IMI2 821520 - ConcePTION

ConcePTION

WP5 – Dissemination and education for HCPs and pregnant and breastfeeding women and the general public

D5.3 Report with procedures for evidence retrieval and synthesis for the knowledge bank

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Document History

Version	Date	Description
V0.1	Jan 2021	First draft
V0.2	18 March 2021	Team review (task 5.2.4)
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V0.4	15 July 2021	Amendments to address MB comments
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Abstract

The aim of task 5.2 is to develop an EU centralised digital Knowledge Bank (KB) providing up to date, evidence-based information to healthcare professionals and members of the public on the use of medicines during pregnancy and breastfeeding. The KB is comprised of individual webpages containing information on the use of specific medicines in pregnancy and breastfeeding. These information pages will be collaboratively developed by experts in the area of medicines in pregnancy and breastfeeding throughout Europe.

The objective of subtask 5.2.4 is to define how the content of the KB will be developed and maintained, including the identification, review and interpretation of published literature using a work-sharing model among KB contributors.

The result of this subtask is a Standard Operating Procedure (SOP) which describes the process and systems which allow development of KB content which is collaboratively written by experts across Europe, is of high-quality and can be maintained in a sustainable manner in the future. This SOP is of relevance to IMI ConcePTION partners involved in work package (WP) 5.2 and contributing to the KB. It is intended that the processes outlined in this SOP will inform development and sustainable maintenance of the KB by contributing experts across Europe in the future.

Background and aim

The aim of task 5.2 is to develop an EU centralised digital Knowledge Bank (KB) providing up to date, evidence-based information to healthcare professionals and members of the public on the use of medicines during pregnancy and breastfeeding. The KB is comprised of individual webpages containing information on the use of specific medicines in pregnancy and breastfeeding. These information pages will be collaboratively developed by experts in the area of medicines in pregnancy and breastfeeding throughout Europe.

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Methods

The subtask 5.2.4 group members included representatives from teratology information services (TIS) and breastfeeding information services throughout Europe. Group members met regularly to develop the SOP and KB structure through an iterative process of review and testing. The following were central to the development of the SOP:

- Group members shared their own experience, processes and systems of developing content for local TIS resources and websites on medication use in pregnancy and breastfeeding which is evidence-based, consistent, timely, and of high-quality.
- Members considered processes used by other international organisations who publish information relating to medicine use in pregnancy and breastfeeding but were not involved in subtask 5.2.4 group or the ConcePTION project. This included the TERIS (Teratogen Information System) and Meta-preg resources.
- Group members also used their own experience of providing services in their own TIS to agree on the structure and content of individual information pages which is focussed on the needs of the KB end-user.
- Group members considered the functionality and technical specifications of the KB platform as outlined in D5.1 Report with description of the functionality of the knowledge database.
- Feedback was obtained from potential end-users and other stakeholders on the structure and content of individual information pages through the Patient-Engagement Open Forum, KB Focus groups and meetings with patient representatives. Feedback was incorporated into the SOP and KB design.
- Key considerations for the sustainability of the KB were considered through a joint meeting with European Network of Teratology Information Services (ENTIS) and ConcePTION. The group explored the potential opportunities and challenges of work-sharing and the need to balance quality of the KB with the finite resources available.

Results

A 'Standard Operating Procedure' for the collaborative development of content for the EU Knowledge Bank has been developed and agreed. This SOP is included below and sets out:

1. A process for collaborative working and work-sharing between KB contributors throughout Europe
2. The proposed structure and content of individual information pages
3. A detailed procedure for the development and update of individual information pages

Standard Operating Procedure (SOP) for Developing and Maintaining Information Pages on the Knowledge Bank

Abbreviations

ENTIS - European Network of Teratology Information Services

KB - Knowledge Bank

SOP - Standard Operating Procedure

WP – Workpackage

UKTIS - UK Teratology Information Services

TIS- Teratology information service

1. Purpose

The ConcePTION Knowledge Bank (KB) is an EU centralised digital knowledge bank providing up to date, evidence-based information to healthcare professionals and members of the public on the use of medicines during pregnancy and breastfeeding. The KB is comprised of individual webpages containing information on the use of specific medicines in pregnancy and breastfeeding. These information pages will be collaboratively developed by experts in the area of medicines in pregnancy and breastfeeding in Europe. Details of current KB contributors for the purpose of IMI ConcePTION are included in Appendix 1.

