27/05/2016

3rupdate.ch: a new online educational tool for improved 3R literature search

Impact assessment of researcher skills to retrieve 3R information after online training

REPORT



This report is licensed under the Creative Commons Attribution-Non-Commercial-Share Alike 4.0 Unported License



Sylvie Vullioud, Isabelle de Kaenel, Stefanie Schindler

- Scientific Information School (SIS), Vufflens-la-Ville, Switzerland
- Bibliothèque Universitaire de Médecine (BiUM), Lausanne University Hospital, Lausanne, Switzerland
- Animalfree Research Foundation, Bern, Switzerland

3rupdate.ch: a new online educational tool for improved 3R literature search

Sylvie Vullioud¹, Isabelle de Kaenel², Stefanie Schindler³

- ¹ Scientific Information School (SIS), Vufflens-la-Ville, Switzerland
- ² Bibliothèque Universitaire de Médecine (BiUM), Lausanne University Hospital, Lausanne, Switzerland
- ³Animalfree Research Foundation, Bern, Switzerland

Keywords

3Rs, information retrieval, animal experimentation alternatives, scientific validity

Summary

Animal experimentation has to be indispensable. Researchers have to ascertain and to prove to the competent authority that the objective of their study cannot be accomplished using other methods than in vivo experiments. If animal experiments remain the only approach, it is then mandatory to use the minimum number of animals and to cause as little distress as possible. The way for achieving these goals is the 3R-concept,

Published 3R-methods, however, may remain unretrieved due to deficiencies in literature search and information retrieval skills, resulting in unnecessary animal experimentation/distress levels. In Switzerland, researchers aiming to be study directors of in vivo experiments have to attend a mandatory one-week course (the Module-2) which, since 2012, comprises a 3-hour training for 3R information search. An assessment of 176 researchers' case reports dating from 2012 to 2014 and made prior to the course unraveled numerous shortages in the reported 3R information search methodologies and strategies. For instance, less than 35% of researchers mastered basics of information retrieval such as keywords enrichment, Boolean operators or nesting, leading to poor results regarding precision and recall.

Consequently, in 2015, we designed the online course <u>3rupdate.ch</u> (including a test) to help researchers acquire this necessary knowledge. The passing of the test was a prerequisite for the participation in the Module-2 seminar. A first assessment of reports after implementation showed huge improvements.

We are convinced that our online course will contribute to the implementation of the 3R concept and to the scientific validity of research.

Terms and definitions used in the study

Automatic (term) mapping¹: the process used by PubMed to find a match to unqualified terms that are entered into the query box. Untagged terms are matched in this order: Medical Subject Headings (Goss et al.) translation table, journals translation table, authors and investigators translation table, author index, full investigator translation table and investigator index.

Boolean operators¹: **AND**: Boolean operator that narrows the search and is used to combine search components of a search string. **OR**: Boolean operator that broadens the search and is used to combine synonyms or related keywords within a search component starting and finishing with brackets for nesting.

Field tag¹: addition of a tag to a term enclosed in square brackets allowing for search in a specific field, such as in PubMed; [tiab] searching in title and abstract of the paper, and [mh] searching in the MeSH table controlled vocabulary. Use of field tag deactivates automatic mapping.

MeSH¹: MeSH is the acronym for "Medical Subject Headings." MeSH is the authority list of the vocabulary terms used for subject analysis of biomedical literature at the National Library of Medicine. MeSH vocabulary is used for indexing journal articles for MEDLINE, meaning that there is a specific set of terms used to describe each article.

Nesting: specifies the order of a search with the use of brackets. These are required when a string search contains two or more Boolean operators. Brackets are used to group related and synonymous keywords, connected by "OR", forming a search component. The computer searches for the nested keywords first.

Truncation: truncation retrieves all variations of a root word in a single search, by using a special symbol to replace word endings, i.e. different endings but the same root, singular and plural word forms, spelling variations, variations in tense. This broadens the search. The truncation symbol is often a question mark or an asterisk.

Module-A: the online course www.3Rupdate.ch on basics on information retrieval and open access (commented presentations, screen castings and test). Module-A is used as prerequisite for Module-B.

Module-B: 3-hour face-to-face course on 3R information issues such as systematic review, ARRIVE reporting guidelines, pre-clinical reproducibility initiatives, and post-reviewing. It is part of the Module-2 one week course.

¹ From http://www.nlm.nih.gov/bsd/disted/pubmedtutorial/020 040.html

Module-2: according to Swiss Animal Welfare Ordinance 455.109.1 (Anon, n.d.), researchers in charge of the filling of animal experimentation request (called Form A in Switzerland) are licensed after one week (40 hours) of mandatory course called Module-2organized by the Institute of Laboratory Animal Science mandated by the FSVO and organized by the Institute for Laboratory Animal Science, University of Zurich.

Researchers: aspiring study directors of animal experimentation in this paper are referred to as "researchers".

Recall/Precision: recall in information retrieval is the fraction of the documents relevant to the query that are successfully retrieved. Precision is the fraction of retrieved documents that are relevant to the query.

Search component: concept translated into related terms, synonyms, and variants of terms articulated by the "OR" Boolean operator.

Search string: one to (maximum) four search components connected by the "AND" Boolean operator are forming a search string to be used in a search box.

Introduction

Prior to conducting in vivo experimentation, researchers in all European countries are required by animal welfare legislation to ascertain that the use of live animals is indispensable for reaching the project goal, to decide whether and how to include alternative methods into the project plan and to plausibly justify this to the responsible authorities as part of the approval procedure. This consideration and incorporation of all available scientific information on alternative methods is not only an obligation, but also scientific standard (Sauer et al., 2009). The Swiss Animal Welfare Legislation clearly states that the performance of an animal experiment is prohibited if a suitable other 3R-relevant approach exists. Such methods have now been developed and published for almost six decades. Briefly, scientific approaches within the 3R-concept provide the possibility to forgo animal use altogether, to significantly reduce the number of animals in a given procedure, and/or to diminish harm and stress as far as possible.

In order to achieve this, good skills in scientific literature retrieval are essential. With regard to reporting on possible 3R-relevant methods, the degree of difficulty is further enhanced by the fact that in this particular case, animal experimenters have to prove that something does <u>not</u> exist – within an appropriate timeframe. At the 3rd World Congress on Alternatives and Animal Use in the Life Sciences in 1999, it was stated that an urgent need exists for an easier and more successful approach to retrieve 3R-relevant information (Janusch-Roi et al., 2000).

To do so, two different approaches were attempted: the first one is summarized in (Nesdill and Adams, 2011), (Grune et al., 2004), (Hudson-Shore, 2012) focusing on the use of concentrated 3R-relevant information in specialized databases and in the semantic search engine Go3R, using expert knowledge-based ontology (Sauer et al., 2009). The second one are the publication of 3R search guides by the European Center for Validation of Alternatives Methods (ECVAM, n.d.) and by NORECOPA (Norwegian consensus platform for replacement, reduction and refinement of animal experiment) (NORECOPA, n.d.), that inform researchers about general search tools, step strategies, and identification of some relevant keywords.

Despite all these efforts, some findings have shown inefficacy of these initiatives: a report from Korea found that most scientists are well aware of the requirement, but have no idea how to comply with it (Choe and Lee, 2013); work from the Netherlands demonstrated that scientists as well as animal welfare officers spend mostly little time on the search, and there is fear that 3R-relevant methods are overlooked (Leenaars et al., 2009), (van Luijk et al., 2011); and a survey on Institutional Animal Care and Use Committee (IACUC) members showed that one of the two most significant problems encountered were inadequate searches for alternative methods (Silverman et al., 2012).

In Switzerland, since 2012, aspiring study directors have to attend a mandatory one-week course (the Module-2) for researchers with at least three years of experience in animal experimentation. Since the beginning, the Module-2 comprises a three-hour face-to-face 3R information retrieval seminar. In 2012, 2013 and 2014, all Module-2 participants (altogether 176) were assigned "homework" prior to the seminar. Participants worked on a 3R information retrieval case study, reporting their search methodologies. After 4 sessions, reports evaluation revealed poor basics skills of information retrieval. Less than 35% of researchers mastered basics of information retrieval: search strings were lacking, keywords enrichment, Boolean operators and nesting were not correctly used, leading to poor results with regard to precision and recall. When using PubMed, less than 25% used it efficiently: a combination of MeSH and free terms was rarely attempted to disable automatic mapping to keep control on the search, and to improve recall and precision of results.

Moreover, to our best knowledge, at the time of writing, the search for 3R-relevant literature and corresponding reporting of search methodology and results are not executed in a manner which is meaningful and comprehensible for the Swiss approving authorities.

Therefore, it was decided to create an online open access education course (commented presentations, screen-castings and final test) about the basics of information retrieval and open access), as a prerequisite for the participation in the Module-2. First assessments of reports after introduction of the mandatory online course demonstrated that now 72% of researchers mastered information retrieval basics, including the use of search components and search string building with Boolean operators, nesting and keywords enrichment, and 59% of researchers used combinations of MeSH and free terms.

Methods

Homeworks: common and differing points

Every year the case study was designed: (i) to allow researchers to improve their knowledge of different search databases, (ii) to draw the participants' attention on the possible difficulties in searching 3R information; (iii) to generate additional interactions for the face-to-face seminar. The final goal was to create common knowledge - to share and discuss about delicate issues of 3Rs scientific information (for details on the homework documents sent to researchers, please refer to Appendix 1).

