**Information for course users: E-learning module EU-52: "Searching for, and identification of, existing alternative non-animal methods and approaches"**

Welcome to this instruction guide for users. This document aims to provide information on the content of this eModule, and give some recommendations to better comprehend and use this module efficiently.

This instruction guide is sub-divided as follows:

1) Module content

      Target audience

      Prior knowledge required and expected level after module completion

2) How to use this eModule – some recommendations

      Where can I find reference material or additional materials in the eModule?

      What may I expect from the additional materials?

      Can I divide the module in several parts?

      Should I prepare or study before this eModule?

3) In-depth explanation lesson by lesson

### 1) *Module content*

This module focusses on the concept and the importance of the Three Rs, and in particular Replacement of animal use, in research, education and training. It provides necessary practical skills on how to conduct extensive searches for identifying alternatives, non-animal methods and approaches. A self-assessment quiz is available at the beginning and at the end of the module to test yourself and see your progression. The module consists of 4 parts (Figure 1): 1) the meaning of Replacement, 2) developing research questions, 3) development of effective searches to find alternatives, and 4) documentation and reporting of searches (for project applications and other contexts).

To optimise learning, we would highly recommend dividing the module into several sessions. Parts should be followed in the order indicated above. You may divide the module into two or more sessions (e.g., session 1: part 1 and 2; session 2: part 3 and 4). If you are new to the concept of Replacement and searching, we advise to make 4 sessions (one per part) to leave yourself sufficient time to look into references, further reading material, and optional assignments.

For detailed recommendations on the order, see Table 1 (next page).

**Table 1:** Parts content and advised order

| PARTS | TOPICS ADDRESSED | ORDER |
|---|---|---|
| Part 1 | Three Rs, definition, ethical meaning, application and significance | Independent; set context; should be done first |
| Part 2 | How to formulate research questions in the line of Replacement and non-animal methods | Independent; For more coherence followed after Part 1 |
| Part 3 | *Section 1:* Type of sources used in searches, important factors when starting a non-animal search<br><br>*Section 2:* Simple and extensive searches characteristics, comprehensiveness and sensitivity, consequences for non-animal searches<br><br>*Section 3:* Searching non-specific sources, judging search reliability, and factors to consider<br><br>*Section 4:* How to build effective searches, how to translate them to other sources, and how to identify experts | Independent; Section 1 and 2 should be followed together<br><br>Section 3 and 4 should be followed together<br><br>For more coherence, keep the order section 1-4. |
| Part 4 | Reporting and documentation of non-animal searches from differences sources and further analysis | Independent; For more coherence followed after part 3. |

*Target audience*

(Bio)medical researchers, laboratory animal science students, university students, biology/medical teachers, ethical board members, or more generally anyone interested in learning more about retrieval techniques to search for non-animal methods/alternatives in research.

*Prior knowledge required and expected level after module completion*

No specific prior knowledge is required. However, a basic understanding of searching bibliographic databases and a background in laboratory animal science and/or non-animal methods can be helpful.

After completion, you should know about the Three Rs (Replacement, Reduction, Refinement) and their significance; how to phrase research questions in the context of non-animal methods; and, above all, know about how to search for non-animal methods and alternatives in several sources (i.e. bibliographic databases, grey literature, Three Rs specific databases), how to identify experts to help you in this endeavour, and be capable of reporting your searches in a transparent and complete manner.

| | | Learning objectives |
|---|---|---|
| **Introduction** | Lesson 1-2 | • Get to know the learning objectives.<br>• Assess your current knowledge. |
| **PART 1: The meaning of Replacement** | Lesson 3-6 | • Describe and discuss the concept of, and need for, the Three Rs according to legislation.<br>• Explain how Replacement differs from Reduction and Refinement.<br>• Discuss ethical and scientific arguments for the importance of Replacement.<br>• Describe different types of Replacement or non-animal approaches.<br>• Explain why one-on-one Replacement is not the only way of achieving Replacement. |
| **PART 2: Developing research questions** | Lesson 7-9 | • Discuss the importance and various elements of formulating research questions.<br>• Describe different or novel ways to approach research questions.<br>• Critically evaluate research questions as to whether non-animal approaches can be applied to solving them.<br>• Explain why identifying non-animal approaches is an interdisciplinary endeavour and requires a team approach. |
| **PART 3: Searching for relevant information** | Lesson 10 | • Describe the main categories of information sources for the identification of non-animal alternatives and give examples. |
| | Lesson 11-13 | • Explain what factors should be considered when selecting and prioritising the appropriate search method for a specific research question and specific context.<br>• Distinguish and discuss the strengths, weaknesses and appropriateness of simple and effective searches in relation to the type of project.<br>• Discuss the different levels of comprehensiveness of search methods to identify non-animal approaches, and how this might affect the completeness and analysis of the search results. |
| | Lesson 14-15 | • Explain the principles of judging the general reliability and relevance of a specific information source.<br>• Describe the disadvantages of searching in non-specific information sources.<br>• Explain what factors should be considered when selecting the appropriate information sources for a specific research question and specific context. |
| | Lesson 16-18 | • Explain the key elements of building an effective search for large bibliographical databases and describe how to apply them.<br>• Explain the key elements of translating an effective search into a strategy for searching the grey literature (including Three Rs-or Replacement-specific databases) and describe how to apply them in practice.<br>• Explain the key elements of designing a strategy to identify and contact relevant experts and organisations, and describe how to apply them in practice. |
| **PART 4: Documentation and advanced analysis** | Lesson 19-21 | • Judge the extent to which the search results are complete and fit for purpose.<br>• Explain the importance of, and apply the principles for, documenting/reporting a search process in a transparent manner.<br>• Explain the added value of analysing effective search results through a complete review. |

