



**International Guideline  
Harmonization Group**  
for Late Effects of Childhood Cancer



# Handbook for Guideline Development

---

Version 1

Authors:

Renée L. Mulder, Emma Children's Hospital/Academic Medical Center, Amsterdam, the Netherlands

Morven C. Brown, Newcastle University, Newcastle upon Tyne, UK

Roderick Skinner, Great North Children's Hospital, Royal Victoria Infirmary /Newcastle University, Newcastle upon Tyne, UK

Melissa M. Hudson, St. Jude Children's Research Hospital, Memphis, US

Leontien C.M. Kremer, Emma Children's Hospital/Academic Medical Center and Cochrane Childhood Cancer Group, Amsterdam, the Netherlands on behalf of the IGHG core group and the PCSF-WP6 group

September 2014

This handbook has been developed by a collaborative effort of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) ([www.ighg.org](http://www.ighg.org)), the PanCareSurFup Consortium (PCSF) ([www.pancaresurfup.eu](http://www.pancaresurfup.eu)) and the Cochrane Childhood Cancer Group (CCG) ([ccg.cochrane.org](http://ccg.cochrane.org)). This handbook provides information about guideline development chaired by IGHG and PCSF.

This handbook can be used by the chairs and members of topic groups after they have been assigned to develop a special guideline.

Copyright © IGHG and PCSF 2014

This Handbook should be cited as Mulder RL, Brown MC, Skinner R, Hudson MM, Kremer LCM. Handbook for guideline development; collaboration between International Guideline Harmonization Group, PanCareSurFup and Cochrane Childhood Cancer Group.

Other contributors: Armenian SH, Bárdi E, Bhatia S, Constine SL, Frey E, Haupt R, Kühni C, Landier W, Levitt G, Michel G, Oeffinger KC, Wallace WH.

Funding

Dutch Cancer Society, the Netherlands (UVA 2011-4938)

7<sup>th</sup> Framework Programme of the EU, PanCareSurFup (257505)

KiKa grant Cochrane Childhood Cancer Group KiKa 123

# Contents

- 1 Introduction.....4
  - 1.1 Aim of the handbook.....4
  - 1.2 Clinical practice guidelines.....4
  - 1.3 Guidelines for the long-term follow-up of CAYA cancer survivors.....5
  - 1.4 Structure of this handbook .....5
- 2 Methodology utilised by IGHG/PCSF to develop evidence based CPG's.....6
  - 2.1 Preparation phase .....6
  - 2.2 Development phase .....7
    - Step 1: Evaluate concordances and discordances of current recommendations .....8
    - Step 2: Formulate clinical questions.....9
    - Step 3: Identify and select the evidence.....10
    - Step 4: Summarize and appraise quality of evidence.....13
    - Step 5: Formulate recommendations .....14
  - 2.3 Finalisation phase.....15
- 3 Communication and monitoring of progress.....16
  - 3.1 Expected timeline for guideline development .....16
  - 3.2 Webconferences.....16
  - 3.3 Shared-calendar .....17
- 4 Overview of other key sources of information and support.....18
  - Appendix 1.....20
  - Appendix 2.....23
  - Appendix 3.....24
  - Appendix 4.....25
  - Appendix 5.....26
  - Appendix 6.....27
  - Appendix 7.....28

# 1 Introduction

## 1.1 Aim of the handbook

The principle aim of this handbook is to serve as a reference tool and provide guidance to the members of the working groups involved in the guideline development work of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG)<sup>1</sup> ([www.ighg.org](http://www.ighg.org)) and the PanCare Childhood and Adolescent Cancer Care and Follow-up Studies (PCSF) Consortium ([www.pancaresurfup.eu](http://www.pancaresurfup.eu)). It is expected that the systematic approach will improve the methodological quality of the clinical practice guidelines for the follow-up of survivors of childhood, adolescent and young adult (CAYA) cancer. It is believed this will have a positive impact on the quality of care CAYA cancer survivors receive.

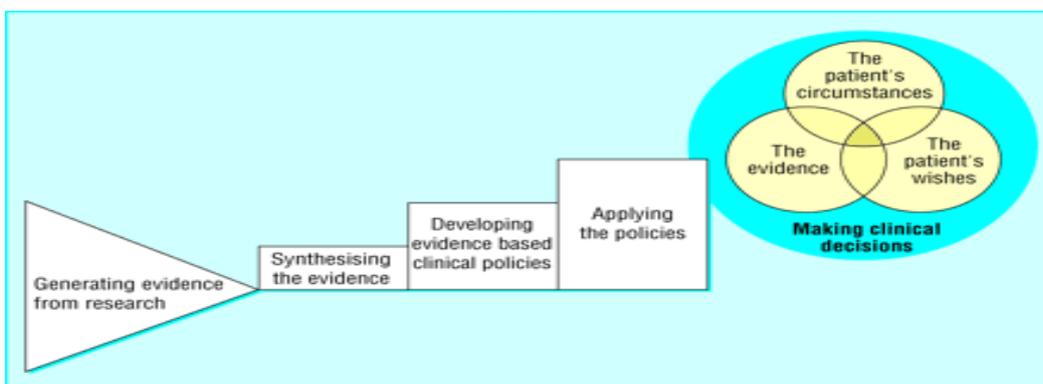
## 1.2 Clinical practice guidelines

Clinical practice guidelines (CPGs) are defined by the Institute of Medicine as “*statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.*”<sup>2</sup>

CPGs aim to provide appropriate recommendations for practice based on a transparent process and informed by evidence. CPGs are essential to ensuring that CAYA cancer survivors receive optimum health care.<sup>2,3</sup> However, it is essential to ensure optimum quality of guidelines if they are to improve both the process and outcome of care.

It is vital that CPGs are developed based on the methods of evidence-based medicine (EBM). EBM is “*the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients*”.<sup>4</sup> EBM begins with the formulation of clinically relevant questions based on the Participants, Interventions, Control group & Outcome (PICO) system, followed by a synthesis of the evidence based on an extensive literature search (e.g. systematic review or evidence tables). The data is then used to develop evidence based clinical policy (recommendations) before applying these policies or CPGs in practice (**Figure 1**).

EBM is an integration of best research evidence, clinical expertise and patient concerns.



**Fig. 1: The path from the generation of evidence to the application of evidence**<sup>5</sup>



If time permits, members are encouraged to listen to the first web-training conference given by L. Kremer. This provides audio commentary and PowerPoint slides to give useful background information to evidence based clinical practice guidelines. This is available at:  
<https://connect.sunet.se/p5ggc2b67eg/>

### **1.3 Guidelines for the long-term follow-up of CAYA cancer survivors**

Several guidelines for the long-term follow-up of CAYA cancer survivors have been developed and published, including those produced by the US Children's Oncology Group (COG), Dutch Childhood Oncology Group (DCOG), United Kingdom Children's Cancer Study Group (UKCCSG) and Scottish Intercollegiate Guidelines Network (SIGN). A recent survey performed by PCSF found that these guidelines were in widespread use across Europe and that some European nations have also developed additional local guidelines.