There were three homework assignments. The first was to perform a search on available study models of human disease (Huntington disease and skin cancer). The second one was to report the best search strategies, outlining search strings used in two search tools selected by researchers in suggested list with the corresponding relevant references and generated bibliography (Google scholar, Go3R, PubMed, PubMedCentral, Science Direct, Web of Science, Scopus, Embase, Springer protocols, Wiley Protocols, CRCNetbase, NEBIS, RERO, IDS, or a research tool listed by AWIC Center, NCR3R or Altweb websites). The third assignment invited researchers to comment about their tool choices, tool differences, and criticisms of the preliminary search strategy, and to propose a better formulation of the initial query to improve the information retrieval process.

No individual feedback was provided to the participants. The face-to-face seminar was planned to provide researchers with additional clues and search strategies to improve their initial knowledge of information search retrieval. In other words, the homework was not originally designed to allow for a systematic survey on information retrieval or search methodology skills. Consequently, the present study tries to take advantage of the available material for an evaluation of the impact of the introduction of our f online education tool. For example, the homeworks in the sessions between 2012 and 2014 differed in several aspects(for details on the homework documents sent to researchers, please refer to Appendix 1):

- The case studies given in 2012, 2014, and 2015 were "Which mice, or non-vertebrate, or *in vitro* models are used to study Huntington disease?" while the case study for year 2013 was focusing on the search for "skin cancer models".
- The two 2012 sessions homework documents did not contain examples on details of a PubMed search. Although a majority of researchers selected PubMed as the database for their search, it was noticed after 2 sessions that few used correct MeSH terms, if any. As a consequence, and as a help for researchers, the following homework documents contained PubMed search strings showing combinations of Mesh and free terms as examples.

Homeworks: limitations

The present study took advantage of the available material in order to evaluate the impact of the newly introduced online education tool on researcher's information retrieval skills. Case study about information search on study model homework was not originally designed for survey of information retrieval skill, and/or to mark researcher's search methodology reporting.

Therefore, we are aware of the possible objection that the present study has a limited rigor analysis due to:

- lack of randomization and blinding of the outcome assessment. Quantitative outcome assessment was
 performed twice by the same person, once after the sessions of 2012-2014 and the other after the 2015
 session, reflecting the need for particular information: the first assessment was done for designing 3rupdate
 and the second for getting an idea on the impact of the online tool introduction by simple comparison.
- other factors which could explain the sudden improvement of researcher's reports such as significant differences in terms of geographical provenance, age, experience, and educational background of researchers.
- analyses of reports were not crossed with analyses of how many times commented presentations and screencasts were viewed, or other user behaviors, such as the number of trials to succeed in reaching 60% of right answers and passing the test.
- · differences between homework assignments.

Moreover, a rigorous educational survey would include the personal motivation of the researchers and evaluate the effects on reporting quality.

Anonymization of researcher's homework

Prior to the analysis, all submitted homeworks (before and after implementation of the online course) were anonymized. Visible confidential data such as name, address, institution or industry, and contact data were

suppressed with Adobe Pro XI Redaction tool. Hidden data, such as metadata, were suppressed using a sanitization tool.

Assessment criteria for researcher's homework evaluation

Four outcome assessment criteria were defined:

- 1. Did researchers use Boolean operators? Yes/No.
- 2. Did researchers report correct logical search strings made of search components connected by the "AND" Boolean operator, and search components made of related, synonymous and variant terms articulated with the "OR" Boolean operator, as well as search components starting and ending with brackets for correct nesting? Yes/No.
- Did researchers use MeSH vocabulary developed by PubMed database, if PubMed was chosen? Yes/No.
 - (MeSH terms presence following a copy/paste of automatic PubMed mapping was not considered as a proven ability to effectively handle Mesh terms to retrieve information).
- 4. Did researchers make correct use (MeSH terms [mh] combined with free terms [tiab]) of the PubMed database for the best possible recall and precision of results?

Yes/No.

Presence or absence of these defined elements were calculated as percentages in order to detect the effects of the online course introduction.

Observations of 2012, 2013, and 2014 were used to design contents of commented videos, screen-castings, and the final test for the online education of researchers. At the end of 2015, after the autumn session of Module-2 and after introduction of the course, the same criteria were applied to evaluate the putative impact on report quality. Reports lacking search strings in tables or screenshots were not taken into account, because they reflected the failure to complete the assigned work requirement.

Online basics of information retrieval definition content

The online course consists of three commented presentations basics on information, 3R information retrieval and open access and six screen castings (showing how to do something). They all allow the participant to succeed in an online test. The online test is a multiple choice questionnaire, with 20 questions and 4 possible answers. (Appendix 2). Questions are designed to be answered without the help of commented presentations and screen castings, allowing the researcher to use personal knowledge or any other source of information. Researchers can try as many times as they required to achieve 60% right answers resulting in the automatic delivery of the success certificate. Certificate and homework reports have to be submitted to the organizer of the Module-2. The following outcomes were aimed at:

- The participant masters fine tuning of keywords, builds correct search components and search strings with Boolean operators and nesting, as preparation for systematic search;
- The participant knows about 3R search tool differences in term of coverage, type of documents, automatic mapping/lemmatization, MeSH terms, search engine/semantic search engines/bibliographic databases, citation/citing tools and multidisciplinary/specialized tools;
- The participant knows about open access funding agencies, and Green and Gold roads. He knows how to prepare a pre- or post- referee manuscript of publication for Green Open Access compliance.

Results

Because a large majority of researchers (93%) reported search strings, it was possible to evaluate the use of Boolean operators and nesting. Reports without string reporting in tables or screen casting were not used for evaluation (Table 1)

Because a majority of researchers (88%) chose PubMed as search tool to look for study models, it was possible to evaluate the use of MeSH terms. Reports without string reporting in tables onscreen casting or without PubMed were not used for evaluation (Table 2).

Table 1. Final number of usable reports for Boolean operators and nesting evaluation

Session	Available reports	No reporting	Usable reports
2012 Zürich	56	7	49
2012 Lausanne	31	0	31
2013 Lausanne	42	4	42
2014 Lausanne	54	3	54
2015 Lausanne	32	0	32
		Total	93%

Table 2. Final number of usable reports for MeSH use evaluation

Session	Available reports	No reporting	Usable reports
2012 Zürich	56	13	43
2012 Lausanne	31	3	28
2013 Lausanne	42	5	36
2014 Lausanne	54	5	49
2015 Lausanne	32	0	32
		Total	88%

In general, expected relevant elements of reports should have been:

- Rich search strings balancing or making a choice between recall and precision and grammar adapted to the selected search tool
- Accurate reporting, enabling the reader to reproduce the search by a simple copy/paste of the search query
- Comments about the necessity to work with different tools for good recall, because different coverage of search tools

Before online module introduction, relevant references could be obviously found with the use of two simple terms or simple search strings. However, reports revealed lack of technical mastering of search tool, and gave an impression of random search. Main observations were that reported search strings were short and lacking keywords enrichment; Boolean operators and nesting, if any, leading to poor precision and recall. In 2015, after introduction of online module, a quick reading of reports suggested a general improvement of researcher's information retrieval skills.

Before online introduction course, it was observed that 90% and more of researchers reported AND Boolean operator in their search string (Fig 1).But OR Boolean operator and nesting to express synonyms of closed concepts were rare, thus lowering recall. In fact, only 16-32% of researchers were able to formulate correct search string with Boolean operators and nesting. After online module introduction, 72% of researchers reported correct search strings.

A majority of researchers decided to select PubMed to perform the information retrieval exercise, because they wrote it was the most used search tool in their everyday practice, and new best about it. However, they failed to take advantage of the most interesting option offered by the database, namely combination of controlled vocabulary and free terms combination for best possible recall and precision. Only 11-23% of researchers

reported MeSH terms in search strings, and correct use was even lower: 3-19% (Fig.2). After the online module introduction, the presence of MeSH terms reached 88%, and correct combination of free and MeSH terms improved to 60%.

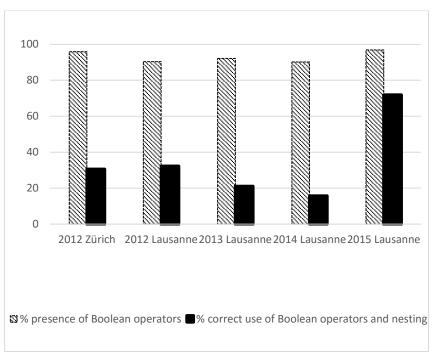


Figure 1. Boolean operator and nesting use in homeworks, 2012-2015

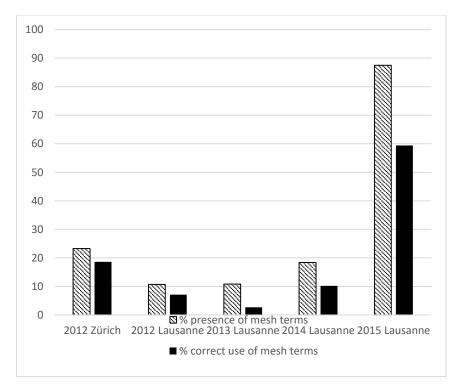


Figure 2. MeSH term use in homeworks, 2012-2015

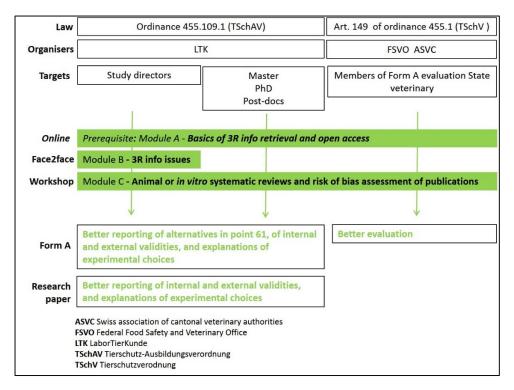


Figure 3. 3Rupdate modules education in existing mandatory animal experimentation courses: from law to effects. According to the Swiss Animal Welfare Ordinance 455.109, aspiring directors of animal experimentation in charge of the filling of animal request (Form A) are licensed after one week (40 hours) of mandatory course (the Module-2). The 3 hours face-to-face Module-B course is part of Module-2. According to the Ordinance TSchAV 455.109.1, study directors and experimenters should undergo four days of continuing education at least every four years (Anon, n.d.). The education of members of the cantonal commissions evaluating Form A is set down in Article 149 of the animal welfare ordinance (TSchV). The workshop Module-C will be created and will be tested in 2016, as a new course for continuing education. Module-C may take place 1-4 times per year in Switzerland

2012-2014 sessions revealed considerable differences in researcher's background knowledge about search tools; some reported they had only now discovered search tools or how they worked, because they knew PubMed, WOS, Scopus, ScienceDirect etc. only by name. After introduction of www.3Rupdate.ch, these differences were diminished and participants of the Module-2 were found to be at a much more homogenous level. In general, more accurate and relevant free comments were written: despite promises of the name Go3R, researchers wrote about usefulness of the tool for starting information retrieval only that should be completed anyway with other search tools using rich formulated search strings. Several comments emphasized and/or discussed advantages and disadvantages of search tools such as citing, narrative reviews, semantic technology functions (data not shown).

