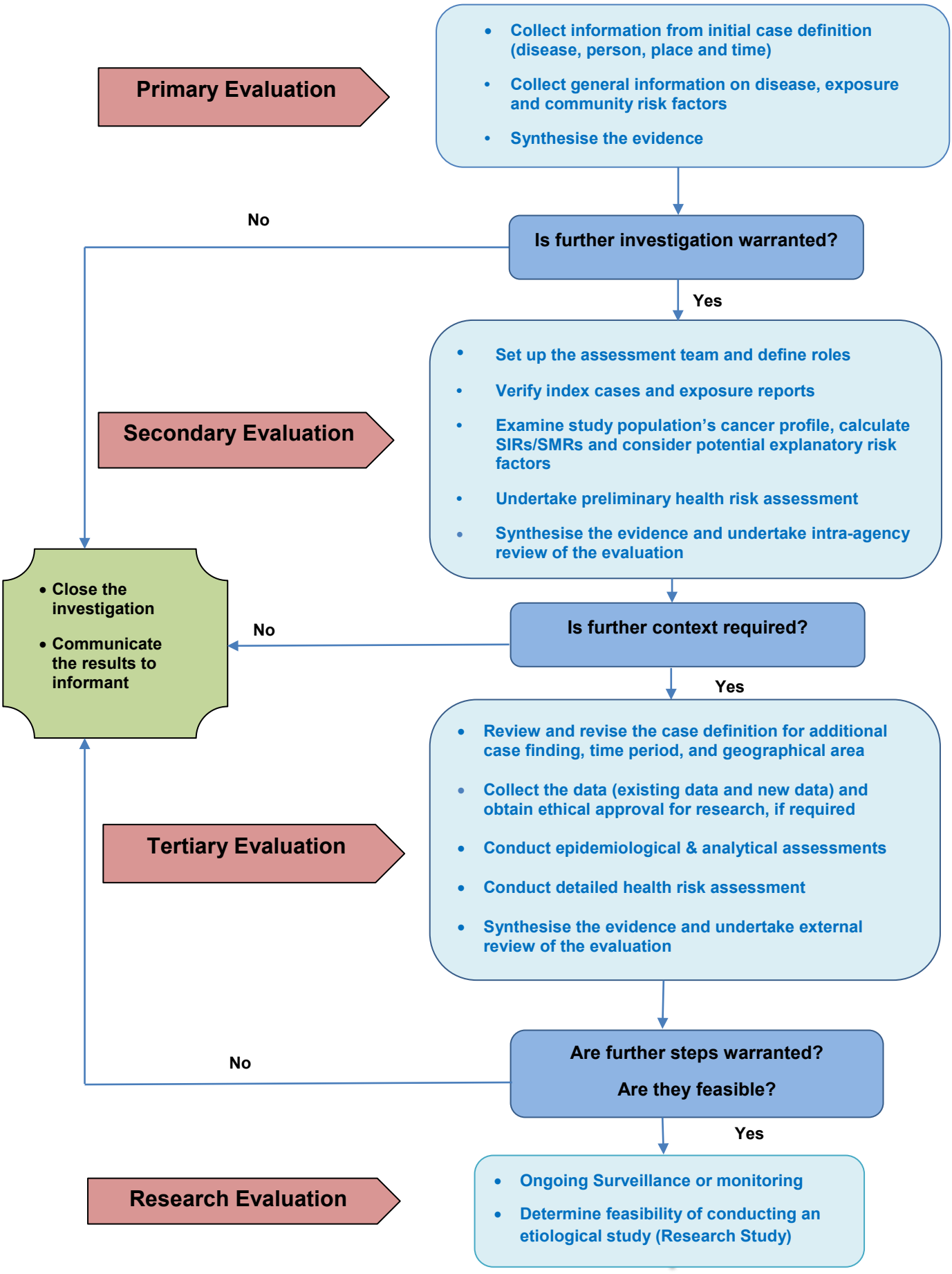
   The purpose of tertiary evaluation is to further quantify the excess of disease and undertake a detailed exposure assessment of biologically plausible causal agents. If an excess of disease occurrence is still evident after verification of known cases through secondary evaluation, investigators might expand the assessment and undertake additional case-finding to better define cluster characteristics. This involves a multidisciplinary team using information and reviews from previous assessments as well as a possibility of collecting and analysing new data. Typically collection of new data would involve the use of existing linked data for better case ascertainment and a collection of data for a detailed, quantitative environmental health risk assessment. This should include hazard assessment, identification and evaluation, as well as, exposure assessment.

4. **Phase 4 Research evaluation (RE) - Feasibility of conducting a research study and ongoing surveillance.**

   This step is optional and considers the feasibility of conducting an etiological investigation or research study to examine the association between the cancer cluster and a particular environmental or occupational contaminant. If justified, a research evaluation may require ongoing health surveillance and environmental monitoring.

Criteria for decision making for proceeding or ceasing a phase at conclusion of each phase need to be considered and a decision needs to be made by the Cluster Assessment Team, or Cluster Assessment Advisory Committee, if appointed. In general, a “Yes” to most of these criteria increases the need for further follow-up/investigation.

Figure 2: Overview of the Cluster Investigation Process



2.0 Phase 1 - Primary Evaluation

2.1 Overview, Procedures and Details of Primary Evaluation

All cancer cluster investigations should begin with a primary evaluation. The procedure for a primary evaluation (PE) is shown in **Figure 3**, with more detailed information provided in **Tables 1 and 2.**

The purpose of a primary evaluation is to collect information from the person or organisation (*informant*) reporting a suspected cancer cluster in order to determine whether more detailed follow-up is required. Following the initial report of a suspected clustering of cancer events, open communication must be established between the informant and a representative of the assessment team.

The suspected clusters can be identified by anyone, including members of the public, media, health professionals and local, regional or national agencies. If a cluster is suspected from monitoring or vital statistics, the procedure begins at the Secondary Evaluation.

Effective communication is vital throughout the entire assessment and should involve regular updates about the process and progress. To be an effective initial responder, the responder should be empathetic, listen to the informant's concern and record the information received. The initial responder needs to understand the context of the informant's concerns, the nature of the perceived problem, and the history of reporting to authorities, as well as gathering other necessary information as detailed in **Table 2.** These include:

PE1 Collecting identifying information on the informant. Any request to investigate a cancer cluster should be directed to the Principal Epemiologist in the first instance, regardless of the setting.

PE2 Determining general epidemiological variables such as type of cancer, number of cases (person), age of people with cancer, geographic area/workplace of concern (place), and period over which cancers were diagnosed (time).

PE3 Establishing a preliminary case definition (demographic characteristics) of the persons with cancer and the population group of which they are member.

PE4 Determining exposure information (any significant exposure to occupational/environmental hazards, likely frequency and duration of occupational /environmental contaminant exposures, other risk factors such as diet, smoking, infections and family history). Any known, suspected or suggested biologically plausible causative agent should be considered.

PE5 Compiling and reviewing the information on the basis of the information gathered in PE1-PE4 **(Figure 2 and Table 1)** and making a judgement of whether or not further investigation is warranted **(Decision Point criteria in Table 2)**. The decision should be made in discussion with the Principal Epidemiologist, Epidemiology Branch, DoH. Additional information may need to be obtained from a literature review.

2.2 Decision Point

The decision to finalise the primary evaluation is made by the initial responder in conjunction with the Principal Epidemiologist, DoH. While no higher level sign off is required to finalise the primary evaluation, approval is required to move to the next evaluation. It should be based on expert multidisciplinary knowledge and should take account of both epidemiological and environmental aspects, as well as the level of community concern. The responder should collect the information and discuss the case with colleagues who have the necessary expertise before responding to the informant.

2.3 Outcome of primary evaluation

Communication with the informant is an essential part of all stages of the investigation. Following the information review and preliminary decision-making steps considering the rationale in Table 2, the informant should be notified about any conclusions or next steps. This may include education about general disease information, results of the primary evaluation, and reasons for closure or expectations for the next evaluation (if applicable). Approval from the ADGPH is required before proceeding to the next evaluation. The actions necessary to appropriately close the assessment are described in Appendix 2.