However, as these guideline development groups worked independently, inconsistencies exist in the methodology used and also in the final recommendations of these guidelines. A major consequence of this is uncertainty among clinicians regarding which guidelines to implement.

Therefore, the goal of the IGHG and of PCSF is to harmonise efforts and employ a systematic and rigorous methodology to produce clinical consensus in guidelines for long-term follow up of major late adverse effects in CAYA cancer survivors. We aim to promote healthy lifestyles, provide on-going monitoring of health status, facilitate early detection of late effects, and advise about timely intervention strategies to preserve health.

### **1.4 Structure of this handbook**

In this handbook we aim to provide information that may be useful to members of the IGHG/PCSF guideline working groups, and the working group leaders in particular as they prepare for and proceed through the guideline development work.

Specifically the handbook will:

1. Outline the key steps in the development of clinical practice guidelines.
2. Direct members to other important sources of information/documentation integral to the guideline development work.
3. Provide practical information regarding the organisation and management of the working groups.

As opposed to fully reproducing information which is documented elsewhere, this handbook shall provide an overview and direct members to other documents which explain the relevant issues in more detail. Links to these other documents are embedded in the text, and can be accessed by clicking on the document name. These documents include a published methodology paper, protocols from previous guideline topics which have been completed by IGHG/PCSF, and also worked examples from the published breast cancer surveillance guidelines to illustrate more clearly the process

## 2 Methodology utilised by IGHG/PCSF to develop evidence based CPG's

Developing a guideline encompasses three phases:

1. Preparation phase
2. Development phase
3. Finalisation phase



If time permits, members are encouraged to listen to the second web-training conference given by R Mulder. This provides useful background information to the development of clinical practice guidelines. This is available at:

<https://connect.sunet.se/p2a8jwypnwg/>

### 2.1 Preparation phase

Convening an effective guideline development group is a crucial stage in producing a guideline. Each guideline topic group will consist of a working group including:

- Chair(s): leaders in the field
- Coordinator(s): project managers administrating group activities
- Advisors: Leontien Kremer, Melissa Hudson, Renée Mulder, Rod Skinner
- Working group leaders: leaders supervising literature reviews of focused clinical questions
- Working group members

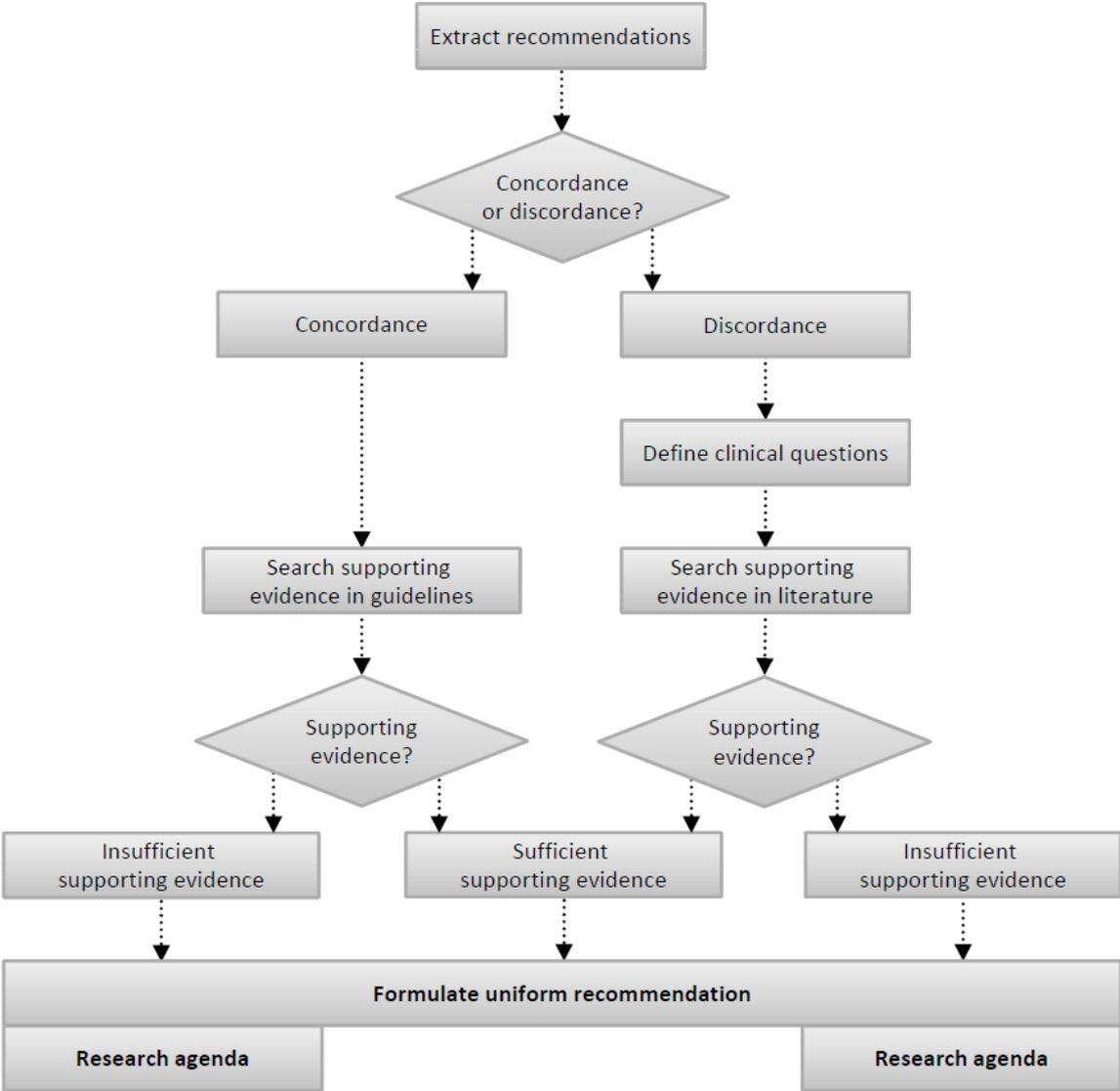
Diversity is an essential feature of a guideline development group. Its exact composition should be tailored to the guideline topic and reflect the range of stakeholders involved. As a minimum the group should comprise at least of content experts, non-expert clinicians, health care providers and methodologists. In addition, patients and their representatives may be eligible members.