Discussion

With growing experience, networks, and confidence, researchers tend to increasingly gather information on the latest developments in their respective field directly from their colleagues and from educational events such as congresses, and to a decreasing extent by searching the literature. This development is well-known and natural. Unfortunately, 3R-relevant information is not necessarily part of or related to their area of research, but (for refinement aspects) related to laboratory animal science, or (for replacement/reduction) to specialized knowledge of the latest in vitro developments, such as 3D tissue cultures, stem cells, and screening techniques. In this case, good information retrieval skills are essential to implement the 3R-concept. It is admittedly not an easy task for biomedical researchers to follow the creation and developments of all new and potentially relevant models. Once possible models are pre-selected, it is not easy to choose one or several of them, especially (i) because papers using a specific model are not retrieved with traditional citation search tools, (non-indexation of material and method section of a paper containing the specific label of strain used); (ii) because choice explanation of a study model is rarely reported in papers (iii) and because of still dominating subscription-based journals and copyright transfer to publishers, preventing easy and free reuse of papers for text and data mining (TDM) (Van Noorden, 2012).

Better validity and better translational research are increasingly in the center of attention of funding agencies (Collins and Tabak, 2014), journals (McNutt, 2014), and researchers (Begley and Ioannidis, 2015), because of alarming number of preclinical studies that were later found to be irreproducible (Freedman et al., 2015), (Macleod et al., 2014).

Homework assignments preceding the creation of the online course and providing the information for its development focused on information retrieval of study models, because study model choice is crucial for the validity of the scientific results. More robustness in term of internal, external validity and reproducibility mean also avoidance of unnecessary use of animal experimentation, hence better application of the 3Rs. Internal scientific validity may be correct for a study model, but external validity and translation of results may fail, because they are not simulating real situations.

One could object that this very simple evaluation of reports was actually measuring search reporting ability rather that information search ability. However, we believe that good search abilities would have been visible in reports if researchers had a long practice of information strategies in their own routine field research. General improvement of reports after introduction of the online prerequisite suggests also that evaluation did not measure reporting ability only. As introduction of search string examples with MeSH and free terms combination in homework documenting 2013 and 2014 had no visible effect on reported string, we believe that online module only could improve general level of information retrieval. We assume that sudden improvement is not due to special brilliant participants in 2015, neither that it is a chance improvement.

For the moment, we do not know what particular part of our online course affected the reporting quality the most: test, and/or commented presentations and/or screen castings.

What is sure is that common acquired knowledge of participants allowed very lively discussions about 3R information impacted by international Open Science tendencies: open access and systematic review linkage, open access funding agencies compliance, use of ARRIVE (Kilkenny et al., 2009) or GSPC (Hooijmans et al., 2011) guidelines for the reporting of animal experimentation reproducibility initiatives (Center for Open Science (COS), 2014), (Morrison, 2014), (Nosek et al., 2015), and post-publication open evaluation (Hartshorne and Schachner, 2012).

The acquired information retrieval skills may also help researchers to report available scientific information on alternative methods (refinement, reduction and replacement) in the mandatory application form for animal experimentation (Form A in Switzerland). It may include the search methodology reporting in case of non-existing alternative method to prove that the use of live animals is indispensable for reaching the project goal.

The newly introduced online course www.3Rupdate.ch is intended to assist researchers in their practical work in two ways: Retrieving information from the web and reporting their search for alternative methods to approving authorities. Additionally, it may help to increase scientific validity by improving general literature search skills. It was developed in the context of Swiss requirements, and was first designed for aspiring directors of animal experimentation. It is intended to reuse the online module also prior continuing education on systematic reviews for PhD, laboratory technicians, post-docs, and members of commission for the evaluation of animal experimentation request form. Animal systematic review techniques will be practiced in a workshop with already made animal search component (Hooijmans et al., 2010), to prepare researchers to risk of bias assessment of papers (Hooijmans et al., 2014) and meta-analysis with open access Revman software (Deek et al., 2008) as a powerful tool to increase translational validity of pre-clinical study results (de Vries et al., 2014).

We were already, at this early stage, able to show that information retrieval skills of researchers were largely improved by this blended learning strategy, comprising development of passive knowledge with online commented presentations, screen-castings and test, followed by individual active application by the practice of case study and reporting, prior a face-to-face session on 3R information issues. After online module introduction, presence of MeSH terms reached 88%, and correct combination of free and MeSH terms improved to 60%, the latter suggesting that passive knowledge built by the online module is maybe not entirely sufficient to be automatically transformed into active competence and has to be reinforced by the following face-to-face course. Further practice may also be offered in new workshop to achieve high information retrieval ability necessary for a systematic review.

We hope that 3Rupdate contents will spread worldwide along other national animal experimentation course organizers, thanks to the open-access approach of www.3Rupdate.ch, with creative common licenses allowing quick and easy reuse and/or adaptation.

References

- Anon. Article 149 Cantonal committees on animal experiments in 455.1 Animal Welfare Ordinance (TSchV) of 23 April 2008 (position at 1 April 2011), English translation initialised and co-financed by Interpharma. Available at: http://www.admin.ch/opc/de/classified-compilation/20080796/index.html [Accessed March 21, 2016].
- Anon. RS 455.109.1 Ordonnance du DFI du 5 septembre 2008 sur les formations à la détention d'animaux et à la manière de les traiter (Ordonnance sur les formations en matière de protection des animaux, OFPAn). Confédération Suisse. Available at: http://www.admin.ch/opc/fr/classified-compilation/20080798/index.html [Accessed March 21, 2016].
- Begley, C.G. and Ioannidis, J.P.A. (2015). Reproducibility in Science Improving the Standard for Basic and Preclinical Research. *Circulation Research 116*, 116–126. Available at: http://circres.ahajournals.org/content/116/1/116.long
- Center for Open Science (COS) (2014). Transparency and Openness Promotion (TOP) Guidelines. Available at: https://cos.io/top/ [Accessed March 21] 2016].
- Choe, B. I. and Lee, G. H. (2013). Searching and review on the Three Rs information in Korea: time for quality assessment and continued education. *BMB Rep* 46, 335-337. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4133912/
- Collins, F.S. and Tabak, L. A. (2014). NIH plans to enhance reproducibility [accepted author manuscript on PubmedCentral]. Originally published in *Nature 505*, 612–613. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4058759/
- Deek, J. J., Higgins, J. P. T., and Altman, D. G. (2008). Chapter 9. Analysing Data and undertaking meta-analyses. In J. P. T. Higgins and S. Green (eds), *Cochrane Handbook for systematic reviews of interventions* (243-296). Wiley-Blackwell, West Sussex, England. Available at Available at: http://onlinelibrary.wiley.com/book/10.1002/9780470712184.
- http://onlinelibrary.wiley.com/book/10.1002/9780470712184.