**Figure 1:** Learning objectives per parts and lessons.

## 2) *How to use this eModule? – Some recommendations*

*Q&A: how to use the eModule*

### Where can I find reference material or additional material in the eModule?

All references and further readings are provided at the end of each lesson. They comprise scientific articles, sections of books, websites, and videos. Clicking on any link will open a new window, from which you can download or visualise the additional material.

To note: the collection of references and further reading was created during 2020-2021 and was checked in May 2021.

### What may I expect from the additional materials?

In Figure 2 (A-C), we show the topics per lesson and the additional knowledge you may get from the additional material. For information on the content of each lesson, please refer yourself to the detailed explanation (part 1, page 2-5).

### Can I divide the module in several parts?

Yes, you can; all parts can be done independently. However, some parts belong with each other and should be done in a specific order to sustain coherence. If you would like to divide the module into several sessions or focus only on some parts/lessons, we would advise cutting part 1 from the rest as it proposes a lot of further reading and sets the context. Part 2, 3 and 4 may be done independently from each other. However, part 2 would be more coherent if followed after part 1 and part 4 after part 3. Part 3 has 4 sections; if you'd like to cut this large part in two, you should follow section 1 and 2, and the section 3 and 4.
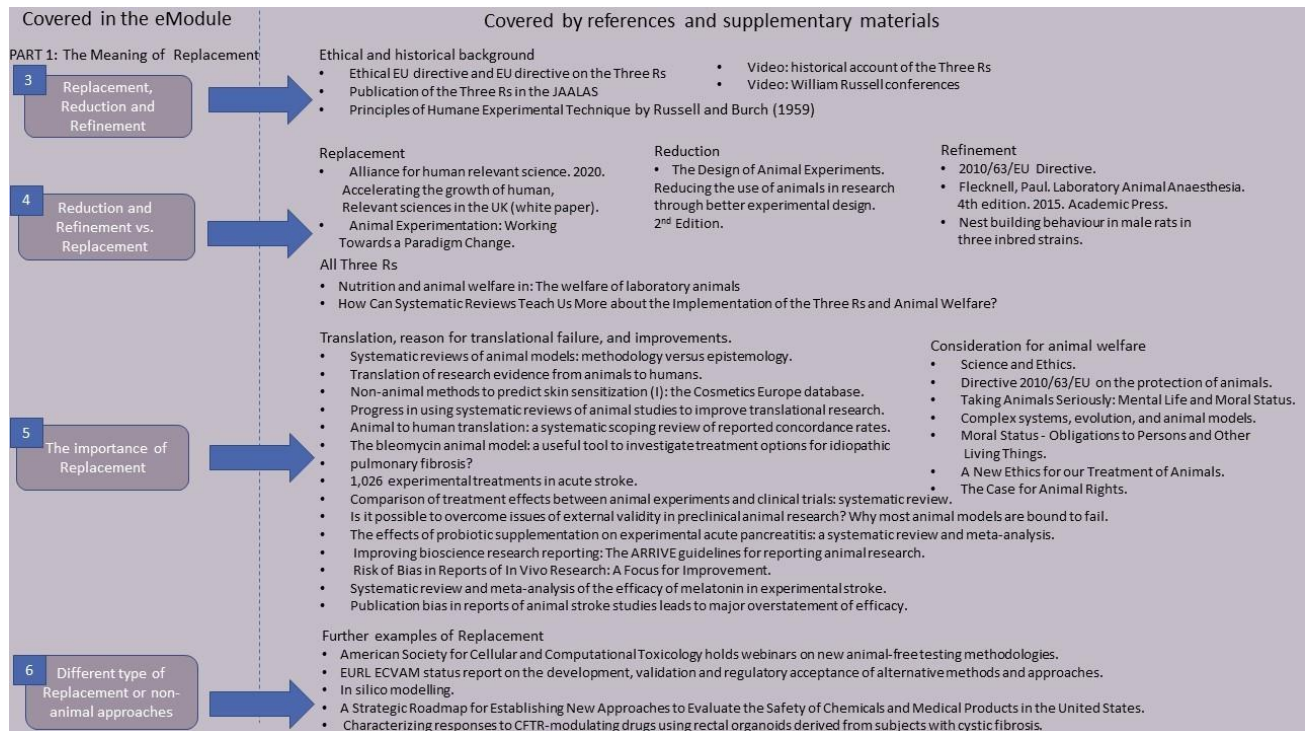