## 2.2 Development phase

In general, the guideline development process consists of five steps:

1. Evaluate concordances and discordances among recommendations in existing guidelines
2. Formulate clinical questions
3. Identify available evidence
4. Summarize evidence
5. Formulate recommendations

Figure 2 outlines the main steps that IGHG & PCSF will be undertaking in the development of guideline recommendations.



**Fig. 2: Key stages in the development of recommendations**

## Step 1: Evaluate concordances and discordances of current recommendations

The first step is to extract the recommendations for the topic from the existing COG, DCOG, UKCCLG and SIGN guidelines. The level of discordance/concordance between these recommendations is then evaluated.

If recommendations are concordant, supporting evidence will be reviewed to determine if it is sufficient or insufficient. Extensive evidence summaries will not be developed for concordant recommendations.

Discordant recommendations will form the basis for the formulation of clinical questions. These clinical questions will clearly state what the evidence aims to answer.

Below is an example of the evaluation of the concordance and discordance regarding the surveillance of breast cancer in survivors (Table 1).

*Table 1: Concordance and discordance 'Who needs breast cancer surveillance?'*

	COG	DCOG	UKCCLG	Concordant/ discordant
<b>Who needs breast cancer surveillance?</b>				
<b>At risk</b>				
<b>Chest radiation</b>	Yes	Yes	Yes	<b>Concordant</b>
<b>± Alkylating agents</b>	Not specified	Not specified	Yes	<b>Discordant</b>
<b>High risk</b>	Not specified	≥7-20 Gy chest radiation (excl. TBI)	Not specified	<b>Discordant</b>
<b>Highest risk</b>	≥20 Gy chest radiation	≥14-40 Gy abdominal radiation ≥20 Gy chest radiation ≥40 Gy abdominal radiation TBI	Not specified	<b>Discordant</b>

## Step 2: Formulate clinical questions

Effective and efficient guideline development involves asking and answering key clinical questions. These questions should be clear, focused and closely define the boundaries of the topic. They will serve as a starting point for the systematic searching of the literature which aims to identify all the available evidence. These questions also form the basis of development of the recommendations.

The **PICO** (Participants, Interventions, Control group & Outcome) framework is helpful to identify the main elements of the clinical question. It breaks the question down into four key elements:

- Who are the **P**articipants you want to study? (e.g. gender, age, disease)
- What is the **I**ntervention you want to examine? (e.g. type of treatment)
- What do you want to **C**ompare against your intervention of interest? (e.g. alternative interventions - this is not always necessary or relevant)
- What are the **O**utcomes you want to measure? (e.g. improved quality of life, late effects)

For every guideline topic, the clinical questions should address five key issues which are important for the final recommendations:

- Who needs surveillance?
- At what age or time from exposure should surveillance be initiated?
- At what frequency should surveillance be performed?
- What surveillance modality should be used?
- What effective treatment options are available if health problems are identified?

An example of the formulation of a clinical question is shown in Table 2. This is taken from the breast cancer surveillance guidelines.

Table 2: Example clinical question for 'Who needs breast cancer surveillance?' derived from the PICO structure

<b>P</b>	<b>I</b>	<b>C</b>	<b>O</b>	<b>Final question</b>
Female childhood cancer survivors	Low dose chest radiation	Childhood cancer survivors treated without chest radiation	Breast cancer risk	What is the risk of breast cancer in female childhood, adolescent and young adult cancer survivors treated with 1-9 Gy chest radiation compared to survivors treated without chest radiation?

### Step 3: Identify and select the evidence

It is important that the searching of the literature is thorough, objective and rigorous. An inefficient or biased literature search can compromise the validity of the recommendations and the guidelines. The aim is to identify as many relevant studies as possible (within the limits of resources and time). It is also essential that the literature search is transparent, well documented and is reproducible.

Where adequate published systematic reviews exist, additional searching may be limited to updating, covering the time period since the review was conducted.

Carrying out a literature search to identify and select relevant studies will involve:

1. Designing search strategies
2. Defining in- and exclusion criteria
3. Selecting studies for review/inclusion

#### 1. Design search strategies

**Where to search?** Searches are carried out in bibliographic databases. There are several which can be searched but Medline and Embase are two of the key international health databases. Although there is significant overlap in these databases, differences do exist, therefore it is important to search more than one. The Cochrane Central Library of Controlled Trials is also a database for systematic reviews that can be searched.

In addition to searching bibliographical databases, papers should also be identified through references in the existing guidelines, important reviews and key papers known to the group members.

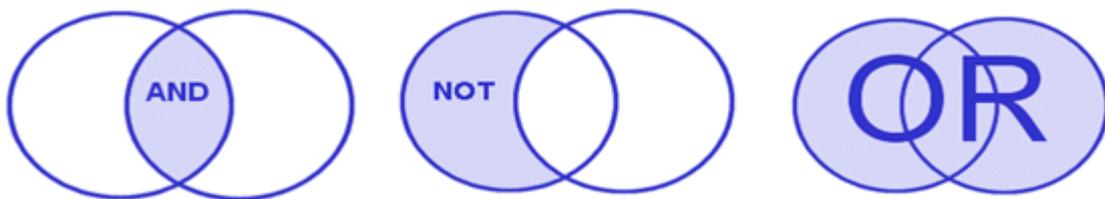
**What to search?** In order to search for and identify relevant studies, a search strategy must be developed. The search strategy is based on the main concepts in the clinical question identified through the PICO framework e.g. population, intervention, comparison and outcome. The clinical questions should be translated into key words and/or search terms. The Cochrane Childhood Cancer Group ([ccg.cochrane.org](http://ccg.cochrane.org)) will develop the search strategies. However, members of the group will be asked to suggest appropriate search terms and to check if the final search strategy is comprehensive.

Searches can be conducted in databases using either controlled vocabulary based on Medical Subject Headings (MeSH) or by using free-text/keywords. MeSH headings are useful as they index all articles which use different spellings/words to describe the same concept (e.g. cancer, lymphoma, leukemia, Ewing's sarcoma) under the same subject heading (e.g. Neoplasms). This saves you having to search for a large list of synonyms. Keywords however, look for the exact word you are searching for within the title and/or abstract of the articles within the database.

It is important to consider and include all the related terms, variations in spellings and synonyms for each concept included in your search. A combination of subject headings and keywords is usually recommended to ensure that as many relevant records as possible are identified.

In **Appendix 1** standard search strategies as used by the IGHG-PCSF group are shown. In addition, an example of a full search strategy taken from the male gonadal dysfunction guidelines protocol can be found in **Appendix 2**.

**How to search?** In the example in Appendix 2 many of the terms relating to the PICO framework are combined by 'OR'. This is a Boolean operator. Other Boolean operators are 'AND' and 'NOT'. Boolean operators make it possible to combine the results from two or more different searches using controlled vocabulary or keywords.