 De Vries, R. B. M., Wever, K. E., Avey, M. T. et al. (2014). The Usefulness of Systematic Reviews of Animal Experiments for the Design of Preclinical and Clinical Studies. *ILAR Journal 55*, 427–437. Available at: http://dx.doi.org/10.1093/ilar/ilu043
- Freedman, L. P., Cockburn, I. M. and Somcoe, T. S. (2015). The Economics of Reproducibility in Preclinical Research. *Plos Biol* 13(6):e1002165, e1002165. Available at: http://dx.doi.org/10.1371/journal.pbio.1002165
- Goss, P. E., Strasser-Weippl, K., Lee-Bychkovsky, B. L. et al. (2014). Challenges to effective cancer control in China, India, and Russia. *Lancet Oncol 15*, 489-538. Available at: http://dx.doi.org/10.1016/S1470-2045(14)70029-4
- Grune, B., Fallon, M., Howard, C. et al. (2004). Report and recommendations of the international workshop "Retrieval approaches for information on alternative methods to animal experiments." *ALTEX 21*, 115–127. Available at: http://www.altex.ch/All-issues/lssue.50.html?iid=31&aid=2
- Hartshone, J. and Schachner, A. (2012). Tracking replicability as a method of post-publication open evaluation. *Frontiers in Computational Neuroscience 6*: p.8. Available at: http://dx.doi.org/10.3389/fncom.2012.00008
- Hooijmans, C.R., Rovers, M. M., De Vries, R. B. M. et al. (2014). SYRCLE's risk of bias tool for animal studies. *BMC medical research methodology 14*, 43. Available at: http://www.biomedcentral.com/1471-2288/14/43
- Hooijmans, C.R., Tillema, A., Leenaars, M. et al. (2010).Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed.*Laboratory Animals 44*, 170–175. Available at: http://dx.doi.org/10.1258/la.2010.009117
- Hooijmans, C.R., De Vries, R.B.M, Leenaars, M. et al. (2011). The Gold Standard Publication Checklist (GSPC) for improved design, reporting and scientific quality of animal studies GSPC versus ARRIVE guidelines. *Laboratory Animals* 45, 61. Available at: http://dx.doi.org/10.1258/la.2010.010130
- Hudson-Shore, M. (2012). Searching effectively for three Rs Information. *Alternatives to Laboratory Animals 40*, 22–23. Available at: http://altweb.jhsph.edu/pubs/journals/atla/406/ hudson.pdf
- Janusch-Roi, A., Libowitz, L., Grune, B. and Kreger, M. (2000). Alternative method databases specialised informationsources on alternatives to support scientists and authorities responsible for granting project licences (1731-1736). In M. Balls, A.-M.van Zeller and M. E. Halder (eds.), Progress in the Reduction, Refinement and Replacement of Animal Experimentation. Elsevier Science.
- Kilkenny, C., Parsons, N. Kadyszewski, E. et al. (2009). Survey of the quality of experimental design, statistical analysis and reporting of research using animals. *PloS One 4*, e7824. Available at: http://dx.doi.org/10.1371/journal.pone.0007824
- Lenaars, M., Savenije, B., Nagtegaal, A. et al. (2009). Assessing the search for and implementation of the Three Rs: a survey among scientists. *Alternatives to laboratory animals: ATLA 37*, 297–303.
- MacLeod, M. R., Michie, S. Roberts, I. et al. (2014). Biomedical research: increasing value, reducing waste. *The Lancet 383*, 101–104. Available: http://dx.doi.org/10.1016/S0140-6736(13)62329-6
- McNutt, M. (2014). Journals unite for reproducibility. *Science 346*, 679–679. Available at: http://dx.doi.org/10.1038/515007a
 - Morrison, S. J. (2014). Time to do something about reproducibility. eLife 2014;3:e03981. Available at: http://dx.doi.org/10.7554/eLife.03981

- Nesdill, D. and Adams, K. M. (2011). Literature search strategies to comply with institutional animal care and use committee review requirements. *Journal of Veterinary Medical Education* 38, 150–156. Available at: http://dx.doi.org/10.3138/jvme.38.2.150
- Norecopa. 3R Guide The Norwegian Reference Centre for Laboratory Animal Science & Alternatives. Available at: http://oslovet.norecopa.no [Accessed March 21, 2016].
- Nosek, B. A., Alter, G., Banks G. C. et al. (2015). Promoting an open research culture. *Science 348*, 1422–1425. Available at: http://dx.doi.org/ 10.1126/science.aab2374
- Roi, A. J. and Richmond, J. (eds) (2013). The EURL ECVAM Search Guide on Alternatives to Animal testing, Good Search Practiceon Animal Alternatives, Re-Edition. Luxembourg: Publications Office of the European Union. Available at: http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/now-available-ecvam-search-quide-on-alternatives-to-animal-testing [Accessed March 21, 2016.
- Sauer, U. G., Wächter, T. Grune, B. et al. (2009). Go3R semantic Internet search engine for alternative methods to animal testing. *ALTEX* 26, 17–31. Available at: http://www.altex.ch/Current-issue.50.html?iid=104&aid=2
- Silverman, J., Baker, S.P. and Lidz, C. W. (2012). A self-assessment survey of the Institutional Animal Care and Use Committee, Part 1: animal welfare and protocol compliance. *Lab Animal 41*, 230–235.
- Van Lujk, J., Cuijpers, Y. van der Vaart, L. et al. (2011). Assessing the search for information on Three Rs methods, and their subsequent implementation: a national survey among scientists in the Netherlands. *Alternatives to laboratory animals* 39, 429–447.
- Van Noorden, R. (2012). Trouble at the text mine. *Nature* 483, 134–135. Available at: http://dx.doi.org/10.1038/483134a

Acknowledgements

The authors would like to express their gratitude to the following persons:

- Course organizer of Module-2: Philippe Bugnon, University of Zürich;
- Face-to-face Module-2 3R information trainers 2012: Josiane Bonetti at University of Lausanne and Francine Dreier at University of Geneva;2015: Cécile Lebrand at Bibliothèque Universitaire de Médecine (BiUM) atLausanne University Hospital
- Support of 3R information retrieval course in Module-2 2012-2015: Isabelle Desbaillets and Marcel Gyger.
- Website 3Rupdate.ch creation: Pierre-André Vullioud (inetis.ch).
- Reading and corrections of manuscript: Cécile Lebrand and Aitana Nives

Funding

The creation of the website 3Rupdate.ch contents was sponsored by Animalfree Research (http://www.animalfree-research.org/en/), the Haldimann Foundation (http://www.haldimann-stiftung.ch), the Margaret and Francis Fleitmann Foundation and the Foundation "Stumme Brüder".

Supplementary material

Appendix 1: annual session homework documents Appendix 2: online test questions and answers

Data availability

Since the homeworks were not originally designed for a survey, researchers were not asked to give their written consent about publication of self-reports (personal data protection). Therefore, original self-reports are not freely accessible. Persons wanting to read anonymized self-reports should ask corresponding author a temporary access to the closed dataset depositon Zenodo (DOI 10.5281/zenodo.18379), providing that that homework will not be copied locally and/or further disseminated.

Conflict of interest

The authors declare no conflict of interest.

Correspondence to

Dr. Sylvie Vullioud Scientific Information School SIS Grand Vigne 7 1302 Vufflens-la-Ville Switzerland

Phone: 0041 21 550 38 44

Email: sylvie.vullioud@scientific-info-school.ch

APPENDIX 1 - HOMEWORK ASSIGNMENTS

Homework assignments, Zürich session, March 2012

Aim of the homework

To be able to report an information research methodology in order to justify an experimental choice (please answer the 3 assignment questions)

Theory

A good literature search of 3R animal experimentation information is based on a relevant information research <u>question</u>

- The 3Rs research question is formulated only in the field of experimental methods corresponding to the coverage of Module 2 training, and not ethics, law, pharmacokinetics, or toxicology aspects of the 3R
- The information research question contains only 1R concept at the time, refine OR reduce OR refine.
- In order to be able to use Bibliographic Data Bases (BDB), choose precise keywords and
 equations corresponding to an accurate information question and use general keywords or
 equations corresponding to a general information need covered by book catalogs.

Literature subject

Are there m ice or rat models, or non-vertebrate or in vitro models to study Huntington disease?"

(Huntington disease and the 3Rs)

Assignment 1

Perform an information **search** using keywords or equations reflecting the above question in a search tool

Suggestions to help you in your literature search:

- Free search: combine keywords to formulate an equation to be used in the research field, with OR AND Bolean operators and "..." (...) * wildcards.
- Try to use controlled vocabulary if any existing in the research tool, i.e. MeSH terms in PubMed.
- Use filters of Bibliographic Data Bases (BDB)
- Use citations to find new references (Google scholar, Web of Science, Scopus)
- The search can performed with Google, Google scholar, Go3R, PubMed, PubMed central, Science Direct, Web of Science, Scopus, Embase, Springer protocols, Wiley Protocols, CRCNetbase, NEBIS, RERO, IDS, or a research tool listed by AWIC Center, or NCR3R or Altweb websites.

Assignment 2

Report your search strategy to obtain the highest relevant documents with 2 selected research tools minimum and corresponding best references.

An example of literature search and how to write down your research methodology document: Question: "What are some recent developments of polyurethanes synthesis for sport shoes?"

Assignment 3

Write down a paragraph about:

- What criteria did you choose to select a 3Rs search tool? Why did you choose these 2 tools?
- Compare 2 selected tools: what is common, what is different?
- Do you think that your strategy is relevant to answer the question?
- Could you phrase another question on "Huntington disease and the 3Rs"
- than the one used for this exercise-

Web of Science	Key-words /equation /filters / Mesh terms	Number of results	Number of relevant references on first 2 pages	Selected references from 2 first pages
	polyurethanes	27'115	BAD	
	(polyurethanes AND sport)	22	half	[1]
	polyurethanes AND (ski OR running OR sport)	190	half	[2]
	polyurethanes AND (ski OR running OR sport) AND shoe*	9	all	[3] [4][5]
	polyurethanes AND synthesis	6302	half	[6]
	polyurethanes AND synthesis + filter review + sort by Times cited	632	half	[7]
	"polyurethanes synthesis" AND (renewable OR oil OR vegetal)	4	4	[8][9]
	From [9], use of Times cited: 7	7	4	[10][11]

Science direct	Key-words /equation /filters / Mesh terms	Number of results	Number of relevant references on first 2 pages	Selected references
	polyurethanes AND (renewable OR oil OR vegetal) in All fields including Full text	12'859	BAD	
	polyurethanes AND (renewable OR oil OR vegetal) in Advanced search in Title/Abstract/Keyword	202		[15]

Engineering Village	Key-words /equation /filters / Mesh terms	Number of results	Number of relevant references on first 2 pages	Selected references
	polyurethanes AND (renewable OR oil OR vegetal)	1391	? mixed languages	
	polyurethanes AND (renewable OR oil OR vegetal) + filter English only	1190	all	[12][13]
	(polyurethanes OR urethanes) AND synthesis AND (renewable OR oil OR vegetal)	262	all	[14]

- [1] G. R. E. Maries, « Thermal Analysis of Some Mechanical and Physical Properties of Thermoplastic Polyurethanes Used in Manufacturing of Performance Sport Products », *Mater. Plast.*, vol. 46, n°2, p. 169–172, juin 2009.
- [2] Hirschmueller, H. Baur, S. Mueller, P. Helwig, H.-H. Dickhuth, et F. Mayer, « Clinical effectiveness of customised sport shoe orthoses for overuse injuries in runners: a randomised controlled study », Br. J. Sports Med., vol. 45, n°12, p. 959– 965, sept. 2011.
- [3] D. P. Pfister, Y. Xia, et R. C. Larock, « Recent Advances in Vegetable Oil-Based Polyurethanes », *ChemSusChem*, vol. 4, n°6, p. 703–717, 2011.