**Figure 2A:** References and further readings given per lesson for part 1

**Covered in the eModule**

PART 2: Developing research questions

**7** Formulating proper research questions

**8** Approach research questions differently as part of Replacement

**9** Formulating proper research questions

PART 3: Searching for relevant information

**10** Categories of information sources for the identification of non-animal alternatives

**11** The factors affecting a search

**12** Qualities of simple and extensive searches

**14** Disadvantages of searching in non-specific information sources

**Covered by references and supplementary materials**

Further readings on phrasing research question and identifying studies
- A step-by-step guide to systematically identify all relevant animal studies.
- EFSA guidelines on phrasing research questions.
- Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes.

Guidelines and framework for Replacement
- FRAME: Strategic Planning Chart For Reducing Animal Use in Biomedical Science.
- EFSA guidelines on using systematic reviews methodology to identify suitable questions (risk assessment, and framework for food/nutrition related topics).
- Planning for Reduction.

Further readings on phrasing research question
- EFSA guidelines on phrasing research questions.
- A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States

Further references to database and useful website as relevant sources
Databases:
- Cochrane, PubMed, Embase, Web of Science.
- Adverse outcome pathway knowledge base.
- Grey literature platforms for thesis, clinical trials and preprints

Websites/platforms:
- SYRCLE, Norecopa, Inventory of Three Rs Knowledge sources.
- The Joint Research Centre, the European Centre for Validation of Alternative Methods.

Guidelines for comprehensive searches
- A typology of reviews: an analysis of 14 review types and associated methodologies.
- A step-by-step guide to systematically identify all relevant animal studies.
- A review over automated screening using computer softwares

Guidelines for searching the literature effectively
- Searching the Literature: A Guide to Comprehensive Searching in the Health Sciences. Precision vs. Sensitivity - Key to Effective Searching.
- Example of a great non animal search

Further guidance on improving searches in non-specific information courses
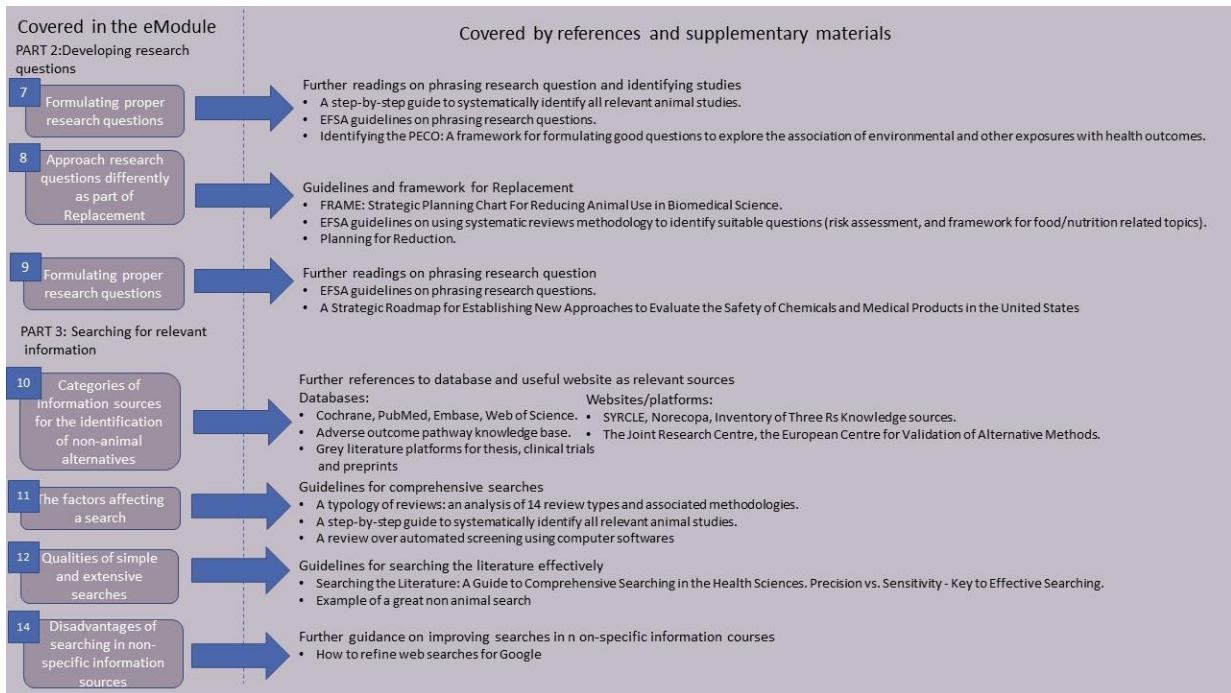- How to refine web searches for Google