- **AND** – retrieves only those articles in which all of the terms appear
- **NOT** – used to exclude a term from your search
- **OR** – retrieves those articles in which either of the terms appear



For an explanation of search strategies and Boolean operators please see Lundh et al (2007). [Development of a search strategy](#).<sup>6</sup>

## 2. Defining in- and exclusion criteria

It is important to define clear in- and exclusion criteria for the selection of studies, based on the **PICOs**. Using the breast cancer example, the following criteria can be considered:

- **Patients:** female childhood, adolescent and young adult cancer survivors aged < 30 years at diagnosis (at least ≥ 75% of the study group)
- **Treatment:** radiation to fields that include breast tissue
- **Sample size:** ≥ 20 patients
- **Follow-up:** ≥ 50% of study population followed ≥ 2 years after cancer diagnosis

- **Outcome:** breast cancer risk
- **Analyses:** univariate and multivariate
- **Study design:** all studies; systematic reviews provide the highest level of evidence followed by randomized controlled trials, observational studies, and case studies
- **Language:** all studies must be written in English
- **Regarding reviews:** During screening of abstracts include all reviews (both systematic and narrative reviews). In case it is a systematic review, then include and use conclusions for generating evidence tables. In case it is a narrative review, then exclude, but screen reference lists at the end of process (when the draft evidence tables are ready) in order to check if we missed any relevant papers.

### 3. Identify and select studies

Once the literature search of the electronic databases is complete, the following steps should be taken for selecting the studies:

- Based on the titles and abstracts select studies that possibly meet the inclusion criteria. This will be done by two reviewers.
- For every abstract report if the study should be included, excluded, or if you are uncertain.
- The results of the two reviewers are then combined and compared. Discuss the discrepancies with your companion.
- All “included” and “uncertain” abstracts will be obtained in full text to determine if the inclusion criteria are met. This will also be done by two reviewers.
- For every full text paper note if the study should be included, excluded, or if you are uncertain. If excluded, note the reason why you excluded the study.
- Report for which clinical question the study should possibly be included.
- Discuss the discrepancies with your companion to reach consensus.

#### Step 4: Summarize and appraise quality of evidence

The evidence found in the literature should be summarized in evidence tables (**see Appendix 3**). The evidence tables provide information about study and patient characteristics, primary study outcomes, and additional remarks, such as factors that may bias results.



For an explanation of the different types of bias, please see van Dalen et al (2007) [Quality of studies included in a systematic review and associated risk of bias](#)<sup>7</sup> and the [Cochrane Bias Methods Group](#).

For every single study a conclusion will be formulated by those who prepared the evidence table (**see Appendix 3**). Subsequently, the conclusions of the single studies should be combined in one overall conclusion for that specific clinical question (**see Appendix 3**). The level of evidence for the overall conclusion will then be graded according to the grading schema shown in **Appendix 5**.

Grading the evidence gives an impression of the quality of the included studies. It is not related to the importance of the recommendation but to the strength of the supporting evidence.

The evidence is graded according to three categories:

- Level A, high level of evidence: evidence from well performed and high quality studies or systematic reviews with a low risk of bias, and direct, consistent and precise results.
- Level B, moderate to low level of evidence: evidence from studies or systematic reviews with few important limitations.
- Level C, very low level of evidence: evidence from studies with serious flaws (high risk of bias, indirect, inconsistent, imprecise).

## Step 5: Formulate recommendations

Once the selection and summary of the evidence is complete, the available evidence must be combined and translated into recommendations. The group members will discuss the evidence and formulate the recommendations considering the quality of the evidence, the benefits versus harms of the surveillance intervention, patient values, and the need to maintain flexibility of application across health care systems.

Recommendations will be classified into four categories: class I (green), strong recommendations to do; class IIa (yellow), moderate recommendation to do; class IIb (orange), weak recommendation to do; class III (red), recommendation not to do (**see Appendix 6**). There is an explicit link between the recommendations and the supporting evidence. If a recommendation is based on consensus, this should explicitly be stated in the guideline.

The recommendations should be a stand-alone text written in a complete sentence. The wording should be unambiguous, clearly defined, easy to translate into clinical practice, and agreed by the complete guideline development group.

The recommendations should include the following items:

- Who needs surveillance?
- At what age or time from exposure should surveillance be initiated?
- At what frequency should surveillance be performed?
- What surveillance modality should be used?
- What effective treatment options are available if health problems are identified?

A first draft of the recommendation will be prepared by a smaller group (i.e. chairs, advisors, and working group leaders). Next, the recommendation will be discussed and further formulated by the total working group. Once group consensus has been reached, the recommendations will be discussed in the IGHG and PCSF groups. Additional experts and patients/survivors in the field should be invited to be involved in this final discussion.

Below are the recommendations from the breast cancer surveillance guidelines (**Table 3**).

Table 3: Recommendations 'Who needs breast cancer surveillance?'

Who needs breast cancer surveillance?
Providers and female childhood, adolescent and young adult cancer survivors treated with chest radiation should be aware of breast cancer risk.
Breast cancer surveillance <i>is recommended</i> for female childhood, adolescent and young adult cancer survivors treated with ≥20 Gy chest radiation.
Breast cancer surveillance <i>is reasonable</i> for female childhood, adolescent and young adult cancer survivors treated with 10-19 Gy chest radiation based on clinical judgment and considering additional risk factors.
Breast cancer surveillance <i>may be reasonable</i> for female childhood, adolescent and young adult cancer survivors treated with 1-9 Gy chest radiation based on clinical judgment and considering additional risk factors.

## 2.3 Finalisation phase

### 1. Writing the guideline

All guideline topics will be summarized in a manuscript appropriate for publication in a peer-reviewed journal. The guideline should include the following items:

- Background
- Methods: clinical questions, search strategy, selection of literature
- Results: description of evidence, overall conclusions, quality of the evidence
- Considerations: translation evidence into recommendations, balance benefits vs. harms, patient values, different health care systems
- Recommendations
- Reference list

### 2. External review

After recommendations have been formulated, there will be a commentary phase where external experts review the guideline for content and implementability. Feedback is sought preferably among the scientific, professional and patient organisations involved. Feedback can also be invited from methodological experts who review the guideline for methodological validity.

### 3. Updating the guideline

Guidelines should be kept up to date. All IGHG/PCSF guidelines will carry a statement indicating that they will be considered for revision 2 years after publication. Searches for new evidence should be performed and updating of the recommendations might be considered.

## 3 Communication and monitoring of progress

### 3.1 Expected timeline for guideline development

Please note that the timelines of guideline development work are dependent on many factors, therefore, timelines will differ between topic groups. An example timeline is shown in **Appendix 7**. This provides an illustration of the stages that are expected to occur in development work and approximate timelines for these. However, these timelines will be modified according to the work of each topic group and most likely revised as the group progress through their work.

