Instructions for Authors

Instructions for Authors for the Preparation of Drafts for the *IARC Handbooks* – Screening

These Instructions for Authors were prepared by the scientific staff of the *IARC Handbooks* programme for the members of the Working Group to guide them in preparing the first drafts of a *Handbook* on screening before the Working Group meeting. For transparency, they are accessible to the scientific community and the general public. Authors are also provided with a detailed outline, which defines the structure of the *Handbook*, and with instructions specific to each *Handbook* topic as appropriate. Authors are also advised to consult a recent volume of the *IARC Handbooks*.

Although individual authors (members of the Working Group) prepare the preliminary drafts, the final *Handbook*, including the resulting evaluations, is a consensus document that is reviewed and validated by the entire Working Group.

The Instructions for Authors were modified in 2019 to align with the Preamble to the *IARC Handbooks* as updated in October 2019, as recommended by the Advisory Group to Recommend an Update to the Preamble to the *IARC Handbooks*.

This document should be read in conjunction with the Preamble to the *IARC Handbooks*, which describes the scientific principles and procedures used in developing a *Handbook*, the types of evidence considered, and the scientific criteria that guide the evaluations.

Please read these instructions carefully.

Note: The sections below cover all the different topics that may be reviewed in an *IARC Handbook* on screening. Not all topics will be addressed in every *Handbook*.

Contents

Instructions at a glance, valid for all writing assignments

Each IARC Handbook *is composed of sections that are narrative reviews and sections that are systematic reviews. When you receive your writing assignment, make sure to verify which type of review you will be asked to conduct.*

- IARC uses an online tool for draft sharing and peer review during the preparation and conduct of *Handbooks* meetings: the IARC Online Publications System (IOPS).
- Working Group members are provided with the results of preliminary searches performed by the IARC Secretariat. PDF files of all retrieved articles are made available on a dedicated FTP site.
- The searches are preliminary. It is the responsibility of each Working Group member to ensure that all relevant studies or a representative set of studies (depending on the section assigned to you) are included, that is, not all articles retrieved may be included, and Working Group members are expected to include any other informative studies that they may identify.
    - It is important to search for and include data from low- and middle-income countries to the extent possible. Where data are lacking for important regions or countries, this may be noted.
- Working Group members draft text in Microsoft Word. Tables are created using the templates provided (see Annex 1). Please submit your drafts electronically via the IARC Online Publication System (IOPS).
    - Please adhere to the word limits, content description, and format indications where indicated.
    - Use of text that is a direct copy and paste from original publications is considered plagiarism and can be detected by specialized software.
- The writing assignment (including, where applicable, study selection diagram, study summary, study design and outcome tables, quality assessment of individual studies, and synthesis of the body of evidence, depending on the section assigned to you) should be prepared before the meeting according to the deadline provided to you.

- Working Group members are expected to conduct peer reviews of other sections. Detailed information will be provided after the Working Group members have submitted their writing assignments.
- At the meeting, within subgroups, the Working Group members critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus subgroup drafts. During the plenary session, each subgroup presents its drafts for scientific review and discussion, for adoption as a consensus Working Group product.
- Summaries are written in subgroups as a result of the revised subgroup drafts, and reviewed in detail during the plenary session. Summaries are the most-read part of the *Handbook* and should be finalized by the end of the meeting.

Instructions for the narrative reviews

In the narrative reviews, the text should give a representative overview, and not all available data are considered comprehensively. Information is obtained from research studies, government reports, and other publicly available sources, with all statements of scientific fact substantiated by a fully referenced article, report, or website.

Characterization of the disease (up to 10 pages; about 1000 words for each subsection, and tables and/or figures)

This section is composed of several subsections, generally including but not restricted to: descriptive epidemiology, natural history of the disease, treatment and survival, and risk and preventive factors.

The distribution of the disease in terms of the worldwide burden of the cancer is described (incidence, mortality, prevalence, and survival rates). Regional differences and time trends are noted. Expected trends in the absence of screening are a relevant component of this section. The natural history of the disease and the established risk and preventive factors are briefly described (see the table template in Annex 1). Information on treatment and survival in different settings is reviewed, with a worldwide perspective.

Table template:
Risk and preventive factors

Global screening practices (up to 15 pages; 500–2000 words and 1 table per subsection, as appropriate)

This section is organized by geographical region (Europe; Canada and USA; Latin America; Africa; Western, Central and South Asia; South-East Asia; Australia and New Zealand) or WHO region, limiting the description to those countries or settings where screening takes place.