Figure 3: Procedures for Primary Evaluation

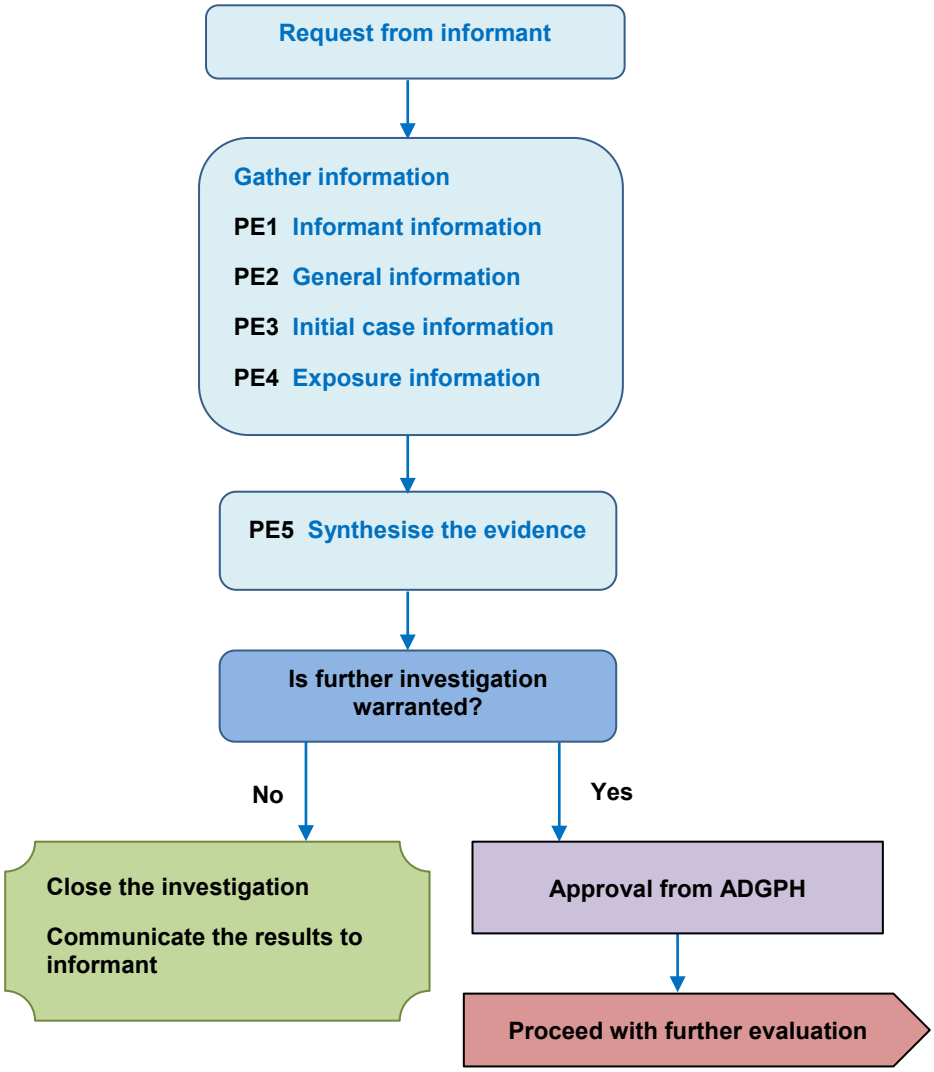


Table 1: Details of Primary Evaluation

	Task (responsible role)	Actions
PE1	**Informant information** **(Initial responder)**	**Information to obtain:** ☐ Name, street address, postcode, telephone number, email. ☐ Occupation of informant. ☐ How the informant learnt about the cluster. ☐ Is the informant willing to be contacted further? ☐ Has the informant contacted anyone else about the cluster (health agencies, General Practitioner (GP), employer representative or the media, other).
PE2	**General information** **(Initial responder)**	**Information to obtain:** ☐ Types of cancer ☐ Age at diagnosis of people with cancer ☐ Number of cases ☐ Number of deaths attributed to this cancer ☐ Time period of concern ☐ Geographic boundaries of cluster ☐ Setting of the suspected cluster (neighbourhood, workplace, school, other).
PE3	**Case information** **(Initial responder)**	**Information to obtain:** ☐ Sex, age, ethnicity ☐ Current address, contact details, and how long the cases have lived there. ☐ If a residential cluster, obtain residential history (address, dates moved in and out) over the last 10 years. ☐ Addresses of cases at diagnosis and date of diagnosis ☐ Family history of cancer ☐ Name of medical facility where diagnosis was made ☐ If deceased – date and place of death, home address at time of death ☐ Name and address of GP ☐ Other medical conditions ☐ Risk factors for cancer (e.g. smoking, diet, infections, family history)
PE4	**Exposure information** **(Initial responder)**	**If occupational cluster:** ☐ Activity in the area and type of potential exposure —ask whether the study population has currently/previously had any known unusual or high exposures. ☐ What is the informant's perception of the cause of the apparent cluster? **If residential cluster:** ☐ Ask informant to describe the surrounding environment (nearby industrial activities). ☐ What is the informant's perception of the cause of the apparent cluster?
PE5	**Synthesis of the evidence and register** **(Initial responder & Principal Epidemiologist)**	☐ Gather and review the information ☐ Evaluate the evidence ☐ Determine outcome of evaluation ☐ Enter all information required into Cluster Assessment Register, maintained by Epidemiology Branch, DoH

Table 2: Criteria for Decision Making at Conclusion of Primary Evaluation

	Criteria to Proceed or Cease
Factors that support the need for further investigation	☐ The presented evidence fits the definition of a cluster and the presence of biologic plausibility between the reported disease and potential exposure to the environmental or occupational hazards exists. ☐ It is a rare cancer or an atypical demographic distribution of a certain type of cancer (e.g. multiple cases of breast cancer in men). ☐ There are apparent high numbers of cases of the rare cancer. ☐ The cases are within a specific geographic area and within a certain time period. ☐ There is consensus in the scientific literature between exposure to a specific occupation or environmental contaminant and the cancer of concern. ☐ There is a high level of community concern or public interest. ☐ Further investigation is feasible. If not, other actions can be considered to address community concerns. In general, a "YES" answer to most of these criteria increases the need for further investigation (Secondary evaluation).
Factors that do not support the need for further investigation	☐ Cancers known to be strongly genetically related within family members ☐ A small number of cases of very common cancers (e.g. breast, lung) ☐ Reported disease that might not be cancer ☐ Different types of cancers not known to be related to one single carcinogen ☐ Cancer cases among persons who did not have the same occupational or environmental exposures during the relevant timeframe. Based on known latency of the cancer, it is determined that cases could not have experienced a common carcinogenic exposure. In general, a "YES" to these criteria reduces the need for further investigation.

3.0 Phase 2 - Secondary Evaluation

3.1 Overview, Procedures and Details of Secondary Evaluation

An overview of secondary evaluation (SE) is shown in **Figure 4**, with more detail provided in **Tables 3 and 4.**

The purpose of the secondary evaluation is to determine whether the suspected cancer cluster represents a statistically significant excess of cancer cases in the setting of concern and a biological plausible exposure to a carcinogen exists. It involves analysis of existing data to further investigate the cluster, as well as an assessment of the necessity and feasibility of further action.

The secondary evaluation includes 10 important actions:

SE1 Appointment of a cluster manager and set-up of the secondary evaluation team.

SE2 Consultation with the study community. This is an important first step in the secondary evaluation, to discuss any issues from the previous evaluation and to identify if any new community concerns have arisen.

SE3 Use of the information obtained in the primary evaluation, and through consultation with clinical or surveillance experts as necessary, to define characteristics for case ascertainment. It is necessary to set parameters that have the potential to capture the suspected cluster without dilution of the possible observed health effects. For example, it may be necessary to select a geographic area large enough to capture all potential cases but small enough to able to detect any localised difference in outcome.

SE4 Determination of the reference population for comparison. The reference population could be the surrounding ABS Statistical Areas (SA1and/or SA2), other geographical areas in the state, or the state as a whole (not including the study population). An area used by the WA Cancer Registry in reporting cancer incidence would be preferable.

SE5 Conducting a literature review of potential risk factors for the cancer type including lifestyle and known or suspected occupational and environmental exposures. In addition, a review of existing data sources available in DoH to assess the trends of the cancer type or exposure of concern may identify other factors that might affect excess cancer cases

detected, such as screening rates. This can be done using available epidemiological information of the study population through HealthTracks Reporting (an online application maintained by Epidemiology Branch) and WA Cancer Registry reports.

SE6 Examination of the reference population's cancer profile for comparison by determining the background cancer incidence in the reference population from information available from the WA Cancer Registry, as well as describing the demographic characteristics of the cases in the reference population. More detailed information is provided in Table 4 for this step.

SE7 Examination of the study population's cancer profile to estimate the likelihood that an excess of cases exists compared to what would be expected in the reference population. To interpret the excess of cases, the type(s) of cancer, number of cancer cases, the period of concern, the geographic area of concern, the demographic characteristics of the cases and the reference population are needed. A Standardised Incidence Ratio (SIR), Standardised Mortality Ratio (SMR) and 95% CIs also need to be calculated. More detailed information is provided in Table 4 for this step.

SE8 Conducting a preliminary environmental health assessment consisting of a desktop study, site inspection and interviews with relevant personnel. This is required to assess whether there has been significant exposure to a biologically plausible causal agent of the cancer reported. It may also include limited sampling and analysis. The information is used to develop an initial exposure profile to potential sources of contamination. The lack of evidence of a known or suspected agent at this stage should not preclude further assessment if other evidence is suggestive of a cluster.

SE9 Synthesis of the evidence and preparation of a report.

SE10 Undertaking of an internal review of the report may be necessary, depending upon the circumstances of the investigation, involving a quality assurance review conducted by internal DoH advisors, such as key Epidemiology Branch staff, Public Health Physicians and Manager of the WA Cancer Registry. See **Table 4** for more information.