### 3.2 Webconferences

To arrange web-conference times, Doodle ([www.doodle.com](http://www.doodle.com)) is useful. Invitations are sent and group members select which days/times they can/cannot attend. Switching on the time-zone support will automatically adapt the time to each participants own time-zone so there is no confusion.

Web-conferences can be held through the Adobe Connect system supported by PanCareSurFup. However, you may have another system you would rather use. Adobe Connect is a free service which provides a chat room with instant messaging facilities. It is also possible to upload documents onto the chat room screen to provide a shared view for all attendees. Before using the Adobe Connect system you will need a **web-link** and a **room-code**. This can be arranged by contacting Elise Witthoff ([elise.witthoff@med.lu.se](mailto:elise.witthoff@med.lu.se)).

All participants in the web-conference will need a **headset with a microphone** otherwise background noise and feedback may interfere with the sound quality.

When logging into the connect system, the system will automatically install an add-in. Please check with your organisation that add-ins will not be blocked, for instance by a fire wall. A trial run with a colleague may be useful to ensure there are no problems.

When you log into the room, there is a **microphone icon** to the top left of the screen. Click on this to switch it to **'Connect my audio'**.

If after doing this you still cannot hear the audio, click on the **'Meeting'** tab (also on top left) and select **'Audio Setup Wizard'**. Following the instructions will take you through a setup to check that your microphone/headset is detected by the system and that your volume settings are suitable.



For more information on Adobe connect, including screen grabs directing you through the log-in stage, please refer to the [Quick Manual to the Adobe connect conference system](#). Also if experiencing problems please refer to [Resolving Sound Problems in Adobe Connect](#).

### **3.3 Shared-calendar**

It may be useful to set up a shared-calendar system for your working group, or to send calendar invitations for meetings for teleconferences / webconferences . These can be set-up in Microsoft Outlook. They allow tasks and events to be entered and for reminder alerts to be set. This can be useful to provide a visual representation of the programme of work and for working groups to keep track of tasks and progress.

## 4 Overview of other key sources of information and support

Briefly, others main sources of information available are:

- The [methodology paper](#) describing the rationale behind the harmonisation effort and the planned methodology published by Kremer et al (2013)<sup>1</sup>
- [Recommendations for breast cancer surveillance](#): a report from the IGHG published by Mulder et al (2013)<sup>8</sup>
- Recordings of two one-hour training web-conferences on evidence based guidelines given by Leontien Kremer and Renée Mulder to PCSF WP6 members in June 2012:
  - <https://connect.sunet.se/p5gqc2b67eg/>
  - <https://connect.sunet.se/p2a8jwypnwq/>
- Protocol for Guideline Development PanCareSurFup Work Package 6 on request
- Protocol from previous guidelines on request

Useful websites are:

- International Guideline Harmonization Group: <http://www.ighg.org/>
- Cochrane Childhood Cancer Group: <http://ccg.cochrane.org/ebch-cochrane-journal/>
- Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group: <http://www.gradeworkinggroup.org/>
- Appraisal of Guidelines Research & Evaluation (AGREE): <http://www.agreetrust.org/>

### References

1. Kremer LCM, Mulder RL, Oeffinger, KC, et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guidelines Harmonization Group. *Pediatr Blood Cancer* 2013;60:543-549.
2. Institute of Medicine. *Clinical practice guidelines we can trust*. Washington: The National Academies Press, 2011.
3. Burgers J, Grol R, Eccles M. Clinical guidelines as a tool for implementing change in patient care. In Grol R, Wensing M & Eccles M (eds). *Improving patient care: the implementation of change in clinical practice*. 2005. Edinburgh: Elsevier.
4. Sackett DI, Rosenberg WMC, Muir Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312:71.
5. Haynes B. Barriers and bridges to evidence based clinical practice. *BMJ* 1998;317:273.

6. Lundh A, Kremer LCM, Leclercq E. Tips and tricks for understanding and using SR results. No. 6: development of a search strategy. Evidence-Based Child Health: A Cochrane Review Journal 2007; 2:937-939.
7. van Dalen EC, Kremer LCM, Moyer VA. Tips and tricks for understanding and using SR results. No. 8: quality of studies included in a systematic review and associated risk of bias – ‘garbage in, garbage out’. Evidence-Based Child Health: A Cochrane Review Journal 2007; 2:1321-1324.
8. Mulder RL, Kremer LCM, Hudson MM, et al. Recommendations for breast cancer surveillance for female childhood and young adult cancer survivors given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology 2013;14:e621-629.

## Appendix 1

### Standard search strategies

#### **Cancer**

Cancer OR cancers OR cancer\* OR oncology OR oncolog\* OR neoplasm OR neoplasms OR neoplasm\* OR carcinoma OR carcinom\* OR tumor OR tumour OR tumor\* OR tumour\* OR tumors OR tumours OR malignan\* OR malignant OR hematocological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo\*

#### **Childhood cancer**

((leukemia OR leukemi\* OR leukaemi\* OR (childhood ALL) OR AML OR lymphoma OR lymphom\* OR hodgkin OR hodgkin\* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom\* OR sarcoma, Ewing's OR Ewing\* OR osteosarcoma OR osteosarcom\* OR wilms tumor OR wilms\* OR nephroblastom\* OR neuroblastoma OR neuroblastom\* OR rhabdomyosarcoma OR rhabdomyosarcom\* OR teratoma OR teratom\* OR hepatoma OR hepatom\* OR hepatoblastoma OR hepatoblastom\* OR PNET OR medulloblastoma OR medulloblastom\* OR PNET\* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom\* OR meningioma OR meningiom\* OR glioma OR gliom\*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor\* OR brain tumour\* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor\* OR central nervous system tumour\* OR brain cancer\* OR brain neoplasm\* OR intracranial neoplasm\*) OR testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR testicular cancer OR cancer of testis OR testis tumour OR testis neoplasm\* OR testis tumour\* OR testis tumor\* OR (leukemia, lymphocytic, acute[mh])

#### **Children**

Infan\* OR toddler\* OR minors OR minors\* OR boy OR boys OR boyfriend OR boyhood OR girl\* OR kid OR kids OR child OR child\* OR children\* OR schoolchild\* OR schoolchild OR school child[tiab] OR school child\*[tiab] OR adolescen\* OR juvenil\* OR youth\* OR teen\* OR under\*age\* OR pubescen\* OR pediatrics[mh] OR pediatric\* OR paediatric\* OR peadiatric\* OR school[tiab] OR school\*[tiab]