The following aspects are summarized, if available:

- policies and guidelines for, and regulation of, screening;
- type of screening offered (e.g. opportunistic screening, pilot, organized population-wide programme), infrastructure for diagnosis and treatment, standard diagnostic procedures;
- screening modalities most commonly used or recommended; and

- extent of population coverage and participation rates.

Results may be summarized in tables, in particular for those regions where many countries are presented.

Table templates:

Screening programmes in well-established settings

Screening programmes in low- and middle-income countries

Screening techniques (2000–3000 words for each technique or subchapter)

It is important to distinguish between the screening technique and the screening procedure, i.e. between the technique itself and the way in which it is administered.

At the beginning of each section summarizing the efficacy and/or effectiveness of a screening method, the method under consideration is briefly described. Information may be tabulated (e.g. for data on test performance). The technical aspects and the state-of-the-art application of the method are described concisely, highlighting:

- equipment and staff expertise;
- technical quality control;
- screening performance (ability of test to detect cancer and to distinguish cancer from non-cancer conditions); and
- host factors affecting screening performance.

Table template:

Test performance (individual studies or meta-analyses)

Considerations of methodological issues in included studies (3000–4000 words and 20–30 references)

This section provides a narrative on methodological considerations specific to the types of studies under review, or to the assessment of the population, intervention, or outcomes investigated. These may include, for example, methodological considerations on randomized trials, observational studies, and the definitions of harms in the given context, of the balance of benefits and harms, and of cost–effectiveness analyses.

Emerging methods (up to 2500 words and 20 references per method)

These subsections are narrative reviews of methods that may be available in some countries but are not yet in routine use, methods for which there are not enough data available to make an evaluation, or methods that are still under development.

For the most important, relevant, and/or mature methods, this section is typically organized similarly to the sections for methods for which an evaluation is conducted; it includes information on the screening technique, studies evaluating the efficacy or effectiveness of the methods – usually relying on end-points such as detection rate of precancerous lesions or other intermediate end-points – and studies on adverse effects, benefit–harm ratio, and cost–effectiveness.

For emerging methods that are still in development, the text briefly presents the detection method and its most recent developments.

This section may contain tables, for example for comparing the methods described with respect to key features and patient considerations, or to present the performance in detecting neoplasia.

Table templates:

Comparison of emerging methods

Test performance (individual studies or meta-analyses)

Participation in screening (4000–5000 words and about 50 references)

This section is a narrative review of studies on participation in screening for the cancer under review. It first presents the main determinants of participation in screening with the different methods evaluated, at the policy level, at the organizational level, at the provider level, and at the patient level. Demographic, cultural, and behavioural considerations that affect participation in screening are presented in a global perspective, with some specific, local characteristics, as appropriate.

The section then summarizes the studies of interventions to increase participation in screening with the various methods and, if data are available, on studies that compare participation between different methods. The information may be tabulated if there are numerous studies or important results to present. Another important part of this section is an overview of information available on informed decision-making.

Table template:

Studies (RCTs) of interventions to increase participation

Populations at increased or decreased risk (1000–3000 words and 20–30 references per differential-risk population)

This section is a narrative review of studies of screening or surveillance in defined high-risk or low-risk groups. For each category of population at increased or decreased risk (genetic predisposition, family history of cancer, personal history of precancerous lesions, comorbidities, etc.), this section describes the condition leading to an increased or decreased risk, the evidence from epidemiological studies that assess the effectiveness of screening or surveillance in such a population, and the current surveillance strategies. This section should not aim to summarize all studies evaluating the increase in risk for the cancer under study in these populations.

Instructions for the systematic reviews

Sections that lead to evaluations of the preventive and harmful effects of the intervention(s) will follow the principles of a systematic review, and specific instructions apply.

This section is a comprehensive, critical review that presents, for each screening procedure, all of the pertinent studies on efficacy, effectiveness, and adverse effects, and identifies the level of evidence for the cancer-preventive effects. The length of the section will be determined by the number of studies reviewed.

1. Comprehensive searches of the literature and selection of studies (IARC Secretariat)

(1) The IARC Secretariat develops systematic search strategies and carries out preliminary searches of the peer-reviewed literature. The search terms used, as well as the full final search strategy, are recorded and are made available to the Working Group.

(2) The IARC Secretariat screens the search results by title and abstract (in EndNote), focusing on excluding studies that do not address the intervention or cancer-related outcomes.

(3) The IARC Secretariat sorts the studies by section or subsection (see the outline) and documents the numbers of studies identified and categorized by topic on the FTP site.

2. Screening and organizing the results (individual Working Group members)

The IARC Secretariat provides to the Working Group member the articles (in PDF format) for the studies from these preliminary searches and from previous *Handbooks* (when applicable).