3.2 Decision point

The decision to close an investigation or move forward to the next evaluation is based on multiple factors including whether there is evidence to support taking further steps and, should such evidence exist, the feasibility of taking additional steps.

When an excess of cancer cases is not statistically significant, coupled with a lack of known association with an environmental/occupational contaminant, closing the investigation is justified. A statistically significant excess of cancer cases can occur by chance; without supporting evidence of a rare cancer type, unusual demographic characteristics of the cases or a plausible causal agent closure would again be justifiable..

When an excess of cancer cases is supported by the characteristics of the cancer cases or evidence of a causal agent, further investigation should be considered – provided it is feasible to obtain further evidence.

3.3 Outcome of secondary evaluation

Depending upon the decision made as a result of the secondary evaluation, permission will need to be sought from the ADGPH to close the assessment or proceed to the next evaluation. The actions necessary to appropriately close the assessment are described in Appendix 2.

Figure 4: Process for Secondary Evaluation

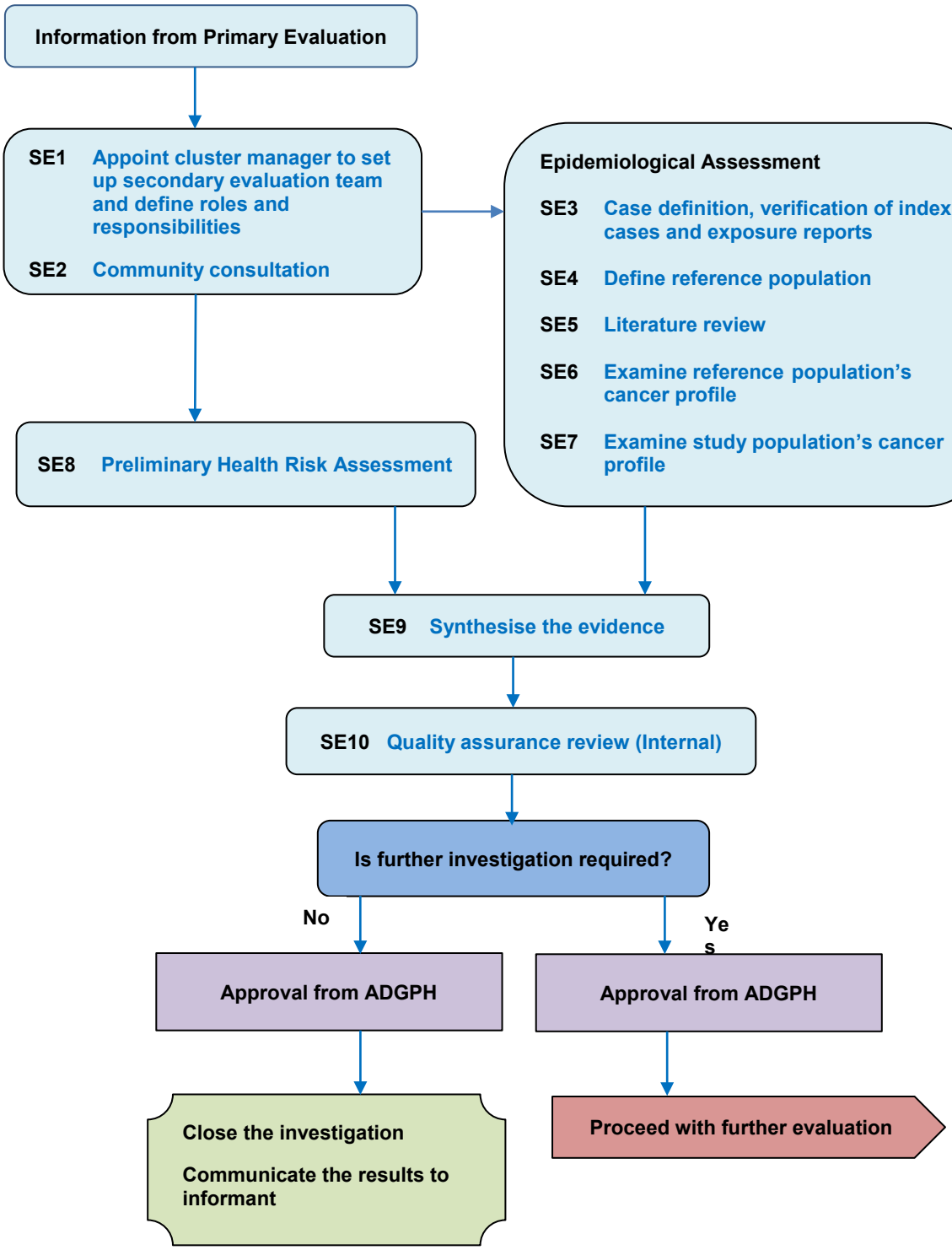


Table 3: Details of secondary evaluation actions

	Task (responsible role)	Analytic Actions
SE1	**Appoint cluster manager and set-up secondary evaluation team; define roles and responsibilities** **(Cluster Assessment Team)**	☐ Define role of DoH ☐ Identify and consult with cluster manager (a representative of the study population) ☐ Identify informant liaison (on-going communication with informant) ☐ Identify working group/committee • an epidemiological assessor • an environmental health assessor , or occupational hygienist • a communication officer • a representative from the setting
SE2	**Consultation with study population representative** **(Cluster manager)**	☐ Use communication principles in Appendix 2 ☐ Identify if any new community' concerns have arisen ☐ Collect new information if required
SE3	**Case ascertainment** **(Epidemiological assessor)**	**Form an initial Case definition** ☐ What: type of cancer (primary site, histology and grade) ☐ Where: cluster setting (geographical area, workplace or community facility). ☐ When: exposure period in this context is the period of time the study population has been exposed to the 'risk'. ☐ Who: cases might be limited to a specific age, sex, ethnicity (index cases/first reported cases) ☐ How: the suspected specific exposures **Review the appropriate records and verify case and exposure** ☐ Use case definition as guidance in deciding what data are to be used. ☐ Verify cancers (review hospital records, any diagnosis on pathology reports, doctor records, and cancer registry). ☐ Verify cause of death (death certificate, review medical records). ☐ Verify that specific cases provided by informant (if any) represent actual cancer diagnoses. ☐ Verify exposures (consult with epidemiologists, occupational and environmental health experts) to gain information about the availability of, access to and use of data such as employment records and residential histories. **Study population** ☐ The study population at risk must align with the case definition. ☐ Review inclusion and exclusion criteria such as age, sex, race/ethnicity, residential location or workplace.
SE4	**Define reference population** **(Epidemiological assessor)**	☐ Must be a comparable population to the study population, in terms of demographic characteristics, that have not been exposed. ☐ The reference population should be based on ABS Statistical Areas (SA1 and/or SA2), other geographical areas in the state, or the state as a whole (not including the study population) to allow access to population estimates.
SE5	**Conduct a literature review** **(Epidemiological assessor and Environmental health assessor)**	☐ Find evidence of any previously reported cancer cluster. ☐ Determine known exposure associations and available toxicological information. ☐ Understand the histopathological classification for the cancer under study. ☐ Establish the latency period of the cancer under study. ☐ Search online databases such as Hazardous Substances Data Bank (HSDB) when exposure to specific hazardous substances has occurred or is suspected (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB). ☐ Obtain available epidemiological information on risk factors for type of cancer(s) in question including: demographic, behavioural, occupational,

		environmental, genetic and social factors: include screening rates if applicable. ☐ Investigate documented changes in the incidence and/or prevalence of disease or risk factors that occur over time.
SE6	**Examine reference population's cancer profile** **(Epidemiological assessor)**	☐ Determine incidence of cancer under study. ☐ Determine the distribution and age at diagnosis distribution of cancer types in the reference population. ☐ Compare cancer incidence, distribution of types and age at diagnosis with study population.
SE7	**Examine study population's cancer profile** **(Epidemiological assessor)**	☐ Calculate a Standardised Incidence Ratio (SIR), Standardised Mortality Ratio (SMR) and 95% CIs. See Appendix 3 for the method to calculate an SIR or SMR. ☐ Determine the latency period in the context of the study and calculate time since exposure for each case. ☐ Determine the distribution, incidence and age at diagnosis of cancer types in the study population.
SE8	**Preliminary Health Risk Assessment** **(Environmental health assessor/Toxicologist)**	☐ Conduct preliminary health risk assessment (refer to links below) http://www.public.health.wa.gov.au/cproot/1499/2/Health_Risk_Assessment.pdf http://www.public.health.wa.gov.au/cproot/3087/2/HRA_Scoping.pdf). ☐ Undertake a site visit and a walk through inspection, if warranted. This should be by an experienced, expert environmental health or occupational health professional to gather general information about local exposure possibilities and to answer following questions: • What hazards are present? • What is the geographical location of the hazards in relation to the population at risk? • Are there known or potential exposure pathways by which these hazards might have affected the population at risk? ☐ Develop an understanding of the study population, its history, social context, and member's local knowledge about the hazards and risk factors in the setting.
SE9	**Synthesis of the evidence** **(Cluster assessment team)**	☐ Gather and review the information. ☐ Review methodology. ☐ Evaluate the evidence. ☐ Prepare draft report including background, methods, results, assessment and recommendations
SE10	**Undertake a Quality Assurance Review** **(Cluster assessment team)**	☐ Send results and reports to internal professionals (Cancer Cluster Assessment Advisory Committee) for their review and comments before making decision and finalising the report. ☐ Enter all information required into Cluster Assessment Register, maintained by Epidemiology Branch, DoH.