#### **Children and young adults**

Infan\* OR toddler\* OR minors OR minors\* OR boy OR boys OR boyfriend OR boyhood OR girl\* OR kid OR kids OR child OR child\* OR children\* OR schoolchild\* OR schoolchild OR school child[tiab] OR school child\*[tiab] OR adolescen\* OR juvenil\* OR youth\* OR teen\* OR under\*age\* OR pubescen\* OR pediatrics[mh] OR pediatric\* OR paediatric\* OR peadiatric\* OR school[tiab] OR school\*[tiab] OR young adult[mh] OR adult[mh] OR young adult

#### **Survivors**

Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR Survivor, Long-Term OR Survivors, Long-Term OR survivo\* OR surviving

#### **Radiotherapy – general**

Radiotherapy OR radiation OR radiation therapy OR irradiation OR irradiat\* OR radiation injuries OR injuries, radiation OR injury, radiation OR radiation injury OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation OR radiation\* OR irradiation OR radiations

### **Radiotherapy – extensive**

radiometry OR radiometr\* OR radiation dosage OR radiation dosage\* OR radiation dose OR radiation doses OR radiation dosis OR radiation dosimetry OR radiation dosimetr\* OR radiotherapy dosage OR radiotherapy[sh] OR irradiation dose OR radiotherapy dose OR dose calculation OR near beam dose OR in beam dose OR outside beam dose OR out of beam dose OR radiation/epidemiology OR Radiation monitoring OR Organs at risk OR radiation effects[sh] OR radiation injury OR radiation injuries OR radiation OR radiation\* OR radiations OR Radiotherapy OR NCTP OR normal tissue complication probability OR DVH OR Dose Volume Histogram OR Radiotherapy Planning OR Conformal/adverse effects OR Dose Response Relationship, radiation OR Radiation Injuries/Prevention and Control OR Chemoradiotherapy/Adverse Effects OR radiation therapy OR irradiation OR irradiat\* OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation

### **Dose-response relationship – combine with radiotherapy search**

Dose response OR threshold dose OR ((minimum OR maximum OR cumulative) AND (dose OR dosage)) OR dose-response relationship, radiation OR radiotherapy dosage OR irradiation dose OR radiotherapy dose OR radiation dosage OR radiation dose OR radiation doses OR radiation dosis OR radiation dosage\*

### **Radiotherapy fields – combine with radiotherapy search**

#### Cranial

Brains OR brain OR brain\* OR encephalon OR encephalons OR encephalon\* OR cranial OR cranial\* OR intracranial OR intracranial\* OR craniospinal OR cranios\* OR skull\*

#### Hypothalamic-pituitary

Hypothalamus OR Hypothalamus, Middle OR Hypothalamus, Anterior, OR Hypothalamus Posterior OR Pituitary Gland, Posterior OR Skull OR Orbit OR Orbits OR Eye OR Ear OR Nasopharynx) AND Radiotherapy OR Cranial Irradiation OR Whole-Body Irradiation

#### TBI

Total body OR whole body OR total body\* OR body whole\*

### **Chemotherapy**

Antineoplastic Protocols OR Antineoplastic Combined Chemotherapy Protocols OR Chemoradiotherapy OR Chemoradiotherapy, Adjuvant OR Chemotherapy, Adjuvant OR Consolidation Chemotherapy OR Induction chemotherapy OR Maintenance chemotherapy OR Chemotherapy, Cancer, Regional Perfusion OR Antineoplastic agents OR chemotherap\*

### **Alkylating agents**

Antineoplastic agents, alkylating\* OR antineoplastic alkylating agents OR alkylating agents, antineoplastic OR antineoplastic drugs, alkylating OR antineoplastics, alkylating OR alkylating antineoplastic drugs OR alkylating drugs, antineoplastic OR antineoplastic alkylating drugs OR drugs, antineoplastic alkylating OR alkylating antineoplastic agents OR alkylating antineoplastics OR Alkylating Agents OR alkylating agent\*  
OR busulphan OR busulfan\* OR myleran\* OR myelosan\* OR Carmustine OR BCNU OR Chlorambucil OR ifosfamide OR iphosphamide OR iso endoxan OR isophosphamide OR isofosfamide OR ifosfa\* OR iphospha\* OR isofosfa\* OR cyclophosphamide OR cyclophosphane OR cytophosphan OR endox\* OR cyclophospha\* OR Lomustine OR CCNU OR lomustine\* OR Mechlorethamine OR mechlorethamine\* OR Chlormethine OR Mustine OR Chlorethazine OR Procarbazine OR procarbazin\* OR Melphalan OR melphalan\* OR Thiotepa OR Thio Tepa OR Thiophosphamide OR thiothepa\* OR temozolomide OR dacarbazine OR decarbazine OR Fludarabine monophosphate\*

**Platinum compounds**

Cisplatin OR Platinum Diamminodichloride OR cis-Platinum OR cis Platinum OR  
Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR  
Platinol OR Platidiam OR Platino OR Biocisplatinum OR CDDP OR CACP OR cisplatin\* OR abiplatin  
OR neoplatin OR cis-DDP OR Carboplatin OR CBDCA OR Carbosin OR Carbotec OR Ercar OR  
Neocarbo OR Paraplatin OR Carboplat OR Paraplatine OR Platinwas OR Ribocarbo OR Blastocarb  
OR Nealorin OR carboplatin\* OR Oxaliplatin OR oxaliplatin\* OR oxaliplatine OR Eloxatine OR Eloxatin  
OR eloxatin\* OR dacotin OR dacplat OR OR I-ohp OR oxalatoplatinum OR Platinum OR Platinum  
Compounds OR platinum\* OR organoplatinum compounds [mh]

**Cytarabine**

cytosine\* OR citosin\* OR cytarabin\* OR citarabin\* OR arabino\* OR arabitin\* OR aracytine\* OR  
aracytidin\* OR cytin\* OR cytidine\* OR ara-c OR arac OR arafcyt OR cytosar\* OR cytozar\* OR ara-C  
OR beta-Ara C

**Anthracyclines**

anthracyclines OR anthracyclin\* OR idarubicin OR idarubic\* OR epirubicin OR epirubic\* OR  
adriamycin OR doxorubicin OR doxorubic\* OR adriamyc\* OR daunorubicin OR daunorubic\* OR  
daunoxome OR doxil OR caelyx OR myocet

**Mitoxantrone**

mitoxantrone OR mitoxantr\*

**MIBG**

131I-Meta-iodobenzylguanidine OR 131I-MIBG OR 131I-metaiodobenzylguanidine OR Iodine-131  
Metaiodobenzylguanidine OR Iobenguane (131I) OR (3-Iodo-(131I)benzyl)guanidine OR Iodine  
Radioisotopes/therapeutic use OR 3-Iodobenzylguanidine/therapeutic use) OR (iodine-131-  
metaiodobenzylguanidine OR 131I-MIBG therapy OR I-metaiodobenzylguanidine OR I-131-MIBG OR  
I-131-Metaiodobenzylguanidine OR (131) I-MIBG OR 3-Iodobenzylguanidine[mh] OR (131) I-  
metaiodobenzylguanidine OR (MIBG AND (treatment OR therapy))