The Working Group member performs a full-text review of all the retrieved articles for relevance to the evaluation. Reasons for additional exclusion by the Working Group member during the preparation of the writing assignments or during the meeting will be recorded.

The searches are preliminary. It is the responsibility of each Working Group member to ensure that all relevant studies are included, that is, not all articles retrieved may be included, and Working Group members are expected to include any other informative studies that they may find.

The epidemiological (experimental or observational) studies may report data on the following outcomes (as applicable):

- Beneficial effects: reduction in risk of incidence, reduction in risk of mortality, shift in disease stage, other measures of screening effectiveness; the effects may also be reported in sub-analyses (e.g. according to invitation or participation, age range);
- Adverse effects: false-positive and false-negative findings, overdiagnosis (likelihood of unnecessary treatment), short- and long-term side-effects, psychological factors;
- The balance of benefits and harms;
- Cost–effectiveness: by setting, development index, age range, etc.

3. Description of the characteristics and results of the included studies (individual Working Group members)

The Working Group member extracts the relevant data in a standardized manner. Tables include the information needed to assess study quality. The text highlights the characteristics of the studies and the key results, and presents the major strengths and limitations of the study. Information given in the tables does not need to be repeated in the text.

Tables

Study design and relevant numerical results of all included studies are presented in tabular format. Each type of study has a table template to enable comprehensive reporting of the pertinent information in a standardized manner.

Table templates for randomized controlled trials:
RCT design
RCT results
Meta-analyses of RCTs

Table templates for observational studies:
Observational studies – Cohort studies
Observational studies – Case–control studies

Text

Included studies are described succinctly, providing essential information about the study (design, location, number of subjects) and the key results (risk estimate, 95% confidence interval). Example of description:

> The United Kingdom Flexible Sigmoidoscopy Screening Trial (UKFSST) was a randomized controlled trial of once-only screening with sigmoidoscopy (Atkin et al., 2010). Men and women aged 55–64 years who were registered with participating general practices in the United Kingdom were eligible for the trial, provided they had no history of colorectal cancer, adenomas, or inflammatory bowel disease, had a life expectancy of at least 5 years, and had not received a colonoscopy or sigmoidoscopy in the previous 3 years. Eligible subjects (368 142) were first sent a questionnaire asking whether they would participate in a randomized controlled trial of colorectal cancer screening. Those who agreed to participate were then randomized in a 2:1 ratio to the control arm or the intervention arm of the trial. Subjects in the intervention arm underwent baseline sigmoidoscopy with polypectomy. Those with polyps meeting any of the following criteria were referred for colonoscopy: ≥ 10 mm in diameter, ≥ 3 adenomas, tubulovillous or villous histology, high-grade dysplasia, malignancy, or ≥ 20 hyperplastic polyps above the distal rectum. Trial enrolment began in November 1994 and was completed in March 1999. A total of 170 432 individuals were randomized, and after exclusions for deaths and previous colorectal cancer, 170 038 were included in the analysis (112 939 in the control arm and 57 099 in the intervention arm); 50.0% were women. The participation rate in the baseline screening was 71%; of those screened, 5% underwent follow-up colonoscopy, of whom 85% subsequently entered a surveillance programme.

The level of detail should be proportional to the importance of the study in the context of all of the studies presented. Information given in the tables does not need to be repeated in the text unless it is especially important for interpreting the results. Risk estimates and 95% confidence intervals should be provided for the main results, without description of statistical significance. *P* values for trend may be reported when available.

Multiple publications on the same study population may result from (i) inclusion in independent studies of overlapping populations, or (ii) successive follow-ups of a single cohort. In these situations, only the most recent, most comprehensive, or most informative report should be reviewed in detail in the text and tables. Other publications will be, in case (i), briefly noted in the text and in the Comments field in the table, and in case (ii), listed in the Reference field in the table.

Less informative studies may be listed briefly, giving key characteristics and results of the study, or as an aggregate of related studies.

For each study or group of studies, an expert assessment of the strengths and limitations as well as important points of interpretation should be indicated in square brackets [e.g. inadequate duration, underpowered study, lead time bias, contamination of non-screened group] and/or in the Comments field in the tables.

Subsections describing a number of studies may have a brief introduction describing the included literature and the reasons for exclusions, if any, and highlighting important issues of interpretation. Example of an introduction:

> This section summarizes findings from the randomized controlled trials on the effects of sigmoidoscopy on colorectal cancer mortality, colorectal cancer incidence, and all-cause mortality. All relative risks and hazard ratios are from intention-to-treat analyses, unless otherwise stated. For per-protocol analyses, the United Kingdom Flexible Sigmoidoscopy Screening Trial (UKFSST) and the Screening for Colon and Rectum (SCORE) trial reported adjusted relative risks derived using the Cuzick method (Cuzick et al., 1997). The Norwegian Colorectal Cancer Prevention (NORCCAP) trial reported per-protocol 10-year risk differences using an instrumental variable approach; these were converted to relative risks to obtain a comparable metric to that reported for the other trials. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial did not report per-protocol analyses.