The purpose of this Standard Operating Procedure (SOP) is to support the collaborative development and maintenance of individual information pages. Screenshots of the proposed KB are included in Appendix 2 for demonstration purposes.

2. Scope

This SOP is of relevance to IMI ConcePTION partners involved in work package (WP) 5.2. This SOP outlines the collaborative process of KB development within WP 5.2 of the IMI ConcePTION project. It is intended that the processes outlined in this SOP will inform further development and sustainable, collaborative maintenance of the KB in the future. This SOP may be updated or modified in the future.

3. Collaborative working and supporting documentation

- The process of developing and reviewing information pages will be supported by Microsoft Teams, Microsoft Planner and Microsoft SharePoint. Information pages will be collaboratively developed by experts in the area of medicines in pregnancy and breastfeeding throughout Europe. Details of current KB contributors for the purpose of IMI ConcePTION are included in Appendix 1.

- KB documents should be collaboratively drafted and reviewed using the online version of Microsoft word on the KB SharePoint. Use tracked changes and comment/resolve comment functionality to facilitate collaborative writing/reviewing and to act as an audit trail of how KB content is agreed
- Each information page should have separate supporting documents for both the pregnancy and breastfeeding, namely an 'Information Page' document containing the text which will appear on the KB and an 'Evidence Summary Table' document containing a comprehensive record of published literature which supports the information presented in the information page itself. A template for each document is included in Appendix 3 and 4 respectively.
- Use the 'Evidence Summary Table' documents to keep a record of literature which was considered when developing the information page, how the available literature was interpreted and how it contributes to the content of the information page. An existing 'Evidence Summary Table' may be made available from the UK Teratology Information Services (UKTIS) as contributors to the KB. This evidence summary table should be updated in line with UKTIS guidance which is included in Appendix 5a and 5b.
- Use the following naming convention for documents:
    - Information page contents: <*Drug name*> <*Pregnancy or Breastfeeding*> Information page V<X.X> (Author initials/Reviewer initials) e.g. Hydroxychloroquine Pregnancy Information page V0.2 AB/CD
    - Evidence Summary Table: *<Drug name> <Pregnancy or Breastfeeding> Evidence Summary Table V<X.X> (Author initials/Reviewer initials)* e.g. Hydroxychloroquine Breastfeeding Evidence Summary Table V3.2 AB/CD
    - Initial documents should be versioned 0.1, 0.2 etc. until they are approved and published, when they become version 1.0. Subsequent edits should be versioned 1.1, 1.2 etc. with subsequent approved and published documents called version 2.0 etc.
- Use the 'Internal Comments' section in the backend to communicate with other KB contributors about an information page (Figure A2.4).
- Once approved, the information page contents and translations can be transferred from the finalised documents into the appropriate section of the KB platform for publication to the KB. (Figure A2.4).
- Save relevant supporting documents in the 'Attachments' section of the KB backend (Figure A2.5). Authors and reviewers are responsible for version control and document management processes.
- Previous versions of the information page will be archived in the 'History' section of the KB. (Figure A2.6)
- Where a KB administrator/manager has not been assigned, the responsibilities will fall to the information page author.
- The KB requires an appropriate governance structure to provide scientific oversight. Such governance structures are yet to be defined but may represent involvement from the European organisations with expertise in teratology, such as the European Network of Teratology Information Specialists (ENTIS).