## Appendix 2

### Example search strategy for male gonadal dysfunction

Search Patient 1:	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR testicular cancer OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor* OR (leukemia, lymphocytic, acute[mh]))
Search Patient 2:	male[tiab] OR males OR boy OR boys OR boyfriend OR boyhood
Search Intervention 3:	Radiotherapy OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation injuries OR injuries, radiation OR injury, radiation OR radiation injury OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation OR radiation* OR irradiation OR radiations
Search Intervention 4:	Testicles OR testicle OR testes OR testis OR testis* OR testicle* OR testes* OR pelvic region OR region, pelvic OR pelvis region OR region pelvis OR pelvis* OR pelvic*
Search Intervention 5:	Brains OR brain OR encephalon OR encephalons OR brain* OR encephalon*
Search Intervention 6:	total body OR whole body OR total body* OR body whole*
Search Outcome 7:	spermatogenesis OR gonadal disorder OR spermiogenesis OR spermatocytogenesis OR spermatogenic failure OR azoospermia OR oligospermia OR asthenozoospermia OR teratozoospermia OR oligoasthenoteratozoospermia OR dysspermia OR normozoospermic OR semen OR semen analysis[text] OR semen quality[text] OR sperm OR sperm count OR sperm motility OR spermatozoa OR progeny OR offspring OR posterity OR fertility OR infertility OR subfertility OR reproduction OR fertilization OR conception OR paternity OR fatherhood OR parenthood OR pregnancy outcome OR fertile OR infertile OR subfertile OR sperm maturation OR aspermia OR spermatozoon abnormality
Search Outcome 8:	androgen hormone insufficiency OR leydig cell OR cells, leydig failure OR testicular interstitium cell failure OR testicular failure OR gonadal failure OR hypogonadism OR low testosterone OR testosterone deficiency OR androgen deficiency OR low testosterone* OR hypogonadism* OR leydig cell*
<b>Search 1 AND 2 AND 3 AND (4 OR 5 OR 6) AND (7 OR 8)</b>	
<b>Filters: published in the last 10 years; Humans</b>	<b>= 488 hits</b>

### Appendix 3

#### Evidence table for 'Who needs breast cancer surveillance?'

What is the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with 1-19 Gy chest radiation?				
<i>Inskip et al.</i> Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol 2009;27:3901–7				
Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-centre case-control study  1970-1986  Follow-up: Median 19.4 (range 6.7-29.6) yr	6,647 5-yr childhood cancer survivors aged ≤21 yr at diagnosis  120 childhood cancer survivors with breast cancer matched to 464 childhood cancer survivors without breast cancer	Chest radiation: 107/120 (89%) cases 328/464 (71%) controls  Absorbed radiation dose: Mean 13.4 Gy controls Dose cases not reported (range >0-0.13 Gy to 30.0-60.0 Gy)	<i>Odds ratio (95% CI)</i> <i>Breast dose</i> <b>&gt;0-0.13 Gy vs. 0 Gy:</b> 1.4 (0.5-4.4) <b>0.14-1.29 Gy vs. 0 Gy:</b> 1.9 (0.7-5.4) <b>1.30-11.39 Gy vs. 0 Gy:</b> 1.9 (0.7-5.0) <b>11.40-29.99 Gy vs. 0 Gy:</b> 7.1 (2.9-17.0) <b>30.0-60.0 Gy vs. 0 Gy:</b> 10.8 (3.8-31.0) <i>P</i> for trend <0.001  <i>Excess odds ratio per Gy to the breasts (95% CI)</i> 0.27 (0.10-0.67)  <i>Recalculated odds ratio (95% CI)</i> <i>Breast dose</i> <b>1.3-9.9 Gy vs. 0 Gy:</b> 1.9 (0.7-5.4) <b>10.0-19.9 Gy vs. 0 Gy:</b> 6.5 (2.3-18.5)	Analyses were adjusted for type of childhood cancer diagnosis.

## Appendix 4

### Example conclusion table for 'Who needs breast cancer surveillance?'

<b>What is the risk of breast cancer in childhood and young adult cancer survivors treated with 1-19 Gy chest radiation?</b>	
<b>Conclusion single studies</b>	
<b>Childhood cancer survivors</b>	
Non-significant increased risk of breast cancer after 1-9.9 Gy and 10-19.9 Gy chest radiation compared to patients treated without chest radiation (RR: 1.5 (0.3-8.1) and RR: 3.7 (0.6-24.2), respectively). Note that this study has a methodological limitation which may have resulted in an underestimation of risk.	<i>Guibout 2005</i>
Significant increased risk of breast cancer in childhood Wilms tumor survivors compared to the general population (SIR: 5.8 (2.6-11.0)). It is unclear whether or not breast cancer was secondary to low dose chest radiation (10-19 Gy), the high abdominal fields, or a combination (likely the latter).	<i>Taylor 2008</i>
Non-significant increased risk of breast cancer after 1-11 Gy chest radiation and significant increased risk of breast cancer after 11.40-29.99 Gy chest radiation compared to patients treated without chest radiation (OR: 1.9 (0.7-5.0) and OR: 7.1 (2.9-17.0), respectively). (Estimated OR based on post hoc analysis for 13 Gy and 19 Gy compared to 0 Gy: 4.51 and 6.13, respectively)	<i>Inskip 2009</i>
<b>Hodgkin disease survivors</b>	
Non-significant increased risk of breast cancer after 4-6.9 Gy chest radiation and significant increased risk of breast cancer after 7-23.1 Gy chest radiation compared to 0-3.9 Gy chest radiation in Hodgkin disease survivors (RR: 1.8 (0.7-4.5) and RR: 4.1 (1.4-12.3), respectively). (Estimated RR based on post hoc analysis for 19 Gy compared to 0 Gy: 3.85)	<i>Travis 2003</i>
Non-significant increased risk of breast cancer after 4-23.2 Gy chest radiation compared to 0.3-3.9 Gy chest radiation in Hodgkin disease survivors (RR: 1.11 (0.32-3.58)).	<i>van Leeuwen 2003</i>
<b>Overall conclusion</b>	
Some evidence suggests that female childhood, adolescent and young adult cancer survivors treated up to 19 Gy chest radiation have an increased risk of breast cancer. It is known that there is a linear dose response, but precise estimates have not yet been published.	<i>5 studies in CAYA cancer survivors</i>