**Figure 2B:** References and further readings given per lesson for part 2 and the two first sections of part 3. *There is no further material provided for lesson 13.*

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**Covered in the eModule**

**15** Qualities of simple and extensive searches

**16** Searching large bibliographic databases

**17** Translating an extensive search into a grey literature search

**18** Identifying and contacting relevant experts/organisation

PART 4: Documentation and advanced analysis

**19** Assessing the usefulness and completeness of a search

**20** Documenting and reporting the search process

**21** Value of analysing search result through a systematic review

**Covered by references and supplementary materials**

Contacting relevant organisation
- The OECD Environmental, Health and Safety (EHS) Programme.
- National toxicology program handbook for conducting literature based health assessment – using Systematic reviews and evidence
- Great example of non-animal methods searches

Guideline on designing search strategies, searches for Replacement, and quizzes
- Guidance on building a structured search (a). Structured approach to comprehensive searching.
- Guidance on building a structured search (b). Construct strategy using OR/AND.

- Searching alternative search keywords.
- Alternative research guide and search terms.
- Practical examples and quizzes.
- Video tutorials on searching

Guideline on searching grey literature
- EFSA guideline on grey literature searching.
- The EURL ECVAM Search Guide.
- The National toxicology program handbook for conducting literature based health assessment

Advice on identifying relevant organisations
- EFSA guideline.
- Systematic evidence maps to identify relevant experts and organisations

Tools to assess searches quality
- Tools for critically appraising different study designs, systematic review and literature searches.
- PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement.
- PIECES Workbook.

Guideline on reporting and documentation of searches
- How to document your search process and report your result (a systematic review example).
- Tools for critically appraising different study designs, systematic review and literature searches.

Systematic review guidance and usefulness
- Defining the process to literature searching in systematic reviews: a literature review of guidance and supporting studies.
- The usefulness of systematic reviews of animal experiments for the design of preclinical and clinical studies.
- Meta-analyses of animal studies: an introduction of a valuable instrument to further improve healthcare.
- Progress in using systematic reviews of animal studies to improve translational research.
- Syrcle website.

**Figure 2C:** References and further readings given per lesson for the last two sections of part 3 and part 4.

**Should I prepare or study before this eModule?**

The module will guide you step by step and no prior studying should be required. For one lesson (lesson 12) a glossary is also provided.

If you are completely new to searching in bibliographic databases (e.g. PubMed, EMBASE, Web of Science), it may be good to look at PubMed's tutorial to understand what we mean by comprehensive searching. (available here: https://learn.nlm.nih.gov/documentation/training-packets/T0042010P/)

If you never heard of alternative methods (e.g. *in vitro* models, *in silico* models), you may want to read this review giving a broad approach of alternatives:

Sonali K. Doke, Shashikant C. Dhawale, Alternatives to animal testing: A review, Saudi Pharmaceutical Journal, Volume 23, Issue 3, 2015, Pages 223-229, ISSN 1319-0164,https://doi.org/10.1016/j.jsps.2013.11.002. (http://www.sciencedirect.com/science/article/pii/S1319016413001096)


*3) In-depth explanation lesson by lesson*

PART 1: Meaning of Replacement

Lesson 1: Introduction to the course & learning objective

Lesson 2: Review your understanding

> -A small quiz to review students' first knowledge and understanding of the topics addressed in this course e.g., reasons and means for Replacement, searching for Replacement alternatives.

Lesson 3: Replacement, Reduction and Refinement

> -Introduction and definitions, legal/ethical history and context for the Three Rs

> -Video introducing "Can we do science without animal testing?"