4. Evaluation of study quality (individual Working Group members)

The Working Group member reviews the included studies and evaluates their quality on the basis of considerations such as the study design, methodology, and reporting of results, as described in Part B, Section 5 of the Preamble to the *IARC Handbooks*. Studies that are considered uninformative are excluded from the evaluation, and the reasons for such exclusion may be explained at the beginning of the chapter (e.g. “Studies reporting … have been excluded because ….”).

For each of the included studies, the Working Group member assesses the study quality by considering the parameters listed in the Preamble (a condensed list is given below). Specific risks of bias will be assessed using the standardized form provided.

Study quality assessment checklist

- Consider the clarity in describing the study design and its implementation
- Consider the completeness of reporting of all other key information about the study and its results
- Has the study been designed and conducted in a manner that would minimize selection bias and other forms of bias?
- Has the screening intervention been assessed in a way that was not related to outcome status?
- Is the study population of sufficient size to obtain precise estimates of effect?
- Is there sufficient elapsed time from intervention to measurement of outcome for an effect, if present, to be observable?
- Is there an adequate intervention contrast?
- Are there relevant and well-defined time windows for intervention and outcome?
- Is the outcome measure (incidence of cancer, mortality from cancer, or an intermediate outcome) appropriate for the screening intervention and the cancer type under consideration?
- Are the methods used to assess the intervention adequate (including validity and reliability)?
- Please discuss if the likelihood (and direction) of present bias in the measure(s) of association is due to intervention measurement error or misclassification.
- Did the authors take into account, in the study design and analysis, potentially confounding variables, including co-exposures, that could influence the occurrence of the outcome and may be related to the intervention of interest?
- Did you identify other potential sources of bias (reporting bias, etc.)?
- Are the statistical analysis methods used adequate?
- Are the statistical methods able to obtain unbiased estimates of intervention–outcome associations, confidence intervals, and test statistics for the significance of measures of association?
- Are the methods used to address confounding, including adjusting for matching when necessary and avoiding treatment of probable mediating variables as confounders, appropriate?

Summaries (about 10–15 pages)

The summaries are written during the meeting and concisely recapitulate the data reviewed in the main sections. Each subgroup is responsible for writing a summary of the data they reviewed.

Summaries are the most-read sections in the entire volume. Therefore, it is extremely important to provide essential and relevant information but remain concise.

The summaries should not contain information about studies or other elements that have not been mentioned in the main text.

Summaries must be understandable by the lay public. Technical jargon should be avoided. Reference citations are useful in developing the summaries but will be removed in the final version. Therefore, information such as the geographical location or the name of the study should be given to enable the reader to identify a study.

Summary of studies leading to an evaluation

A concise summary should be provided of the epidemiological studies considered to be of adequate quality for use in making the evaluations for the beneficial and adverse effects. Those studies considered to be uninformative and not used in making the evaluations should not be included in the summary.

A statement should be made about the type and number of studies (randomized controlled trials, cohort studies, case–control studies) and whether an association was found between the intervention and the decreased incidence of or mortality from cancer, and under which circumstances. Any limitations should be mentioned.

In addition, a synthesis of the results and the quality of the studies (e.g. for beneficial effects, adverse effects, balance of benefits and harms) may also be presented in tabular or graphical format together with the narrative summary.

Summaries of sections not leading to an evaluation

The list below is not exhaustive or comprehensive, and the length of each summary will depend on the length of the corresponding main text and the direct relevance of the topic to the evaluations.

Characterization of the disease (about 500 words)

Data on the cancer being screening for are summarized, as outlined in Section 1 of the *Handbook*.

Global screening practices (about 500 words)

A general overview of the current status of screening practices worldwide is presented, by geographical region or WHO region.

Screening techniques (up to 500 words for each established screening method or group of methods)

This summary text precedes the summary of the body of evidence for beneficial and adverse effects for each method (studies leading to an evaluation). The screening methods are briefly summarized, by giving a short description and the key performance characteristics of each method.

Emerging techniques (about 500 words overall)

This summary presents, for each emerging technique, a short description of the technology and, where appropriate, a summary of the epidemiological studies.