Table 4: Criteria for Decision Making at Conclusion of Secondary Evaluation

	Criteria to Proceed or Cease

Factors that support the need for further investigation	☐ SIR/SMR is significantly greater than 1; there are significantly more cases in the cluster setting than would be expected based on the reference population.
	☐ There is an increasing trend in incidence rate.
	☐ There is a known etiologic relationship between the suspected environmental contaminant and the type of cancer(s).
	☐ There are factors to support biological plausibility such as:
	  ○ the hazard is capable of causing the disease of concern
	  ○ the exposure is of sufficient magnitude to cause the observed adverse effects
	  ○ all cases have been exposed
	  ○ the temporal relationship between the exposure and the disease is in keeping with what is known about the cancer (latency periods).
	☐ The demographic characteristics of these cases are unusual for the type of cancer (e.g. in a younger age group for a cancer such as lung cancer that usually occurs only in older age group).
	☐ The informants concerns have not been addressed.
	☐ There is intense concern among the study population.
	☐ Further context is required.
	☐ Further investigation is feasible.
	
	In general, a "YES" answer to most of these criteria increases the need for further investigation (Tertiary evaluation).

Factors that do not support the need for further investigation	☐ An SIR/SMR of limited magnitude that is not statistically significant. ☐ Limited evidence of an etiologic relationship between the suspected environmental contaminant and the type of cancer(s). ☐ Cancer profile similar in both study population and reference population. ☐ Latency period for cases are not consistent with literature. ☐ Possible effect of migration, as some of the cases involved in the reported cluster may have developed the cancer before moving into the area and encountering the possible exposure, so they should not have been included. ☐ When the diagnoses of the reported cancer cases have been verified, they may be variable types of cancer or may not be cancer. It is unlikely that unrelated cancers will constitute a cluster. ☐ The exposure is of insufficient magnitude to cause observable adverse health effects. In general, a "YES" answer to most of these criteria reduces the need for further investigation.

4.0 Phase 3 - Tertiary Evaluation

4.1 Overview, Procedures and Details of Tertiary Evaluation

An overview of tertiary evaluation (TE) is shown in **Figure 5**, with more detail provided in **Tables 5 and 6.**

The purpose of tertiary evaluation is to validate the excess of disease and undertake a detailed exposure assessment of biologically plausible causal agents by accessing and analysing new data. If an excess of cancer occurrence is still evident after verification of known cases through secondary evaluation, investigators may need to expand the assessment and undertake additional case-finding to better define cluster characteristics. This involves a multidisciplinary team using information and reviews from previous assessments as well as a possibility of collecting and analysing new data.

Tertiary evaluation includes 10 important actions:

TE1 Appoint cluster manager and set up the tertiary evaluation team.

TE2 Commence with an engagement process once again with the study population, to discuss concerns from previous evaluations and identify if any new community concerns have arisen.

TE3 Review and revise the initial case definition, time period, and geographical area if already developed in a secondary evaluation. Reconsider the initial case definition, and determine if greater sensitivity or specificity is desired. A reassessment of the most appropriate study population group of interest, and time boundaries, might be warranted following the secondary evaluation. Tracking cases lost to follow-up in the secondary evaluation may impact on the epidemiological analysis and should be considered. Cases may not be members of the study population at the time of diagnosis, and data on the length of residence or time of employment in a particular setting are also important, where exposure may have occurred 10 or more years previously.

TE4 Ascertain all potential cases within the defined setting and time boundaries, based on the revised case definition. The data collection methods chosen depend on the type of data needed to count all suspected cases. Much of the basic information can usually be

obtained by reviewing existing data and also the data collected by interview/questionnaire at the primary evaluation.

TE5 Based on the case definition, identify appropriate additional database sources or medical records for cases (existing data) and the population at risk, and assess their availability and quality. If needed, obtain additional information from the study population (new data). A survey might find previously unknown cases and could be conducted in conjunction with an environmental health assessment if exposure levels also need to be measured.

TE6 Obtain ethical approval, if required to access new data sources.

TE7 Conduct epidemiological and analytical assessments using enhanced case definitions with additional and new data sources to assess the likelihood that clustered cancer cases are related statistically, temporally, and physiologically, to the potential exposure(s). Much of the analysis will repeat that conducted in the secondary evaluation, but additional statistical techniques could be used to deal with data limitations.

TE8 Assess the degree of association an exposure may have with the cancer by collecting new or existing data/information through a detailed health risk assessment. This assessment involves reviewing the literature review conducted in previous evaluations for completeness to consider whether the supposed association is epidemiologically and biologically plausible based on the latest evidence. An extensive environmental assessment (EA) of the site according to the WA Department of Health Environmental Health Directorate guidance documents on Health Risk Assessment should be conducted [26].

The environmental exposure assessment provides the information to make informed decisions about the potential cause of the cluster as well as whether action is required if the agent of concern is still present. The assessment should combine existing knowledge of the carcinogenicity of the agent of concern with exposure data. The process of gathering and evaluating the information includes:

- hazard identification and evaluation
- exposure assessment.

While information necessary for issue identification and evaluation would be gathered in previous phases, additional data may be needed in cancer cluster investigations as part

of the determination of the possibility of exposure to an environmental contaminant. These include information on the weight of evidence, exposure routes, dose-response relationships, susceptible populations and latency. These data are required to determine if the nature and (estimated) level of exposure is consistent with the outcome. Most of this can be done as a desktop exercise. It is generally not recommended to engage in a general, open-ended inquiry to identify potential contaminants in a setting, in the absence of a suspected etiologic agent. However, if there was an agent previously or currently present in the environment that is not a known/suspected carcinogen solely because of a paucity of data this may trigger the need for further epidemiological research.

For exposure assessment, site testing only rarely provides accurate data on historical exposures needed in the consideration of the latent period of cancers. Most data, if available, will be obtained from historical records held by relevant agencies, such as the Department of Environmental Regulation, Department of Water, and local councils. Environmental testing should be carried out only when there is a clear scientific rationale, including if there is a concern that the agent could still be present. The exposure assessment will aim to answer the questions about the likely route of exposure, how much of the pollutant people were/are still exposed to during a specific time period and how many people were/are still exposed. Having an idea of these issues will help to determine the extra risk of health problems in the exposed population (risk characterisation). Details about conducting a health risk assessment have been published by the Department of Health Western Australia[26].

Based on information obtained from the exposure assessment, decisions are made about the best way to address environmental contamination and exposure, particularly if the agent of concern is still likely to be present. The risk management process also includes an evaluation of social, legal, economic and policy issues to determine the best approach to address the exposure issue. Management of risks identified in the environmental health risk assessment are beyond the scope of these guidelines.

TE9 Synthesis of the evidence and prepare the report

TE10 Undertake an external review of the report, if necessary. An external reviewer may be involved for more complex assessments and when the results may have social, political and economic implications.

4.2 Decision point

If investigators find excess occurrence of disease and compelling evidence for an association with the supposed exposure, they should consider the feasibility of an etiological study. The informant should be notified of the decision, with an explanation of what that entails and an outline of how further results will be provided.

If excess occurrence is not confirmed, or is confirmed with no apparent plausible relationship to the supposed exposure, or if the evidence does not suggest an occurrence of potential biological and public health importance, investigators should prepare a summary report and recommend to the ADGPH to conclude the investigation.

4.3 Outcome of tertiary evaluation

Depending upon the decision made as a result of the tertiary evaluation, permission will need to be sought from the ADGPH to close the assessment or proceed to a final evaluation. The actions necessary to appropriately close the assessment are described in Appendix 2.