Lesson 4: Reduction and Refinement vs. Replacement

> -Focus on Replacement and how it differs from Reduction and Refinement.

> -Interactive game where students need to place propositions in the correct place, stating which is Replacement, Reduction or Refinement.

Lesson 5: The importance of Replacement

> - Provides ethical and scientific arguments for the importance of Replacement

Lesson 6: Different types of Replacement or non-animal approaches

> -Provides information and examples on three main ways to replace: 1) one-on-one Replacement; 2) reformulating the research question; and 3) combination of data sets/evidence streams.

> -Videos on an *in vitro* dynamic simulator of the human digestive system and on Helpathons (new ways to reformulate research questions).

- Interactive game where students need to place propositions in the correct place, stating which is one-on-one Replacement, reformulating the research question, or a combination of data sets/evidence streams.


## PART 2: Developing research questions

Lesson 7: Formulating proper research questions

-Provides guidance on how to phrase clear and adequate research questions matching the aim and objective of one's research. Explanation and use of the PICO format.

Lesson 8: How to approach research questions differently as part of Replacement

-Gives some clues and examples of how to approach research questions differently in the context of non-animal approaches/alternatives.

Lesson 9: Identifying non-animal approaches – an interdisciplinary endeavour

-Explains the different roles of end-users, content experts, researchers, non-animal models experts, information specialists, and regulators in designing a search strategy for non-animal approaches/alternatives.


## PART 3: Searching for relevant information

Lesson 10: Categories of information sources for the identification of non-animal alternatives

-Gives information on three main types of sources for the identification of non-animal alternatives; namely 1) bibliographic databases, 2) grey literature, and 3) contacting experts.

Lesson 11: The factors affecting a search

-Defines some factors required to be identified before designing a search strategy (with examples), e.g., what is the aim of the search, time and resources available. It covers in particular: the aim of the search, availability of time and resources, and the possibility to use advanced techniques (e.g., data or text mining).

Lesson 12: Characteristics of simple and extensive searches

-Provides definition, aim and scope of simple and extensive searches. Explains strengths and weaknesses regarding sensitivity and precision.

-Two explanatory videos covering an example of a simple search and an extensive search in PubMed.

Lesson 13: Explain the degree of comprehensiveness across different search methods

-Defines difference in comprehensiveness between extensive searches and explorative searches.

Lesson 14: Disadvantages of searching in non-specific information sources

-Explains why searches in non-specific sources may provide unpredictable, less transparent and complete results. For instance, a lack of thesaurus or a hierarchy tree.

Lesson 15: Identify what sources are relevant depending on the aim of the research

-Example regarding the combination of sources (the three sources defined in lesson 10) depending on the aim of the search

-Interactive exercise regarding search sources

Lesson 16: Instructions on how to search large bibliographical databases

-Information on how to create search components and select terms for a search strategy (indexed terms e.g., MeSH, and synonyms).

-Interactive panels and links to teach students about indexed terms, synonyms, including a step by step PubMed guide

-Tutorial video about building a search strategy

-Optional assignment: students can run searches of their choice from a list of provided terms related to Replacement

Lesson 17: Translating an extensive search into a grey literature search

-Provides guidelines on how to translate extensive searches in bibliographic databases to grey literature searches (by using the EURL ECVAM guideline steps).

-Covers grey literature databases, citation checking, and hand searching of references

-Tutorial video on grey literature search

Lesson 18: Identifying and contacting relevant experts and organisations

-Provides tools and guidelines on how to identify and contact relevant experts or organisations, including performing evidence maps.

-Video addressing how to use evidence maps.


PART 4: Documentation and advanced analysis

Lesson 19: Assessing the usefulness and completeness of a search

-Provides guidelines on search combinations, methods and robustness needed for project applications.

-Explains the concept of usefulness and completeness depending on different aims and across the three main sources included in this eModule (electronic bibliographic searches, grey literature, and contacting experts and organisations).

Lesson 20: Documenting and reporting the search process

-Explanation and example of all items that should be documented and reported for the three main sources included in this eModule (electronic bibliographic searches, grey literature, and contacting experts and organisations).

-Interactive exercise on what is required for search documentation/reporting.

Lesson 21: Value of analysing search results through a complete review

-Introduction of the concept of systematic reviews to highlight all non-animal approaches or alternatives in a specific topic/area. Explains the different advantages it may provide and gives examples.

-Video on the preclinical systematic review process and its usefulness.

Lesson 22: Final quiz

-Assesses progress and knowledge acquired during the course

We hope that this document provided you with sufficient information to fully comprehend the content and scope of this eModule. We sincerely wish you best of luck in your studies and thank you for considering our eModule.