- [4] M. Sawai, K. Miyamoto, K. Takemura, M. Mori, et K. Kiuchi, « Super low density polyurethane systems for sports shoes (Reprinted) », *J. Cell. Plast.*, vol. 36, n°4, p. 286–+, août 2000.
- [5] A. MEMARI, P. CAVANAGH, et S. MADAN, LINEAR AND NONLINEAR FINITE ELEMENT STUDY OF POLYURETHANE USED IN SPORTS SHOES. Edinburgh: Civil Comp Press, 1994.
- [6] Saetung, L. Kaenhin, P. Klinpituksa, A. Rungvichaniwat, T. Tulyapitak, S. Munleh, I. Campistron, et J.-F. Pilard, « Synthesis, characteristic, and properties of waterborne polyurethane based on natural rubber », J. Appl. Polym. Sci., vol. 124, n°4, p. 2742–2752, 2012.
- [7] Krol, « Synthesis methods, chemical structures and phase structures of linear polyurethanes. Properties and applications of linear polyurethanes in polyurethane elastomers, copolymers and ionomers », *Prog. Mater. Sci.*, vol. 52, n°6, p. 915–1015, 2007
- [8] B. Lazdina, U. Stirna, M. Misane, V. Zeltins, V. Yakushin, et D. Vilsone, *Properties of polyurethanes from vegetable oils polyols*. Vilnius: Vilnius Univ, 2007.
- [9] C. A. Cateto, M. F. Barreiro, A. E. Rodrigues, M. C. Brochier-Solan, W. Thielemans, et M. N. Belgacem, « Lignins as macromonomers for polyurethane synthesis: A comparative study on hydroxyl group determination RID A-4506-2010 », *J. Appl. Polym. Sci.*, vol. 109, n°5, p. 3008–3017, 2008.
- [10] C. A. Cateto, M. F. Barreiro, A. E. Rodrigues, et M. N. Belgacem, « Kinetic study of the formation of lignin-based polyurethanes in bulk », *React. Funct. Polym.*, vol. 71, n°8, p. 863–869, 2011.
- [11] C. A. Cateto, M. F. Barreiro, A. E. Rodrigues, et M. N. Belgacem, « Optimization Study of Lignin Oxypropylation in View of the Preparation of Polyurethane Rigid Foams », *Ind. Eng. Chem. Res.*, vol. 48, n°5, p. 2583–2589, mars 2009.
- [12] D. P. Pfister, Y. Xia, et R. C. Larock, « Recent advances in vegetable oil-based polyurethanes », *ChemSusChem*, vol. 4, n°6, p. 703–717, 2011.
- [13] A. Z. M. Rus, T. J. Kemp, et A. J. Clark, « Degradation studies of polyurethanes based on vegetable oils. Part 1. Photodegradation », *Progress in Reaction Kinetics and Mechanism*, vol. 33, n°4, p. 363–391, 2008.
- [14] T. K. Das, D. Das, B. N. Guru, K. N. Das, et S. Lenka, « Polymers from renewable resources. XXVIII. Synthesis, characterization, and thermal studies of semi-interpenetrating polymer networks derived from castor-oil-based polyurethanes and cardanol derivatives », *Polymer Plastics Technology and Engineering*, vol. 37, n°4, p. 427–435, 1998.
- [15] R. V. Silva, D. Spinelli, W. W. Bose Filho, S. Claro Neto, G. O. Chierice, et J. R. Tarpani, « Fracture toughness of natural fibers/castor oil polyurethane composites », *Composites Science and Technology*, vol. 66, n°10, p. 1328–1335, août 2006

Homework assignments, Lausanne session, September 2012

Aim of the work

To be able to report an information research methodology in order to justify an experimental choice (please answer the 3 assignment questions)

Theory

A good literature search of 3R experimentation information is based on a relevant information research question.

- The 3R research question is formulated only in the field of experimental methods corresponding to the coverage of Module 2 training, and not ethics, law, pharmacokinetics, or toxicology aspects of the 3R
- The information research question contains only 1R concept at the time, refine OR reduce OR replace.
- 3. In order to be able to use Bibliographic Data Bases (BDB), define an accurate search question which reflects a precise information need.

Search subject

"What are mice, or non-vertebrate, or in vitro models to study Huntington disease?" (Huntington disease and the 3Rs)

Assignment 1

Perform an information search using keywords or equations reflecting the above equation in a search tool

Suggestions to help you in your literature search

- Free search: combine keywords to formulate an equation to be used in the research field, with OR AND Boolean operators and "..." (...) * wildcards.
- Try to use controlled vocabulary if any existing in the research tool, ie MeSH terms in PubMed.
- Use filters of Bibliographic Data Bases (BDB)
- Use citations to find new references (Google scholar, Web of Science, Scopus)
- The search can be performed with, Google scholar, Go3R, PubMed, PubMedcentral, Science Direct, Web of Science, Scopus, Embase, Springer protocols, Wiley Protocols, CRCNetbase, NEBIS, RERO, IDS, or a research tool listed by AWIC Center, or NCR3R or Altweb websites.

Assignment 2

Report your search strategy to obtain the highest number of relevant documents with 2 selected research tools minimum and corresponding best references. An example of literature and how to write down your research methodology document:

Assignment 3

Write down a paragraph about:

- 1. What criteria did you choose to select a 3Rs search tool / Why did you choose these 2 tools?
- 2. Compare the 2 selected tools: what is common, what is different?
- 3. Do you think that your strategy is relevant to answer the question?
- 4. Can you suggest any improvement in the formulation of the question "What are mice, or non-vertebrate, or in vitro models to study Huntington disease?" in order to increase relevancy of search results and tend towards an exhaustive search?

Example: How to find documents for recent developments of polyurethanes synthesis for sport shoes?

Web of Science	Key-words /equation /filters / MeSH terms	N° of results	N°of relevant references on first 2 pages	Selected references from 2 first pages
	polyurethanes	27'115	BAD	
	(polyurethanes AND sport)	22	half	[1]
	polyurethanes AND (ski OR running OR sport)	190	half	[2]
	polyurethanes AND (ski OR running OR sport) AND shoe*	9	all	[3] [4][5]
	polyurethanes AND synthesis	6302	half	[6]
	polyurethanes AND synthesis + filter review + sort by Times cited	632	half	[7]
	"polyurethanes synthesis" AND	4	4	[8][9]

	(renewable OR oil OR vegetal)			
	From [9], use of Times cited : 7	7	4	[10][11]
Engineering Village	polyurethanes AND (renewable OR oil OR vegetal)	1391	? mixed languages	
	polyurethanes AND (renewable OR oil OR vegetal) + filter English only	1190	all	[12][13]
	(polyurethanes OR urethanes) AND synthesis AND (renewable OR oil OR vegetal)	262	all	[14]

- [1] G. R. E. Maries, « Thermal Analysis of Some Mechanical and Physical Properties of Thermoplastic Polyurethanes Used in Manufacturing of Performance Sport Products », *Mater. Plast.*, vol. 46, n°. 2, p. 169-172, juin 2009.
- [2] A. Hirschmueller, H. Baur, S. Mueller, P. Helwig, H.-H. Dickhuth, et F. Mayer, « Clinical effectiveness of customised sport shoe orthoses for overuse injuries in runners: a randomised controlled study », *Br. J. Sports Med.*, vol. 45, n°. 12, p. 959-965, sept. 2011.
- [3] D. P. Pfister, Y. Xia, et R. C. Larock, « Recent Advances in Vegetable Oil-Based Polyurethanes », *ChemSusChem*, vol. 4, n°. 6, p. 703-717, 2011.
- [4] M. Sawai, K. Miyamoto, K. Takemura, M. Mori, et K. Kiuchi, « Super low density polyurethane systems for sports shoes (Reprinted) », *J. Cell. Plast.*, vol. 36, n°. 4, p. 286-+, août 2000.
- [5] A. MEMARI, P. CAVANAGH, et S. MADAN, LINEAR AND NONLINEAR FINITE ELEMENT STUDY OF POLYURETHANE USED IN SPORTS SHOES. Edinburgh: Civil Comp Press, 1994.
- [6] A. Saetung, L. Kaenhin, P. Klinpituksa, A. Rungvichaniwat, T. Tulyapitak, S. Munleh, I. Campistron, et J.-F. Pilard, « Synthesis, characteristic, and properties of waterborne polyurethane based on natural rubber », *J. Appl. Polym. Sci.*, vol. 124, n°. 4, p. 2742-2752, mars 2012.
- [7] P. Krol, « Synthesis methods, chemical structures and phase structures of linear polyurethanes. Properties and applications of linear polyurethanes in polyurethane elastomers, copolymers and ionomers », *Prog. Mater. Sci.*, vol. 52, n°. 6, p. 915-1015, août 2007.
- [8] B. Lazdina, U. Stirna, M. Misane, V. Zeltins, V. Yakushin, et D. Vilsone, *Properties of polyurethanes from vegetable oils polyols*. Vilnius: Vilnius Univ. 2007.
- [9] C. A. Cateto, M. F. Barreiro, A. E. Rodrigues, M. C. Brochier-Solan, W. Thielemans, et M. N. Belgacem, « Lignins as macromonomers for polyurethane synthesis: A comparative study on hydroxyl group determination RID A-4506-2010 », J. Appl. Polym. Sci., vol. 109, n°. 5, p. 3008-3017, sept. 2008.
- [10] C. A. Cateto, M. F. Barreiro, A. E. Rodrigues, et M. N. Belgacem, « Kinetic study of the formation of lignin-based polyurethanes in bulk », *React. Funct. Polym.*, vol. 71, no. 8, p. 863-869, août 2011.
- [11] C. A. Cateto, M. F. Barreiro, A. E. Rodrigues, et M. N. Belgacem, « Optimization Study of Lignin Oxypropylation in View of the Preparation of Polyurethane Rigid Foams », *Ind. Eng. Chem. Res.*, vol. 48, n°. 5, p. 2583-2589, mars 2009
- [12] D. P. Pfister, Y. Xia, et R. C. Larock, « Recent advances in vegetable oil-based polyurethanes », *ChemSusChem*, vol. 4, n°. 6, p. 703-717, 2011.
- [13] A. Z. M. Rus, T. J. Kemp, et A. J. Clark, « Degradation studies of polyurethanes based on vegetable oils. Part 1. Photodegradation », *Progress in Reaction Kinetics and Mechanism*, vol. 33, n°. 4, p. 363-391, 2008.
- [14] T. K. Das, D. Das, B. N. Guru, K. N. Das, et S. Lenka, « Polymers from renewable resources. XXVIII. Synthesis, characterization, and thermal studies of semi-interpenetrating polymer networks derived from castor-oil-based polyurethanes and cardanol derivatives », *Polymer Plastics Technology and Engineering*, vol. 37, n°. 4, p. 427-435, 1998.