Figure 5: Process for Tertiary Evaluation

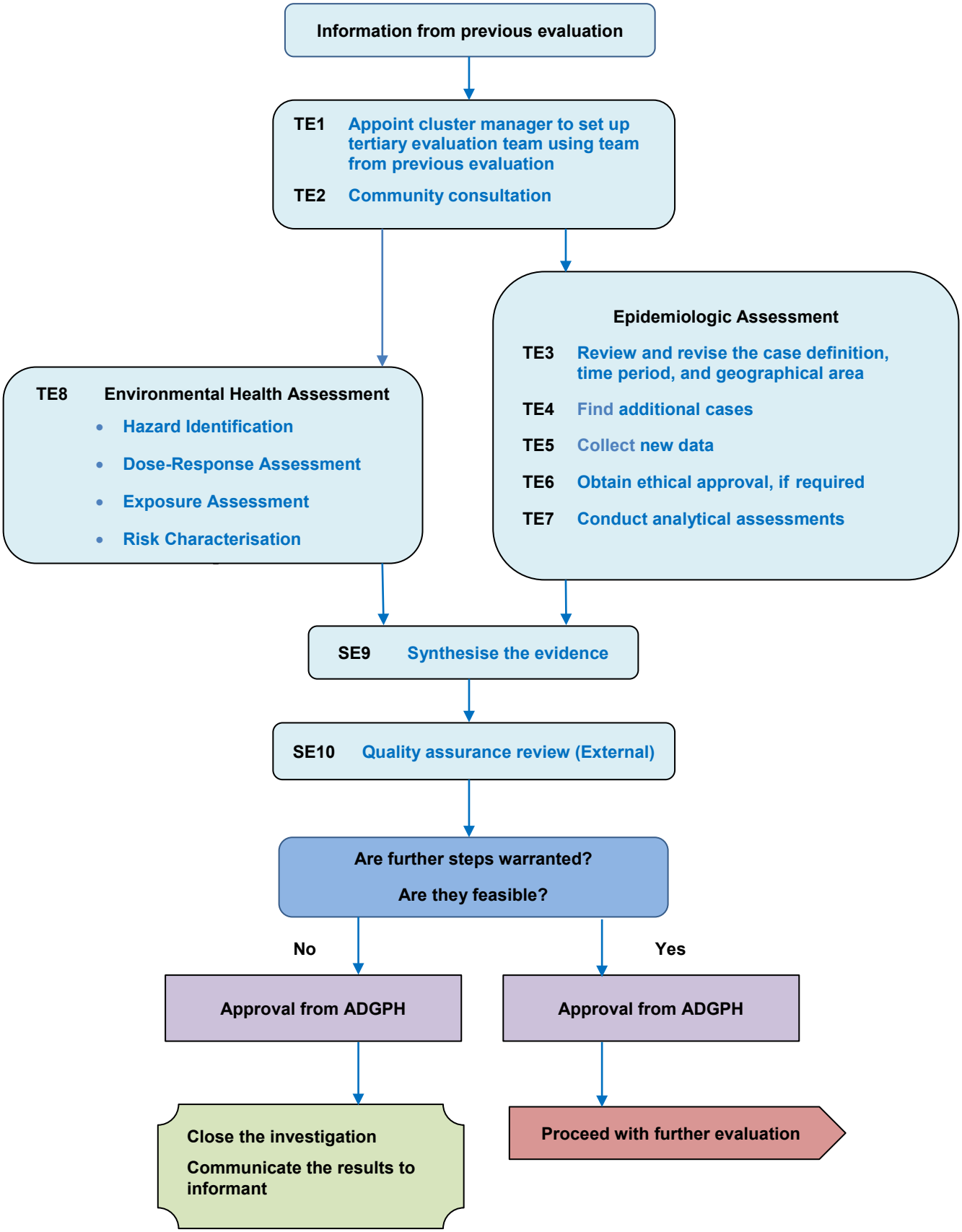


Table 5: Details of Tertiary Evaluation

	Task (responsible role)	Analytic Actions
TE1	**Appoint cluster manager and set up tertiary evaluation team and define roles and responsibilities** **(Cluster Assessment Team)**	☐ Define role of DoH. ☐ Identify and consult with Cluster Manager (a representative from the study population). ☐ Identify working group/committee • an epidemiological assessor • an environmental health assessor, or occupational hygienist • Manager of the WA Cancer Registry • a communications officer • a representative from the setting.
TE2	**Consultation with study population representative** **(Cluster manager)**	☐ Use communication principles in Appendix 2. ☐ Identify if any new community concerns have arisen. ☐ Collect new information if required.
TE3	**Review and revise the case definition** **(Epidemiologic assessor)**	**Develop a complete case definition:** ☐ Apply a strict definition of the specific cancer(s) suspected of clustering. ☐ Define a time period of possible exposure and identify all cases diagnosed during that period using appropriate and variable latency periods (0,5 and 10 years). ☐ Determine whether the study population is focussed on a specific population subgroup involving possible exposure (all women over age of 50 years) or specific occupations within a workplace. ☐ Extend the case definition to include cases not currently counted in the setting, but who could have been exposed.
TE4	**The process of additional case finding (records' sources)** **(Epidemiologic assessor)**	**Decide what records need to be examined:** All cases diagnosed with the cancer in the setting and time period need to be identified. This involves finding and reviewing data from several sources including: ☐ medical records ☐ death records ☐ population-based registries (WA Cancer Registry, Hospital Morbidity, Death, Birth Data, Birth Defects Registry and others) ☐ employment records ☐ other sources (laboratories, pharmacies, disease societies, general practitioners, certain physicians and the public ☐ additional information from the community.
TE5	**The process of collecting data (existing data and new data)** **(Epidemiologic assessor)**	**Determine what data will be collected:** ☐ A questionnaire can be designed so that all the necessary data are obtained in a clear and unambiguous manner. Consultation with experts about the technical aspect of questionnaire design, pretesting, mode of administration, training of interviewers and data coding and processing is advisable. ☐ Use data linkage to link administrative data (WA Data Linkage Branch) to employment, electoral roll or other available data sources (National Death Index). ☐ Adhere to confidentiality during data collection and storage.
TE6	Ethics approval (Epidemiologic assessor)	Obtain ethical approval, if required: Ethics approval may be needed to carry out the data collection from the following sources including: ☐ A questionnaire (participants should sign a consent form) ☐ Data Linkage (Go to http://www.datalinkage-wa.org.au/access-and-application for the process of obtaining ethics approval and access to linked data).

TE7	**Conduct epidemiological and analytical assessment** **(Epidemiologic assessor)**	**Determine the statistical and epidemiological techniques to assess the excess risks:** ☐ Analyse the distribution of age of diagnosis and compare to the reference population. ☐ Calculate SIR/SMR and their confidence intervals using additional/new data. ☐ Consider other statistical analyses to address the limitations of the SIR/SMR conducted in secondary evaluation, such as a Scan statistics using free spatial-scan statistical software SaTScan (see Appendix 4), Point source cluster analysis, Ranking, Funnel plot, if appropriate to the setting. ☐ Consider a Cox regression analysis to assess the association of potential exposure time on cancer incidence or death if sufficient case numbers and study population size allows. ☐ Use the Lexis macro in SAS to accurately calculate the person-years of follow-up by age, sex, year and cancer or death type [38].
TE8	**Environmental Health Assessment** **(Environmental Health Assessor/Toxicologist)**	For details on health risk assessment refer to the links below http://www.public.health.wa.gov.au/cproot/3087/2/HRA_Scoping.pdf http://www.public.health.wa.gov.au/cproot/1499/2/Health_Risk_Assessment.pdf **Hazard Identification and Evaluation:** For any suspected agent at the site review data from toxicological (acute and chronic) and epidemiological human or animal studies (retrospective and prospective) and biochemical activity data and answer following questions: ☐ Is the agent a known or suspected carcinogen? ☐ Is it feasible that the exposure pathway, and dose (if available), could lead to cancer in this situation (including known dose-response relationships). **Exposure Assessment:** ☐ Estimate the amount, frequency, length of time, and route/s of exposure. The exposure assessment process needs to consider the following: a) Sources of exposure • characterisation of production • uses (at home and outside the home) • disposal • environmental releases • exposure pathways identification of principal pathways of exposure b) Measured or estimated concentrations (calculate the amount of toxic substance through sampling or modelling) • uses of both historical data and new measurements • estimation of environmental concentrations c) Exposed human populations • health impact on susceptible populations (young children, older adults, pregnant women and ill individuals). d) Integrated exposure analysis (measurement of total exposure) • Calculation of exposure (how much exposure and dose) ○ identification of the exposed population ○ identification of pathways of exposure (one route or more). ☐ Synthesis of evidence: Gather and review the information collected from the previous steps. ☐ Determine the actual risk of exposure to a specific toxic substance in the area, taking into consideration the quality of the data, the amount of evidence and levels of uncertainty, by varying potencies of the agent, exposures and latent periods. ☐ Prepare an overall picture of the likelihood that this is a potential causative

		agent, including the uncertainties around the likelihood.
TE9	**Synthesise the evidence** **(Cluster assessment team)**	☐ Gather and review the information ☐ Evaluate the evidence ☐ Assess the situation
TE10	**A Quality Assurance Review** **(Cluster assessment team)**	☐ Results and reports may be sent to external professionals (advisory committee) for their review and comments before making decision. ☐ Enter all information required into Cluster Assessment Register, maintained by Epidemiology Branch, DoH

Table 6: Criteria for Decision Making at Conclusion of Tertiary Evaluation

	Criteria for Proceed or Cease
Factors that support the need for further investigation	☐ Is SIR/SMR (observed cases/expected cases) significantly greater than 1? ☐ Are the demographic characteristics of these cases unusual for the type of cancer (e.g. in a younger age group for a cancer such as lung cancer that usually occurs only in older age group)? ☐ Is the type of cancer unusual? ☐ Can the population at risk be defined? ☐ Have cases increased suddenly in a recent period? ☐ Do the result of spatial scan statistics and other analytical methods confirm the suspected cluster? ☐ Is there an etiologic relationship between the type of cancer and the suspected environmental contaminant? ☐ Are cases more concentrated around suspected environmental hazards or in suspected occupational groups? ☐ Based on existing dose-response data, can estimated exposures increase the risk of disease? ☐ Is further investigation warranted or feasible or likely to answer any remaining questions? In general, a “YES” answer to most of these questions increases the need for further follow-up (Final evaluation).
Factors that do not support the need for further investigation	☐ No excess disease and no identified exposure, so no biological plausibility. ☐ No excess disease, a possible exposure, but no biological plausibility that exposure could result in an excess. ☐ Excess disease, no identified exposure and no biological plausibility that the excess rate results from an environmental/occupational exposure. ☐ No evidence of an etiologic relationship between the type of cancer and the suspected environmental contaminant. ☐ The cluster is not detected by spatial scan statistic or other analytical methods. In general, a “YES” answer to most of these questions reduces the need for further follow-up

5.0 Phase 4 – Research Evaluation

5.1 Overview, Procedures and Details of Research Evaluation

The research evaluation phase is optional, with the purpose of assessing the feasibility of performing an etiologic study to examine the association between the cancer cluster and a particular environmental/occupational contaminant. If further study is feasible, an outcome of this step should include a recommended study design.