### Example conclusion of evidence for 'Who needs breast cancer surveillance?'

<b>Who needs breast cancer surveillance?</b>	
<b>Breast cancer risk in <i>childhood, adolescent and young adult cancer survivors</i></b>	
Increased risk after ≥20 Gy chest radiation	Level A
Increased risk after 10-19 Gy chest radiation	Level B
Increased risk after 1-9 Gy chest radiation	Level C
Increased risk after total body irradiation	Level C
Increased risk after high abdominal field radiation	Level C
Decreased risk after alkylating agent chemotherapy	Level B
Decreased risk after ≥5 Gy radiation to the ovaries	Level B

## Appendix 5

### Criteria for grading and formulating overall conclusions

Conclusions of evidence	Study quality	Study findings for risk factors	Wording in conclusions
<b>A</b> <b>High level of evidence</b>	Evidence from well performed and high quality studies or systematic reviews (low risk of bias, direct,* consistent, precise)	If a risk factor is significantly associated with the outcome in <b>≥95%</b> of the studies	'There is evidence that...'
<b>B</b> <b>Moderate/ Low level of evidence</b>	Evidence from studies or systematic reviews with few important limitations	If a risk factor is significantly associated with the outcome in <b>≥50%</b> of the studies reporting on this risk factor, and in the remaining studies this association is not significant	'Evidence suggests that...'
<b>C</b> <b>Very low level of evidence</b>	Evidence from studies with serious flaws (high risk of bias, indirect, inconsistent, imprecise)	<p>If a risk factor is significantly associated with the outcome in <b>1 study</b></p> <p>If a risk factor is significantly associated with the outcome in <b>&lt;50%</b> of the studies, while in the remaining studies this association is not significant</p> <p>If a risk factor is significantly (either positively or negatively) associated with the outcome in <b>&gt;50%</b> of the studies, while the remaining studies show the opposite association of the risk factor and outcome</p>	'Some evidence suggests that...'
<b>Conflicting evidence</b>	N/A	If a risk factor is significantly (both positively and negatively) associated with the outcome in the same number of studies of comparable quality	'There is conflicting evidence...'
<b>No evidence</b>	N/A	If no studies reported on a risk factor	'No studies reported on...'

\* Direct evidence comes from research that directly compares the interventions in which we are interested when applied to the populations in which we are interested and measures outcomes important to patients. Studies are indirect if there are differences in study population (our population of interest is childhood cancer survivors), interventions, or outcome measures, or if there are indirect comparisons of interventions.

## Appendix 6

### Criteria for grading the recommendations

Grade of Recommendation	I Strong recommendation to do	Ia Moderate recommendation to do	Ib Weak recommendation to do	III Recommendation not to do
<b>Conclusions of evidence (based on GRADE)</b>	Benefits >>> risk & burdens	Benefits >> risk & burdens	Benefits >= risks & burdens	No benefit / Potentially harm
<b>A High level of evidence</b> Consistent evidence from well performed and high quality studies or systematic reviews (low risk of bias, direct, consistent, precise).	Strong recommendation based on high level of evidence	Moderate recommendation based on high level of evidence	Weak recommendation based on high level of evidence	Recommendation based on high level of evidence
<b>B Moderate /Low level of evidence</b> Evidence from studies or systematic reviews with few important limitations.	Strong recommendation based on moderate/low level of evidence	Moderate recommendation based on moderate/low level of evidence	Weak recommendation based on moderate/low level of evidence	Recommendation based on moderate/low level of evidence
<b>C Very low level of evidence</b> Evidence from studies with serious flaws. Only expert opinion, or standards of care.	Strong recommendation based on expert opinion	Moderate recommendation based on very low level of evidence Diverging expert opinions	Weak recommendation based on very low level of evidence Diverging expert opinions	Recommendation based on very low level of evidence Expert opinion
	<b>Wording in recommendations:</b>			
	We recommend We should Is recommended Is indicated Is useful Is beneficial Is effective	We suggest Is reasonable Is probably recommended Can be useful Can be beneficial Can be effective	We might suggest Might be reasonable Might be considered Usefulness is unknown	We do not recommend Should not be performed Is not useful Is not beneficial Is not effective Is potentially harmful

## Appendix 7

### Example timeline for guideline development work

Tasks to be finished	By whom	Estimated time to complete task
<b>Preparation phase</b>		
Compose working group Identify coordinator and WG leaders	Chair and advisors	Allow 2 months for this before:
<i>Conference call:</i> introduction and composition of working groups	Total group	
<b>Development phase</b>		
<b>Step 1</b>		
Develop protocol Evaluate concordances/discordances Formulate clinical questions	Chair, coordinator and advisors	Allow 1-2 months for this before:
<b>Step 2</b>		
Send clinical questions to WG leaders and members	Coordinator	Allow 2 weeks for this before:
<i>Conference call:</i> discuss clinical questions and search strategy options	Total group	
<b>Step 3</b>		
Finalize clinical questions Develop search strategy Define in- and exclusion criteria	Chair, coordinator, advisors and WG leaders	Allow 4 weeks for this before:
<i>Conference call:</i> discuss search strategy and in- and exclusion criteria	Total group	
Perform literature search	Cochrane Childhood Cancer Group	Allow 2 months for this before:
Send results literature search and instructions to WG leaders and members	Coordinator	
<i>Conference call:</i> discuss steps for evidence selection	Total group	
Select evidence based on search Send final inclusion of eligible studies to coordinator	WG leaders and members	Allow 1-2 months for this depending on number of articles
<b>Step 4</b>		
<i>Conference call:</i> discuss steps for summarizing the evidence	Total group	
Make evidence tables	Coordinator, WG leaders and members	Allow 1 month for this before:
<i>Conference call:</i> if necessary to discuss difficulties	Total group or separate WGs	Allow 1 month to make modifications before:
Circulate evidence tables to the whole group	Coordinator	
Each WG checks evidence tables (missing studies, completeness, etc) Return comments evidence tables	WG leaders to coordinate within their WG	Allow 1 month for this before:
Agree final evidence tables	Total group	
<i>Conference call:</i> discuss and agree final evidence tables and outline next steps for formulating overall conclusions of the evidence	Total group	
Develop conclusion of evidence tables	WG leaders to coordinate within their WG	Allow 1 month for this before:
Circulate conclusions of evidence tables to the group	Coordinator	
<i>Conference call:</i> discuss and agree final conclusions of evidence tables	Total group	Allow 1 month to make modifications before:

<b>Step 5</b>		
<i>Conference call:</i> formulate draft recommendations	Chair, coordinator, advisors and WG leaders	Allow 2 weeks before:
<i>Conference call:</i> discuss draft recommendations	Total group	Allow 2 months to make modifications before:
<b>Discuss and develop final recommendations, preferably in a face-to-face meeting</b>	IGHG, PCSF and external experts	