Homework assignments, Lausanne session, September 2013

Aim of the work

To complete Form A on the literature research in order to justify an experimental choice (please answer the 2 assignment questions)

Theory

A good literature search of 3R experimentation information is based on a well formulated research question.

- The 3R research question is formulated only in the field of experimental methods corresponding to the coverage of Module 2 training, and not ethics, law, pharmacokinetics, or toxicology aspects of the 3R
- The literature research question contains only 1R concept at the time, refine OR reduce OR replace.
- 3. When using bibliographic databases, define an accurate search question related to a precise information need.

Search subject

"Which mice, or non-vertebrate, or in vitro models are used to study skin cancer?" (skin cancer and the 3Rs)

Assignment 1

Perform a search using keywords reflecting the above question in two or three databases. Report your search strategy including screenshots of the search history. (see example on page 2)

Basic search techniques

- Free search: Combine keywords to formulate a query using boolean operators (AND, OR, NOT), phrases ("...") and/or wildcards (*, ?).
- If available use the **controlled vocabulary** (e.g. MeSH terms in PubMed).
- Use filters.
- Use citations (cited or citing articles) and related articles to find new references (Google scholar, Web of Science, Scopus).

Information resources

The search can be performed with the following databases:

PubMed, Embase, Web of Science, Scopus, Go3R, Sciencedirect, Springer protocols, Wiley,

Protocols, CRCNetbase, library catalogues (e.g. Swissbib, NEBIS, RERO).

Assignment 2

Write a paragraph on

- 1. According to what criteria did you choose these databases?
- Compare the databases: what is similar, what is different?
- 3. Do you think that your strategy is accurate to answer the question?
- 4. How can the relevancy of the search results be increased without missing potentially relevant literature?

An example of literature search and how to write down your research methodology document: How to find documents (articles, reviews, guidelines, observations) on how to announce a bad diagnosis or bad prognosis to a patient: see below.

Database 1

PubMed	Key-words /equation /filters / MeSH terms	Number of results	Number of relevant references on first 2 pages	Selected references from 2 first
	illness AND diagnosis AND information	12145	none	
	illness AND diagnosis AND disclosure	712	10%	[1]
	"bad news" AND (communicat* OR break*)	748	45%	[2] [3] [4]
	Truth disclosure[Mesh]	12292	10%	[5]
	Professional-Patient Relations[Mesh] AND (bad news OR truth disclosure OR diagnosis disclosure)	3994	40%	[6] [7]
	Professional-Patient Relations[Mesh] AND Truth Disclosure[Mesh] + Filter Article Type : Review	264	70%	[8] [9] [10]
	Professional-Patient Relations[Mesh] AND Truth Disclosure[Mesh] AND Patients/psychology[Mesh]	97	80%	[11] [12] [13]

Search history

<u>#7</u>	Add	Search Professional-Patient Relations[Mesh] AND Truth Disclosure[Mesh] AND Patients/psychology[Mesh]	<u>97</u>	11:26:04
<u>#6</u>	Add	Search Professional-Patient Relations[Mesh] AND Truth Disclosure[Mesh] Filters: Review	<u>264</u>	11:25:45
<u>#5</u>	Add	Search Professional-Patient Relations[Mesh] AND (bad news OR truth disclosure OR diagnosis disclosure)	<u>3994</u>	11:25:23
<u>#4</u>	Add	Search Truth disclosure[Mesh]	12292	11:25:07
<u>#3</u>	Add	Search "bad news" AND (communicat* OR break*)	<u>748</u>	11:24:49
<u>#2</u>	Add	Search illness AND diagnosis AND disclosure	<u>712</u>	11:24:34
<u>#1</u>	Add	Search illness AND diagnosis AND information	<u>12145</u>	11:22:53

Database 2

Web of Science	Key-words /equation /filters / MeSH terms	Number of results	Number of relevant references on first 2 pages	Selected references from 2 first pages
	illness AND diagnosis AND information	2'847	none	
	illness AND diagnosis AND disclosure	226	few	[14] [15]
	(bad news OR truth disclosure OR diagnosis disclosure) AND (communicat* OR break*)	1406	half	[16] [17]
	(bad news OR truth disclosure OR diagnosis disclosure) AND (communicat* OR break*) + filter review + sort by Times cited	262	all	[18] [19] [20]

Search history

Set	Results	Save History / Create Alert Open Saved History	Edit Sets	Combine Sets O AND O OR Combine	Select All X Delete
#4	98	Topic=(bad news OR truth disclosure OR diagnosis disclosure) AND Topic=(communicat* OR break*) Refined by: Document Types=(REVEW) Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All years			
#3	1,406	Topic=(bad news OR truth disclosure OR diagnosis disclosure) AND Topic=(communicat* OR break*) Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All years	Edit		
#2	226	Topic=(iliness AND diagnosis AND disclosure) Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All years	Edit		
#1	2,847	Topic=(iliness AND diagnosis AND information) Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All years	Edit		

- 1. de Vinck-Baroody, O., et al., "Disclosure of diagnosis: to tell or not to tell?". J Dev Behav Pediatr, 2012. vol. 33 (5): p. 441-3.
- 2. Antoine, P. and F. Pasquier, "Emotional and psychological implications of early AD diagnosis". Med Clin North Am. 2013. vol. 97 (3) n 459-75
- 3. Martis, L. and A. Westhues, "A synthesis of the literature on breaking bad news or truth telling: potential for research in India". *Indian J Palliat Care*, 2013. vol. 19 (1): p. 2-11.
- 4. Friedman, J.H., "Breaking bad news". R I Med J, 2013. vol. 96 (7): p. 8-9.
- 5. Binder, M. and A. Coad, ""I'm afraid I have bad news for you..." Estimating the impact of different health impairments on subjective well-being". Soc Sci Med, 2013. vol. 87: p. 155-67.
- 6. Thai, J.N., et al., "Every patient is an individual: clinicians balance individual factors when discussing prognosis with diverse frail elderly adults". J Am Geriatr Soc, 2013. vol. 61 (2): p. 264-9.
- 7. Amber, I. and A. Fiester, "Communicating findings: a justification and framework for direct radiologic disclosure to patients". AJR Am J Roentgenol, 2013. vol. 200 (3): p. 586-91.
- Bluebond-Langner, R., E.D. Rodriguez, and A.W. Wu, "Discussing adverse outcomes with patients and families". Oral Maxillofac Surg Clin North Am, 2010. vol. 22 (4): p. 471-9.
- 9. Fujimori, M. and Y. Uchitomi, "Preferences of cancer patients regarding communication of bad news: a systematic literature review". Jpn J Clin Oncol, 2009. vol. 39 (4): p. 201-16.
- 10. Harrison, M.E. and A. Walling, "What do we know about giving bad news? A review". Clin Pediatr, 2010. vol. 49 (7): p. 619-
- 11. Rogg, L., et al., "Direct communication, the unquestionable ideal? Oncologists' accounts of communication of bleak prognoses". Psychooncology, 2010. vol. 19 (11): p. 1221-8.
- 12. Maynard, D.W., ""Does it mean I'm gonna die?": on meaning assessment in the delivery of diagnostic news". Soc Sci Med, 2006. vol. 62 (8): p. 1902-16.
- 13. Kallergis, G., "Informing the cancer patient and family". *J BUON*, 2009. vol. 14 (1): p. 109-14. 14. Li, J., et al., "Whether, when, and who to disclose bad news to patients with cancer: a survey in 150 pairs of hospitalized patients with cancer and family members in China". Psychooncology, 2012. vol. 21 (7): p. 778-784.
- 15. Moore, V. and S. Cahill, "Diagnosis and disclosure of dementia -- a comparative qualitative study of Irish and Swedish General Practitioners". Aging Ment Health, 2013. vol. 17 (1): p. 77-84.
- 16. Locatelli, C., et al., "Physicians' age and sex influence breaking bad news to elderly cancer patients. Beliefs and practices of 50 Italian oncologists: the GIOGer study". Psychooncology, 2013. vol. 22 (5): p. 1112-1119.
- 17. Millar, C., J. Reid, and S. Porter, "Refractory cachexia and truth-telling about terminal prognosis: a qualitative study". Eur J Cancer Care, 2013. vol. 22 (3): p. 326-333.
- 18. Fallowfield, L. and V. Jenkins, "Communicating sad, bad, and difficult news in medicine". Lancet, 2004. vol. 363 (9405): p. 312-319.
- 19. Hagerty, R.G., et al., "Communicating prognosis in cancer care: a systematic review of the literature". Annals of Oncology, 2005. vol. 16 (7): p. 1005-1053.
- 20. Ptacek, J.T. and T.L. Eberhardt, "Breaking bad news A review of the literature". Jama-Journal of the American Medical Association, 1996. vol. 276 (6): p. 496-502.