Surveillance could be recommended in some circumstances for settings with high SIRs which do not meet the criteria for further investigation. Implementation and mode of surveillance will be the responsibility of the cluster manager. Additionally, this step provides the opportunity for further research to evaluate additional public health actions, such as smoking cessation programs, cancer screenings, health risk assessments, removal of environmental hazards, or other activities that should be conducted. The results of assessments, additional public health actions, and the level of community concern will be considered.

The feasibility of performing an etiologic study should contain the research questions to be addressed and the hypothesis to be tested. It should consider the study design required to test the hypothesis and the level of evidence provided. The resources required to complete the study in a specified time should be quantified. See **Figure 6 and Table 7** for more information on procedures for the final evaluation.

5.2 Outcome of research evaluation

While implementation of surveillance is the responsibility of the cluster manager and may not involve DoH, a decision to end it, following a review, should be made in consultation with the ADGPH.

If the results of secondary and/or tertiary evaluation are indicative of an excess of risk and if the findings of the research evaluation suggest that it is warranted, then an etiologic investigation of the suspected cancer cluster may be initiated to determine if the exposure to a specific risk factor, environmental or occupational contaminant is associated with the suspected cancer cluster. This level of investigation can often be seen as research rather than a public health response to a community concern. Conducting etiologic investigations can take several years,

so DoH should consider what can be done in the interim to help protect the health of the affected population and keep its members informed.

However, an etiologic research study alone, and the demonstration of a statistically significant association, does not prove causation as determining causation often relies on clinical and laboratory studies. The research study may be undertaken by parties external to the investigative team, for example international and academic experts in the relevant fields, and may take several years. A plan including a communication strategy should be arranged to foster continued collaboration and risk communication between the etiologic study team and the original investigative team, informant and other concerned parties.

DoH will usually take a peripheral role, if any, in the research team. If DoH is the agency responsible for contracting the research team, approval is required from the ADGPH prior to proceeding with the tender process.

The circumstances of most etiologic studies are unique and the results should be published in a recognised peer-reviewed journal as the results of an investigation are expected to contribute to epidemiological and public health knowledge. The planning of the publication should commence in the research evaluation and include agreement on target journal, scope and authorship.

Figure 7. Process for Research Evaluation

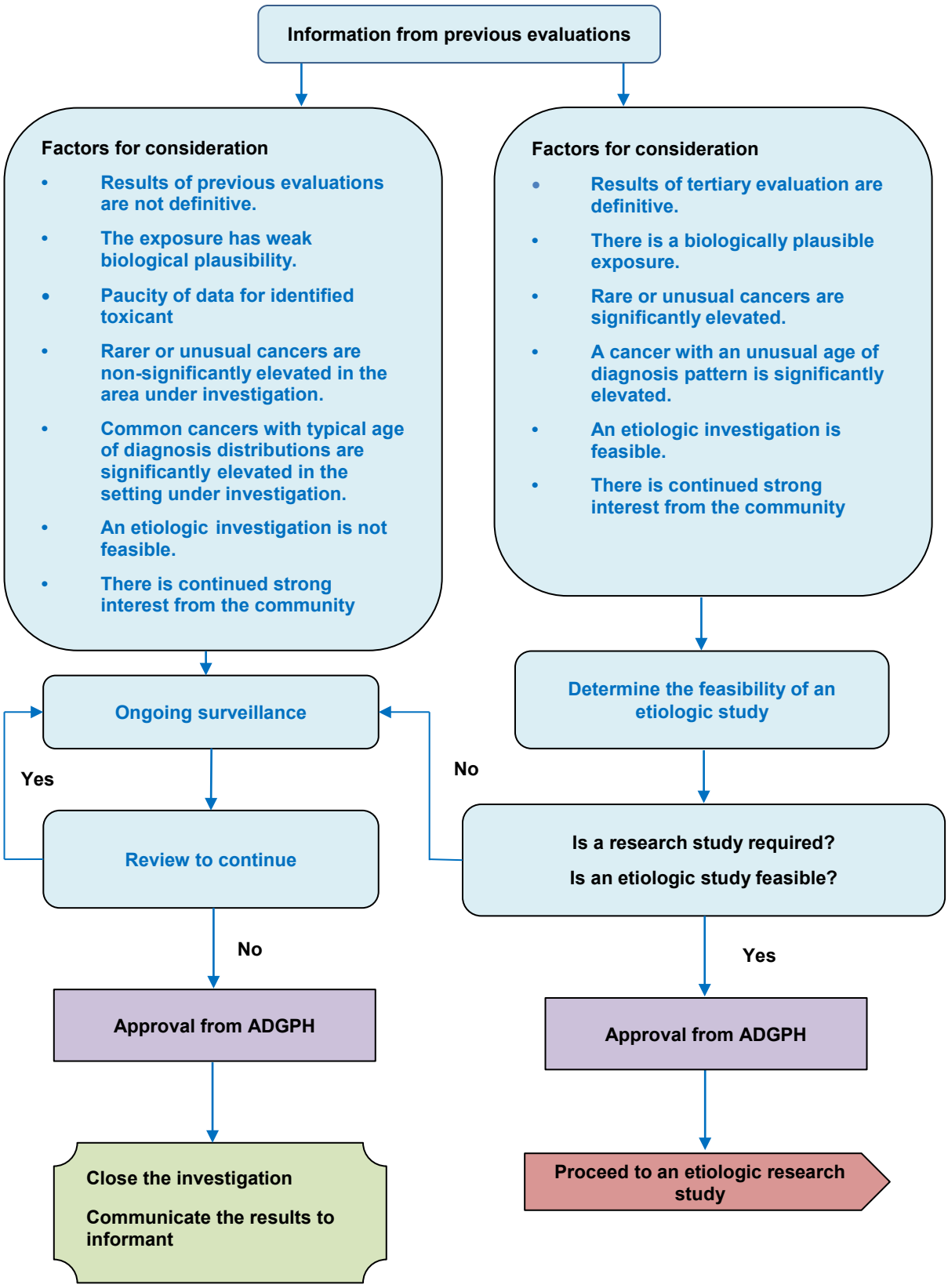


Table 7: Procedures for Research Evaluation

Task (responsible role)	Procedures
Procedures for ongoing surveillance **(Cluster Assessment Team)**	☐ Establish a system to ensure data on cancer cases in the setting are reported. ☐ Calculate five-year rates and trends annually using most recently available WA data or data maintained for the particular setting. ☐ Maintain contact with informant and provide updated rates on a yearly basis. ☐ Advise study population to maintain recommended cancer screening schedules and implement specific screening if determined appropriate. ☐ Re-evaluate need for continued surveillance annually.
Procedures for determining the feasibility of conducting an etiologic research study **(Cluster assessment team)**	**Determining the study hypotheses involving known causes of cancer in question** ☐ Review the scientific literature and past health agency reports. ☐ Investigate any possible environmental risk factors in the area. ☐ Establish a community panel to involve the community to discuss the issues such as cultural sensitivity and also gaining valuable information and diverse perspectives from members. ☐ Share information about time, cost, goals, purpose, and limitations of a potential study with all partners and carefully communicate realistic expectations. ☐ Establish an expert advisory panel to assess potential study design issues such as sample size, a small case number, study power, and study type. The experts should include an epidemiologist, a toxicologist, a physician, an environmental protection specialist, and a community-nominated expert and/or local representative to provide advice on assessment as needed. **Identification of study population and its characteristics** ☐ Consider the feasibility of obtaining descriptive, health, occupation, time lived/employed in that setting, and risk factor data. ☐ Consider the feasibility of obtaining full case ascertainment as described in Table 3-5 (secondary and tertiary evaluation). ☐ Consider the willingness of persons to participate in interviews or studies for gathering data on health and possible exposures. **Assess the plausibility that the cases and contaminants could potentially be associated:** ☐ Verify carcinogenicity of the environmental/occupational contaminants. ☐ Assess if environmental/occupational contaminant is present but there is insufficient evidence for it to be classified definite, probable or possible carcinogen. ☐ Examine possible and plausible routes of exposure to affected persons. ☐ Assessment of exposure dose-response, duration and its consistency with the latency period where it makes the causation with that particular cancer biologically plausible. ☐ Consider the possibility of historical records of chemical use or contamination at the particular location. ☐ Consider obtaining residential and occupational histories for affected person. **Identification of the available data on the possibility of exposure to environmental/occupational contaminant of concern:** ☐ Is there a clear scientific rationale? ☐ Is an historical exposure assessment, due to long latency of cancer needed? (some exposures might have occurred more than 20 years previously or exposure might have changed during that time. In this situation, environmental testing rarely provides accurate data on historical exposure. ☐ Determine whether exposure to suspected environmental/occupational hazards can be characterised accurately at the individual level and in a way that reflects the period of concern. ☐ Identify known current, ongoing, and historical environmental/occupational concerns in the community. ☐ Review and interpret historical exposure assessment in collaboration with the state and regional environmental protection or workplace specialists and toxicologists in order to determine whether there are any known or suspected area environmental or occupational contaminants or any known or suspected exposure pathway (s) that