Determinants of participation (about 500 words)

This summary highlights the main determinants of participation and summarizes the studies on interventions to increase participation, with an emphasis on aspects that are specific to the cancer being reviewed.

Populations at increased or decreased risk (about 500 words per population)

This summary presents data for the defined high-risk or low-risk groups. It briefly describes the condition leading to an increased or decreased risk, and summarizes the evidence from epidemiological studies that assess screening or surveillance in populations at an increased or decreased risk.

Annex 1. Table templates

Section 1:

Risk and preventive factors

Table 1.x Established risk/preventive factors for [organ] cancer and associated relative risk

Risk/preventive factor	Categories	RR (95% confidence interval)	Reference

Section 2:

Screening programmes in well-established settings

Table 2.x Policies and practice for cervical cancer screening in countries with well-established programmes

Country, region	Start year	Target age (years)	Screening method	Follow-up	Interval (years)	No. of screening tests per year	Invitation coverage (%)	Examination coverage (%)	Participation rate (%)	References

Screening programmes in low- and middle-income countries

Table 2.x Policies and practice for cervical cancer screening in LMICs

Country	Type of programme	Start year	Screening method	Target age (years)	Interval (years)	Examination coverage (%)	Colposcopy units per million eligible women	Reference

Section 3:

Studies (RCTs) of interventions to increase participation

Table 3.x Randomized trials of interventions to increase participation in cervical cancer screening (specify method)

Reference	Country	Screening modality	Intervention arm	Control arm	Outcome

Section 4:

Test performance (individual studies or meta-analyses)

Table 4.x Performance of [test] for detection of cervical cancer and precancerous lesions [[for individual studies]]

Reference	Test used	Sensitivity (%)	Specificity (%)
Invasive cervical cancer			
Preneoplastic lesions			

Table 4.x Performance of [test] for detection of cervical cancer and precancerous lesions [[for meta-analyses]]

Number of subjects	Number of lesions	Number of studies	Procedure	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)

Comparison of emerging methods

Table 4.x Comparison of technologies

Technology	Advantages inherent to technology	Disadvantages inherent to technology	Advantages for screening	Disadvantages for screening	Sensitivity	Specificity	Costs for screening	Costs for assessment	Relevance to screening	Current state of development

RCT design

Table 4.x Basic characteristics of randomized trials of the efficacy of cervical cancer screening by (method)

Trial, country	Randomization	No. of women	Accrual period for screening		Age at entry (years)	Intervention	No. of examinations/tests	Screening interval (years)	No. of rounds	Attendance at first round (%)	Determination of end-point
			Invited group	Control group							

RCT results

Table 4.x Results of randomized trials of the efficacy of cervical cancer screening by (specify technique)

Trial, country References	Age (years) at enrolment/screening	Mean duration of follow-up (years)	No. of subjects	Cancer mortality per 100 000 person-years (no. of cancer deaths) in screened/control group	RR	95% CI

Meta-analyses of RCTs

Table 4.x Meta-analyses of randomized controlled trials/observational studies of the efficacy/effectiveness of cervical cancer screening

Reference	No. of studies	Age at entry (years)	Population (thousands)		Cancer deaths		RR	95% CI
			Screened	Control	Screened	Control		

Observational studies – Cohort studies

Table 4.x Cohort follow-up studies of the effectiveness of cervical cancer screening

Reference Location	Cohort description: number of women, screening period, source of screening data, follow-up period, and source of follow-up data	Established programme: year of start, screening age, screening interval	Accrual and follow-up periods Person-years	Cervical cancer or precancer end-point and incidence/death age ranges	Number of cases/deaths	Cancer incidence/ mortality RR (95% CI)	Adjustments	Comments

Observational studies – Case–control studies

Table 4.x Case–control studies of the effectiveness of cervical cancer screening within service screening programmes

Reference	Area, year programme began, screening age and interval, women included	No. of cervical cancer deaths source, time period for cervical cancer deaths, years of diagnosis; proportion of eligible women included	Screening exposure; age of included women	No. of controls, source, whether same source population as cases, matching variables, alive at date of death or diagnosis of case	Linkage or use of screening, cancer registry, death databases; data items available	Adjustments	Cervical cancer mortality OR (95% CI)	Comments

Overdiagnosis

Table 4.x Studies of the estimates of overdiagnosis in cervical cancer screening

Reference	Population		Intervention	Comparison				Outcomes	
	Country (area) Calendar period of screening	Type of population and study design	Age and interval of screening Start year of screening	Reference population	Adjustment for cervical cancer risk	Adjustment for lead time	Mean follow-up after end of screening (range)	Estimate of overdiagnosis (only cancer)	Estimate of overdiagnosis (precancer and cancer)