Homework assignments, Lausanne session, September 2014

Aim of the work

To complete Form A on the literature research in order to justify an experimental choice (please answer the 2 assignment questions)

Theory

A good literature search of 3R experimentation information is based on a well formulated research question.

- The 3R research question is formulated only in the field of experimental methods corresponding to the coverage of Module 2 training, and not ethics, law, pharmacokinetics, or toxicology aspects of the 3R
- The literature research question contains only 1R concept at the time, refine OR reduce OR replace
- 3. When using bibliographic databases, define an accurate search question related to a precise information need.

Search subject

"Which mice, or non-vertebrate, or in vitro models are used to study Huntington disease?" (Huntington disease and the 3Rs)

Assignment 1

Perform a search using keywords reflecting the above question in two or three databases. Report your search strategy including screenshots of the search history and present your selected references. (see example p. 2-3)

Basic search techniques

- Free search: Combine keywords to formulate a query using boolean operators (AND, OR, NOT), phrases ("...") and/or wildcards (*, ?).
- If available use the **controlled vocabulary** (e.g. MeSH terms in PubMed).
- Use filters.
- Use citations (cited or citing articles) and related articles to find new references (Google scholar, Web of Science, Scopus).

Information resources

The search can be performed with the following databases:

PubMed, Embase, Web of Science, Scopus, Go3R, Sciencedirect, Springer protocols, Wiley,

Protocols, CRCNetbase, library catalogues (e.g. Swissbib, NEBIS, RERO).

Assignment 2

Write a paragraph on

- According to what criteria did you choose these databases? B. Compare the databases: what is similar, what is different?
- 2. Do you think that your strategy is accurate to answer the question?
- 3. How can the relevancy of the search results be increased without missing potentially relevant literature?

An example of literature search and how to write down your research methodology document: How to find documents (articles, reviews, guidelines, observations) on how to announce a bad diagnosis or bad prognosis to a patient. See below.

Database 1

PubMed	Key-words /equation /filters /Mesh terms	N° of results	N° of relevant references on first 2 pages	Selected references from 2 first
	illness AND diagnosis AND information	12145	none	
	illness AND diagnosis AND disclosure	712	10%	[1]
	"bad news" AND (communicat* OR break*)	748	45%	[2] [3] [4]
	Truth disclosure[Mesh]	12292	10%	[5]
	Professional-Patient Relations[Mesh] AND (bad news[tw] OR truth disclosure[tw] OR diagnosis disclosure[tw])	3994	40%	[6] [7]
	Professional-Patient Relations[Mesh] AND Truth Disclosure[Mesh] + Filter Article Type : Review	264	70%	[8] [9] [10]
	Professional-Patient Relations[Mesh] AND Truth Disclosure[Mesh] AND Patients/psychology[Mesh]	97	80%	[11] [12] [13]

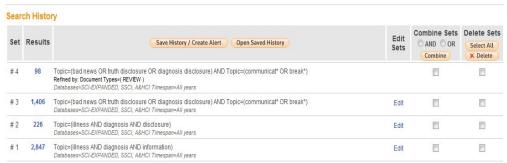
Search history

<u>#7</u>	Add	Search Professional-Patient Relations[Mesh] AND Truth Disclosure[Mesh] AND Patients/psychology[Mesh]	<u>97</u>	11:26:04
<u>#6</u>	Add	Search Professional-Patient Relations[Mesh] AND Truth Disclosure[Mesh] Filters: Review	<u>264</u>	11:25:45
<u>#5</u>	Add	Search Professional-Patient Relations[Mesh] AND (bad news OR truth disclosure OR diagnosis disclosure)	<u>3994</u>	11:25:23
#4	Add	Search Truth disclosure[Mesh]	12292	11:25:07
<u>#3</u>	Add	Search "bad news" AND (communicat* OR break*)	<u>748</u>	11:24:49
<u>#2</u>	Add	Search illness AND diagnosis AND disclosure	<u>712</u>	11:24:34
#1	Add	Search illness AND diagnosis AND information	<u>12145</u>	11:22:53

Database 2

Web of Science	Key-words /equation /filters / Mesh terms	N°of results	N° of relevant references on first 2 pages	Selected references from 2 first pages
	illness AND diagnosis AND information	2'847	none	
	illness AND diagnosis AND disclosure	226	few	[14] [15]
	(bad news OR truth disclosure OR diagnosis disclosure) AND (communicat* OR break*)	1406	half	[16] [17]
	(bad news OR truth disclosure OR diagnosis disclosure) AND (communicat* OR break*) + filter review + sort by Times cited	262	all	[18] [19] [20]

Search history



- 1. de Vinck-Baroody, O., et al., "Disclosure of diagnosis: to tell or not to tell?". J Dev Behav Pediatr, 2012. vol. 33 (5): p. 441-3.
- 2. Antoine, P. and F. Pasquier, "Emotional and psychological implications of early AD diagnosis". *Med Clin North Am*, 2013. vol. 97 (3): p. 459-75.
- 3. Martis, L. and A. Westhues, "A synthesis of the literature on breaking bad news or truth telling: potential for research in India". *Indian J Palliat Care*, 2013. vol. 19 (1): p. 2-11.
- 4. Friedman, J.H., "Breaking bad news". R I Med J, 2013. vol. 96 (7): p. 8-9.
- 5. Binder, M. and A. Coad, ""I'm afraid I have bad news for you..." Estimating the impact of different health impairments on subjective well-being". *Soc Sci Med*, 2013. vol. 87: p. 155-67.
- Thai, J.N., et al., "Every patient is an individual: clinicians balance individual factors when discussing prognosis with diverse frail elderly adults". J Am Geriatr Soc, 2013. vol. 61 (2): p. 264-9.
- 7. Sarafis, P., et al., "Disclosing the truth: a dilemma between instilling hope and respecting patient autonomy in everyday clinical practice.". *Glob J Health Sci*, 2013. vol. 6 (2): p. 128-37.
- 8. Bluebond-Langner, R., E.D. Rodriguez, and A.W. Wu, "Discussing adverse outcomes with patients and families". *Oral Maxillofac Surg Clin North Am*, 2010. vol. 22 (4): p. 471-9.
- 9. Fujimori, M. and Y. Uchitomi, "Preferences of cancer patients regarding communication of bad news: a systematic literature review". *Jpn J Clin Oncol*, 2009. vol. 39 (4): p. 201-16.
- Harrison, M.E. and A. Walling, "What do we know about giving bad news? A review". Clin Pediatr, 2010. vol. 49 (7): p. 619-26.
- 11. Rogg, L., et al., "Direct communication, the unquestionable ideal? Oncologists' accounts of communication of bleak prognoses". *Psychooncology*, 2010. vol. 19 (11): p. 1221-8.
- 12. Maynard, D.W., ""Does it mean I'm gonna die?": on meaning assessment in the delivery of diagnostic news". Soc Sci Med, 2006. vol. 62 (8): p. 1902-16.
- 13. Kallergis, G., "Informing the cancer patient and family". J BUON, 2009. vol. 14 (1): p. 109-14.
- 14. Li, J., et al., "Whether, when, and who to disclose bad news to patients with cancer: a survey in 150 pairs of hospitalized patients with cancer and family members in China". *Psychooncology*, 2012. vol. 21 (7): p. 778-784.
- 15. Moore, V. and S. Cahill, "Diagnosis and disclosure of dementia--a comparative qualitative study of Irish and Swedish General Practitioners". *Aging Ment Health*, 2013. vol. 17 (1): p. 77-84.
- 16. Locatelli, C., et al., "Physicians' age and sex influence breaking bad news to elderly cancer patients. Beliefs and practices of 50 Italian oncologists: the GIOGer study". *Psychooncology*, 2013. vol. 22 (5): p. 1112-1119.
- 17. Millar, C., J. Reid, and S. Porter, "Refractory cachexia and truth-telling about terminal prognosis: a qualitative study". *Eur J Cancer Care*, 2013. vol. 22 (3): p. 326-333. 18. Fallowfield, L. and V. Jenkins, "Communicating sad, bad, and difficult news in medicine". *Lancet*, 2004. vol. 363 (9405): p. 312-319.
- Hagerty, R.G., et al., "Communicating prognosis in cancer care: a systematic review of the literature". Annals of Oncology, 2005. vol. 16 (7): p. 1005-1053.
- 20. Ptacek, J.T. and T.L. Eberhardt, "Breaking bad news A review of the literature". *Jama-Journal of the American Medical Association*, 1996. vol. 276 (6): p. 496-502.

Homework assignments, Lausanne session, September 2015

Aim of the work

To be able to report information research methodology in order to justify the choice of an experimental model (please answer the 3 assignments)

Theory

A good literature search of 3R experimentation information is based on

- a well formulated need of information (=research question)
- if necessary, a research question is divided into sub-questions.
- each sub-question contains 1 to 3-4 maximum search components

Good advice

Use what you learned in the online beginner course and test!