	could potentially be related to cancer cases. ☐ Communicate clearly with the study population and explain why environmental or workplace testing is not feasible or is not appropriate. ☐ Communicate clearly with the public about the information assessment process to determine the possibility of epidemiological study, or independent interventions such as environmental or workplace testing to guide remediation efforts unrelated to the cancer of concern. **Identification of requirements for a research study design and available resources and data to conduct the study** ☐ Identify parameters to use for geographic scope, study time-frame and demographics. ☐ Consider study design, sample size, statistical tests and the effect of a smaller sample size on statistical power. ☐ Consider the analytical plan, hypothesis, and epidemiological and policy implications. ☐ Identify available resources and sources of funding. **Plan publication of results** ☐ Consider audience. ☐ Determine target journal. ☐ Identify scope. ☐ Agree on authorship. ☐ Design public communication strategy.

Appendix 1
Glossary

Terms	Definitions
Agent	Any factor being assessed, such as a chemical substance or a form of radiation, whose presence or absence (in the case of a deficiency disease) is essential for the occurrence of a disease or other adverse health outcomes.
Association	A statistical relationship between two or more events, characteristics, or other variables.
Biologic plausibility	The likelihood that a given factor can cause a biological effect within an individual that leads to disease. It is based on current knowledge of biological processes.
Cancer Cluster	A cancer cluster is the occurrence of a greater than expected number of cancer cases within a group of people in a geographical area over a period of time.
Cancer risk	Cancer risk is the likelihood, or chance, of getting cancer. The potential for exposure to a contaminant to cause cancer in an individual or population is evaluated by estimating the probability of developing cancer over a lifetime. The term “excess risk” is used because we all have a ‘background risk’ of about one in four chances for women and one in three for men of getting cancer in their lifetimes, and excess risk is the risk greater than this background risk. The potential to cause cancer is evaluated by estimating the probability of developing cancer over a lifetime.
Carcinogen	A cancer-causing substance or agent.
Case	A person with a particular disease, injury, or other health conditions that meets selected criteria (see also case definition).
Case definition	A set of uniformly applied criteria for determining whether a person should be identified as having a particular cancer type. In epidemiology, a case definition specifies clinical criteria and details of time, place and person.
Causal agent	A physical, chemical or biological agent where there is sufficient weight of evidence to attribute causation of particular disease or biological effects if sufficient levels of exposure occur.
Chance	Chance is something that happens unpredictably without discernible human intention or discoverable cause.
Cluster Assessment Team	A group of professionals who work together to conduct the cancer cluster investigation. It generally includes, but is not limited to, a public health physician, an epidemiologist, a toxicologist or other environmental health professional, a public communication officer, a representative from the WA Cancer Registry and a representative from the agency of the setting such as a hospital.
Cluster investigation	The scientific process to determine if there is an increased number of cases of a specific disease or condition and to determine if there is a biologically plausible causal agent/s for the diseases.

Cluster management	The process of evaluating alternative actions, selecting options and implementing them in response to cluster assessments. The decision making will incorporate scientific, technological, social, economic and political information. The process requires value judgements based on the tolerability of risks and the reasonableness of costs.
Cluster setting	The geographic boundaries or specified workplace of the reported cluster. This may be a workplace, a specific location within the residential community or a community facility bounded by the sites of a real or perceived exposure to the hazard.
Confidence interval	The interval for a statistical measure (mean, proportion or rate) with a given level of probability (conventionally 95%) that the true value of that measure is contained within that interval.
Confidence limit	The minimum or maximum value of a confidence interval.
Confounding	The distortion of the association between an exposure and a health outcome by other factors (confounding variables) that influence the outcome of the study.
Confounding variable	A factor that is associated with both the exposure and outcome of interest. Common confounders include age, smoking, socio-economic status. For example, smoking can be a confounder because smoking tends to be more prevalent in people exposed to non-tobacco-related toxins (e.g. alcohol consumption) and carcinogens, and may also be more prevalent in people with a range of diseases.
Distribution	In epidemiology, the frequency and pattern of health-related characteristics and events in a population. In statistics, the observed or theoretical frequency of values of a variable.
Dose-response	Association between an exposure and health outcome that varies, in a consistently increasing or decreasing fashion, as the amount of exposure (dose) is varied.
Dose-response assessment	Determination of the relationship between the magnitude of the dose or level of exposure of a population to an agent and the incidence of specified associated adverse effects.
Dose-response effect	The idea that larger doses will result in larger observable effects: one of the most important criteria for a causal relationship in epidemiological studies.
Environmental Health	Those aspects of human health determined by physical, chemical, biological and social factors in the environment.
Environmental health practice	It covers the assessment, correction, control and prevention of environmental factors that can adversely affect health, as well as the enhancement of those aspects of the environment that can improve human health.
Epidemiology	The study of causes, distribution and control of diseases in human populations. It has its origins in the study of epidemics but now broadly encompasses infectious diseases, chronic diseases, injury and determinants of health.
Excess risk	Risk difference, calculated as the risk among the exposed group minus the risk among the unexposed group.
Exposed group	A group whose members have had contact with a suspected cause of, or possess a characteristic that is a suspected determinant of, a particular health problem.
Exposure	Having come into contact with a cause of, or possessing, a characteristic that is a determinant of a particular cancer type. When people have been 'exposed', they have been in contact with something that is hypothesised to have an effect on health, such as. tobacco, nuclear radiation or pesticides in food. Contact may be via any route, oral, inhalation or through the skin. These are typically called 'risk factors' of disease. We are interested in whether the exposure results in higher (or sometimes lower) outcome rates.
Exposure Assessment	The estimation (qualitative or quantitative) of the magnitude, frequency, duration, route and extent of exposure to a potentially hazardous agent for the general population, for different subgroups of the population, or for individuals.

Funnel plots	A method of displaying, at the same time, rates for a large number of settings usually involving small number of events. Funnel plots take into account the variability expected from different population sizes.
Grey literature	Non-academic literature, often in the form of government and non-government reports.
Hazard	The capacity of an agent, situation or event to produce a particular type of adverse health or environmental effect.
Hazard assessment	Hazard assessment comprises hazard identification and dose-response assessment. It essentially identifies whether potentially hazardous agents are present, what type of health effects can arise with sufficient exposures and the incidence of those health effects at various levels of exposure.
Incidence	A measure of the frequency with which new cancer cases occur among a population during a specified period.
Incidence rate	Incidence rate is calculated as the number of new cases over a specified period divided either by the average population (usually mid-period) or by the cumulative person-time the population was at risk.
Informant	A person or organisation that provides information about a potential cancer cluster or raises concern of such a cluster to a health agency.
Latency period	The time from exposure to a causal agent to onset of symptoms of a (usually non-infectious) disease. The year of first exposure and the pattern and magnitude of exposure need to be considered. For cancer cluster assessments, a latency of five years is used as the minimum period for assessment.
Multiple comparisons	Adjustment of the p values from a cluster investigation for implied comparisons with similar populations.
Null hypothesis	The statistical hypothesis that an exposure is not associated with the cancer type under study, so that the risk ratio or odds ratio equals 1. The null hypothesis states that the results observed in a study are no different from those occurring due to chance alone.
***P* value**	The probability of observing an association between two variables or a difference between two or more groups as large as or larger than that observed, if the null hypothesis were true. Used in statistical testing to evaluate the plausibility of the null hypothesis (i.e., whether the observed association or difference plausibly might have occurred by chance).
Point source	A fixed potential source of exposure that is localised to a small geographic area. A point source cluster analysis would examine health outcomes around the point source.
Post-hoc bias	The potential bias that can occur when investigations are started because of a random clustering of events. Also known as the Texas sharpshooter fallacy, which describes a Texan shooting at the side of the barn and afterwards drawing a bull's eye around the biggest clustering of shots.
Reference population	The standard against which the population being studied can be compared. In the context of a cancer cluster investigation, the reference population would be a large unexposed group with similar population characteristics to the study population.
Risk factor	An aspect of personal behaviour or lifestyle, an environmental or occupational exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.
Spatial scan statistics	A statistical method that searches a large geographic area for smaller geographic clusters of higher or lower rates.