Search subject

"Which mice, or non-vertebrate, or in vitro models are used to study Huntington disease?" (Huntington disease and the 3Rs)

Assignment 1

Perform a search using keywords reflecting the above question in two or three databases. Report your search strategy including search strings, selected tools, and corresponding most relevant references. (see example p. 3)

Basic search techniques

- Free search: Combine keywords to formulate a query using boolean operators (AND, OR, NOT), phrases ("...") and/or wildcards (*, ?).
- If available use the **controlled vocabulary** (e.g. MeSH terms in PubMed).
- Use filters
- Use citations (cited or citing articles) and related articles to find new references (Google Scholar, Web of Science, Scopus)

Information resources

The search can be performed with the following databases:

PubMed, PumedCentral, Embase, Web of Science, Scopus, Go3R, Sciencedirect, Springer protocols, Wiley, Protocols, CRCNetbase, library catalogues (e.g. Swissbib, NEBIS, RERO).

Assignment 2

Write down a paragraph on:

- According to what criteria did you choose these databases?
- 2. Compare the selected tools: what is similar, what is different?
- B. Do you think that your strategy is relevant to answer the question?

Assignment 3

Transformation of the query towards systematic review compliance

Transform the original question "Which mice, or non-vertebrate, or in vitro models are used to study Huntington disease?" into 3-4 sub questions, each containing following Search Components (SC):

SC1 Intervention/Exposure

SC2 Disese of interest/Health problem

SC3 Animal/Animal species/Population studied

(SC4 Outcome measures)

Example of reported equations and tools for search methodology reporting

For my strain selection, besides commercial information on transgenic inducible mouse for Huntington studies, I want to know about research papers using them?

Keywords/equations (search of May 2012)	Tools / Alerts	N° of results / relevance	Selected useful references
animal? AND (model? OR laborator*) AND (neurodegenerative OR dementia OR Huntington)	NEBIS Filter books Term search in title	46/ Good	[1]-[3]
(Tet-on OR tet-off OR Tet OR "inducible mouse" OR "inducible mice" OR "conditional mouse" OR "conditional mice") AND Huntington	wos	28 Publication date display / Good	[4]-[5]
	wos	28 Times cited display / Good	[6], cited 606x!
(Tet-on OR tet-off OR Tet OR "inducible mouse" OR "inducible mice" OR "conditional mouse" OR "conditional mice") AND Huntington	Scopus	30	[7],[8]
(Tet-on[tiab] OR tet-off[tiab] OR Tet[tiab] OR "inducible mouse"[tiab] OR "inducible mice"[tiab] OR "conditional mouse"[tiab] OR "conditional mice"[tiab]) AND (huntington[tiab] OR Huntington disease[mh])	PubMed	19	[9]
(Tet-on[tiab] OR tet-off[tiab] OR Tet[tiab] OR "inducible mouse"[tiab] OR "inducible mice"[tiab] OR "conditional mouse"[tiab] OR "conditional mice"[tiab]) AND (huntington[tiab] OR Huntington disease[mh])	PubMed Alert	1-2 / months	
(Tet-on OR tet-off OR Tet OR "inducible mouse" OR "inducible mice" OR "conditional mouse" OR "conditional mice") AND Huntington	WOS Alert	1-2/ months	
[6]	WOS citation alert	1/week	Once per month is enough

- [1] Jesús Avila, Animal models for neurodegenerative disease. Cambridge: Royal Society of Chemistry, 2011.
- [2] P. P. de Deyn, Animal models of dementia. New York: Humana Press, 2011.
- [3] Siegfried Hoyer, Workshop « Cell and Animal Models in Aging and Dementia Research » (1993, et Heidelberg), *Cell and animal models in aging and dementia research*. Wien etc: Springer, 1994.
- [4] Z. Ortega, M. Diaz-Hernandez, C. J. Maynard, F. Hernandez, N. P. Dantuma, et J. J. Lucas, « Acute Polyglutamine Expression in Inducible Mouse Model Unravels Ubiquitin/Proteasome System Impairment and Permanent Recovery Attributable to Aggregate Formation », *J. Neurosci.*, vol. 30, n° 10, p. 3675-3688, mars 2010.
- [5] H. B. Kordasiewicz, L. M. Stanek, E. V. Wancewicz, C. Mazur, M. M. McAlonis, K. A. Pytel, J. W. Artates, A. Weiss, S. H. Cheng, L. S. Shihabuddin, G. Hung, C. F. Bennett, et D. W. Cleveland, « Sustained Therapeutic Reversal of Huntington's Disease by Transient Repression of Huntingtin Synthesis », *Neuron*, vol. 74, nº 6, p. 1031-1044, juin 2012.
- [6] A. Yamamoto, J. J. Lucas, et R. Hen, « Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease », *Cell*, vol. 101, nº 1, p. 57-66, mars 2000.
- [7] X. Gu, V. M. André, C. Cepeda, S.-H. Li, X.-J. Li, M. S. Levine, et X. William Yang, « Pathological cell-cell interactions are necessary for striatal pathogenesis in a conditional mouse model of Huntington's disease », *Mol. Neurodegener.*, vol. 2, n° 1, 2007.
- [8] H. J. Han, C. C. Allen, C. M. Buchovecky, M. J. Yetman, H. A. Born, M. A. Marin, S. P. Rodgers, B. J. Song, H.-C. Lu, M. J. Justice, F. J. Probst, et J. L. Jankowsky, « Strain background influences neurotoxicity and behavioral abnormalities in mice expressing the tetracycline transactivator », J. Neurosci., vol. 32, n° 31, p. 10574-10586, 2012.
- [9] A. Saavedra, A. Giralt, L. Rué, X. Xifró, J. Xu, Z. Ortega, J. J. Lucas, P. J. Lombroso, J. Alberch, et E. Pérez-Navarro, « Striatal-enriched protein tyrosine phosphatase expression and activity in Huntington's disease: a STEP in the resistance to excitotoxicity », J. Neurosci. Off. J. Soc. Neurosci., vol. 31, nº 22, p. 8150-8162, juin 2011.

APPENDIX 2 - TEST

1. Counting	g of article citations is different in Web of Science (WOS) and Google Scholar because
□ V	VOS counts first and last authors, unlike Google Scholar that counts all authors of cited article VOS and Google Scholar coverage (=indexation) are different VOS citations are counted by humans, unlike Google Scholar that computes citations VOS includes self-citations for the counting, unlike Google Scholar that exclude them
2. In Web o	of Science (WOS) and PubMed, how are terms interpreted after their typing into the search box?
□ V	PubMed: automatic mapping WOS and PubMed: automatic detection of synonyms and automatic mapping WOS and PubMed: stemming (lemmatization), automatic detection of synonyms, and automatic mapping PubMed: stemming (lemmatization) and automatic detection of synonyms
3. The add	ition of a search component to a search string increases the number of results
	rue False
	at to identify the effects of supplementation of omega-3 fatty acids on AB plaque load in animal models of Alzheimer's a systematic review. Which search component of search string should be avoided to allow highest recall of results?
	AB plaque Animal models Omega-3 fatty acids Alzheimer's disease
	nt to set up a subject alert on the effects of supplementation of omega-3 fatty acids on AB plaque load in animal Alzheimer's disease. What is the best combination of search components allowing best precision of results?
	Alzheimer's disease Animal models Omega-3 fatty acids AB plaque Alzheimer's disease Animal models Omega-3 fatty acids Supplementation Alzheimer's disease Animal models AB plaque Loading Alzheimer's disease Omega-3 fatty acids Supplementation AB plaque Loading
6. Search o	components of a search string should be combined with OR Boolean operator
	True False
7. Synonyn	ns and related terms are combined with OR Boolean operator
	rue False
8. Combina	ation of free-text [tiab] and mesh [mh] terms increases recall of results in PubMed
	rue False
9. Automat	ic interpretation of terms in PubMed
	s disabled by field tags [tiab] and [mh] and wildcards "…" and * s turned on by Field tags [tiab] and [mh] and wildcards "…" and * Cannot be disabled Can be disabled in myNCBI account
	ant to know what is the effect of probiotic supplementation in mice models for acute pancreatitis. In PubMed, which eves the best results in term of precision and recall?
[1] () () ()	pancreatitis [mh] OR pancreatitis[tiab]) AND (probiotics[mh] OR probiotics[tiab] OR bifidobacterium[mh] OR bifidus tiab]) AND (mice[mh] OR mouse[tiab] OR mice[tiab] OR murine[tiab]) pancreatitis [mh] AND pancreatitis[tiab]) OR (probiotics[mh] AND probiotics[tiab] AND bifidobacterium[mh] AND bifidus[tiab]) OR (mice[mh] AND mouse[tiab] AND mice[tiab] AND murine[tiab]) pancreatitis [mh] OR pancreatitis[tiab] OR probiotics[mh] OR probiotics[tiab] OR bifidobacterium[mh] OR bifidus[tiab]) AND (mice[Mh] OR mouse[tiab] OR mice[tiab] OR murine[tiab]) pancreatitis [mh] OR pancreatitis[tiab]) AND (probiotics[mh] OR probiotics[tiab] OR bifidobacterium[mh] OR bifidus tiab]) OR (mice[mh] OR mouse[tiab] OR mice[tiab] OR murine[tiab])
11. Since 2	2012, systematic reviews on animal studies are easier because

□ PubMed tags 3R related articles with Refine and Reduce mesh terms

haracters of a
nals
mals
mals
vs may be
o may be
Access journals)
d NIH (USA) that