Statistical significance	The measure of how likely it is that a set of study results could have occurred by chance alone. Statistical significance is based on an estimate of the probability of the observed or a greater degree of association between independent and dependent variables occurring under the null hypothesis (see also *P* value and null hypothesis).
Study community	See study population.
Study population	The group of individuals in a community or organisation with a real or perceived exposure to a hazardous agent under assessment as part of the cluster investigation process. The population referred to in the case definition.
Surveillance	Data collection to detect events or identify trends to initiate public health action.
Temporal trends	Changes in the incidence and/or prevalence of a disease or risk factors that occur over time.

Appendix 2
Actions to close an assessment

Communication

Effective communication is vital at all stages of a cancer cluster investigation, but the communication of the findings needs careful consideration due to the public concern and potential impacts. Communicating the findings of a cluster investigation also offers an opportunity to educate the community about cancer and the value of proven strategies of prevention and early detection, as well as explain to the study populations what cancer cluster investigations can – and cannot – provide.

Often the findings of cancer cluster investigations are inconclusive due to the limitations of the scientific analysis when applied to the information available. In these circumstances, as in all cluster investigations, communication is the process through which a satisfactory outcome can be achieved for all groups involved.

Findings of a primary evaluation will normally be communicated in a written response to the informant by email or letter. For other evaluations, the findings will be presented in a report published by the DoH.

All communication, regardless of the form should include a clearly articulated and empathetic outline of the decision rationale. The response should be prompt and provide a clear outline of the criteria used to evaluate the cluster. It should contain relevant, accurate and timely information.

In addition to the findings of the assessment, any report produced should include the rationale for the epidemiological and environmental assessments, as well as consideration of the uncertainty of exposures to agents, case ascertainment and population at risk.

Any report needs to demonstrate that the public's specific concerns are addressed to ensure trust, credibility, competence, fairness and empathy are maintained. Being frank, honest and open as well as working with other credible sources will help in communications with the public.

An integrated communication plan should be developed to guide the release of the report to the study population and wider community with the assistance of the Communications Directorate. The findings of the report should be provided prior to public release to the study population and key external stakeholders identified in the communication plan. Ways to address different goals, audiences and media need to be carefully planned. The messages must be simple and easy to understand and accompanied with interpretation to ensure that the public recognise the implications. Advice should be sought from the Communications Directorate when dealing with the media.

Documentation

A detailed record of the investigation must be maintained.

Briefing and release

For primary evaluations, the ADGPH should be notified at the conclusion of the assessment, if the cluster is likely to be contentious. The ADGPH should also be provided with a copy of the response sent to the informant. The Communications Directorate must be informed if previously involved in the assessment.

When a report of an investigation is released, it must be approved by the ADGPH. The report will be forwarded to the cluster manager. In addition, a briefing should be prepared for the Minister for Health and a copy of the report attached. The briefing should include the communication plan.

Cluster Assessment Register

A cluster assessment register will record all relevant information about the cancer cluster investigation. In the case of a primary evaluation, the initial responder should contact the Epidemiology Branch, Public Health Division for the details required to complete the cluster assessment register. For other evaluations, a record of decisions, actions and any reports produced should be also recorded in the cluster assessment register.

Appendix 3
Calculating a Standardised Incidence/Mortality Ratio (SIR/SMR)

In epidemiology, the standardised Incidence Ratio (SIR) or Standardised Mortality Ratio (SMR), is a quantity, expressed as either a ratio or percentage quantifying the increase or decrease in incidence or mortality of a study cohort with respect to a reference population.

SIR: The standardised incidence ratio is the ratio of observed cases in the study group, to expected incidence cases in the reference population. This ratio can be expressed as a percentage simply by multiplying by 100.

SMR: The standardised mortality ratio is the ratio of observed deaths in the study group, to expected deaths in the reference population. This ratio can be expressed as a percentage simply by multiplying by 100.

If the SIR/SMR is quoted as a ratio and is equal to 1.0, then this means the number of observed cases/deaths equals that of expected cases/deaths. If higher than 1.0, then there is a higher number of cases/deaths than is expected. The process to derive a SIR/SMR constitutes an indirect form of age-standardisation. It has an advantage over the direct method of age-standardisation since age-adjustment is permitted in situations where age stratification of case data may not be available for the cohort being studied or where strata-specific case data are subject to excessive random variability.

The requirements for calculating SIR/SMR for a cohort are:

- the number of persons in each age group in the study population
- the age-specific incidence/death rates of the reference population in the same age groups as the study population
- the observed cases/deaths in the study population.

Expected cases/deaths would then be calculated simply by multiplying the cases/death rates of the reference population by the total number of participants in the study group at the corresponding age group and summing up all the values for each age group to arrive at the number of expected cases/deaths. The study population's cases/deaths are weighted based on

their particular distribution (age), as opposed to the reference population's distribution. This is a fundamental distinction between and indirect method of standardisation like SIR/SMR from direct standardisation techniques.

The SIR/SMR is usually presented with an indication of the uncertainty associated with its estimation, such as a confidence interval (CI) or p value, which allows it to be interpreted in terms of statistical significance.

Standardised incidence or mortality ratios (SIRs/SMRs) are conducted under the following circumstances:

- there are **at least** 5 observed cases/deaths of one type or related types of an uncommon cancer
- there is a plausible reason to suspect more than normal fluctuation over time of cases
- the latency issues are potentially consistent with a common factor (ages, dates of diagnoses and residency)
- community concern is high.

Requirements for Epidemiology Branch to conduct SIR/SMR analyses:

- observed numbers of cases/deaths are those confirmed via the WA Cancer Registry
- addresses are checked for accuracy if feasible
- expected numbers of cases/deaths are derived from state level age-specific rates from the WA Cancer Registry
- appropriate population data are used to calculate numbers of expected cases/deaths for comparison with observed cases/deaths
- SIR/SMRs are calculated separately for each gender OR combined where appropriate
- 95% confidence intervals are calculated
- the Lexis macro can be also used in SAS to accurately calculate the person-years of follow-up by age, sex, year and cancer or death type [38] if needed.

A SIR/SMR report to the cluster assessment team may be prepared which may include:

- tables with observed and expected numbers of cases, SIR/SMRs and 95% CIs
- explanation of likelihood of chance outliers for SIR/SMRs
- discussion of verification of community-reported cases.

Appendix 4
Scan Statistic

Introduction

This is a screening tool for evaluating a reported disease cluster. This method uses aggregated data to provide evidence of a suspected cluster and to identify their approximate location. Scan Statistics uses free SaTScan Software (http://www.satscan.org).[15-17]

SaTScan is free software that analyses spatial, temporal and space-time scan statistics. SaTScan software was developed by Dr. Martin Kulldorff, Professor of Biostatistics at Harvard Medical School.

It is designed for any of the following interrelated purposes:

- to perform geographical surveillance of disease, to detect spatial or space-time disease clusters, and to see if they are statistically significant
- to test whether a disease is randomly distributed over space, over time or over space and time
- to evaluate the statistical significance of disease cluster alarms
- To perform prospective real-time or time-periodic disease surveillance for the early detection of disease outbreaks.

Characteristics of Spatial Scan Statistics

- It takes into account both the heterogeneous distribution of cases and population density in space.
- It adjusts for any confounding variables.
- It searches for clusters with varying size of scanning window without specifying their size or location, which prevents pre-selection bias issues.
- It estimates the log likelihood ratio-based test statistics which takes multiple testing into account and delivers a single P value for the test of the null hypothesis. If the null hypothesis is rejected, we can specify the approximate location of the cluster that caused the rejection.

The spatial scan statistics is a method that searches a large geographic area for smaller geographic clusters of higher or lower rates to the reference population. This method will identify likely clusters in an area for the relevant time period and cancer site to determine if the suspected cancer cluster is among the most likely clusters in all of WA. A scanning window is placed on each geographical centroid and expanded to the next neighbouring centroid until it reaches a maximum defined population size. Calculations are made at each scanning window regarding the relative risk, expected numbers and likelihood. The most likely clusters are ordered in terms of the most significant. This method is created in such a way in order to debunk some of the many cancer cluster alarms that were clearly due to random chance, while at the same time have good power to detect a problem if there was one. That way, we avoid the Texas sharp shooter effect (i.e. a situation in which cases are noticed first and then the "affected" area is selected around them, thus making there appear to be a geographical relationship, similar to an instance in which the sharpshooter shoots the side of the barn first and then draws the bull's-eye around the bullet holes).

The spatial scan statistics can be used as an additional tool to provide further evidence if there is a significant elevation incidence or mortality rates in the study population.

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