4. Information page structure and contents

- Each information page will be specific for one individual medicine. Where appropriate, an information page may be developed for combination products where data are available on the use of the combination product in pregnant or breastfeeding women.
- For the purpose of the IMI ConcePTION project, the topics for new information pages will be determined by KB contributors involved in WP 5.2. After the completion of the IMI ConcePTION project, it is suggested that topics for future information pages are determined and agreed by the appropriate governance structure. Information pages for development may be identified through frequency of information request or on the suggestion of KB contributors which may be prompted by a potential signal published in the literature, by medicines regulator or media reports.

- For the pregnancy summary:
  - The following pregnancy outcomes should be considered: Miscarriage, congenital malformations, intrauterine death, low birth weight/small for gestational age, preterm delivery, neonatal or infant complications, neurodevelopmental disorders, other outcomes of interest.
  - Preference should be given to evidence from comparative studies and meta-analyses where available. Evidence from case reports and case series should only be included where there is a lack of information from comparative studies or when there is a potential signal identified in the literature.
  - The author may also utilise physiochemical and pharmacokinetic data to help inform the assessment (including drug half-life, protein binding, oral bioavailability and presence and properties of drug metabolites).
- For breastfeeding summary:
  - It is unlikely that good quality evidence is available for medication use in breastfeeding. All evidence therefore needs to be considered, including case reports and case series, although the author will need to interpret this carefully.
  - The following information should be considered: amount found in milk by the Relative Infant Dose (RID), infant serum levels, adverse effects reported in infants, longer term outcomes.
  - Because of the lack of evidence for medicine use in breastfeeding, the author may also have to utilise drug profile and pharmacokinetic data to help inform the assessment (including drug half-life, protein binding, oral bioavailability and presence and properties of drug metabolites)
- Information about the quality and quantity of published data should be included in the information page.
- Use the most recent publication if iterative studies on the same database are available. Where data or studies overlap, give preference to the study with the larger sample size or the superior methodology.
- When considering the safety of a medicine in pregnancy or breastfeeding, the absence of data on a specific outcome should not be considered as absence of that effect.
- Information page summaries should be written in line with the proposed structure included in Appendix 3.
- In the future, a more detailed structured summary and analysis of the available pregnancy literature may be uploaded to the backend of the KB for use by TIS centres and KB contributors. A suggested structure of this is included in Appendix 6.
- Consider guidelines for writing for the general public, included in Appendix 7. As much as possible, and where available, use agreed standard statements and sentence structures when discussing available evidence.
- A disclaimer, developed and approved by IMI ConcePTION or the appropriate governance structure, should be included on all KB pages.

5. Procedure for the development of new information pages

The procedure for the development of information pages is provided below. The responsible individual is identified after individual tasks. This process is visually depicted in the figure below. Screenshots of the relevant section of the backend are shown in Appendix 2.

Step 1: Manage the KB backend (KB administrator/manager)

1.1. Assign authors(s) and reviewer(s) to the information page to be developed in the backend of the KB.

- The author(s) and reviewer(s) may be assigned based on area of interest or other criteria including expertise and experience.
- The author and reviewer may be alternated on each review cycle.
- Separate authors and/or reviewers may be assigned to the pregnancy and breastfeeding sections of the information page.
- In some situations, there may be more than one author or reviewer assigned to an information page, for example, where the literature is complex or where a rapid review of the literature is required.
- For the purpose of the ConcePTION project, authors and reviewers will be assigned from WP 5.2.4 sub-task working group. An appropriate governance structure will be required to assign and manage authors/reviewers of individual information pages after the completion of the ConcePTION project.

1.2. Change the status of the information page in the administration section of the KB (Concept, In-review, Removed) (Figure A2.3).

Step 2: Identify literature of relevance (Author)

2.1. For the pregnancy section of the information page, chose option A, B or C as appropriate:

A. Where an existing 'Evidence Summary Table' is available from UKTIS

- Request a copy of the pregnancy 'Evidence Summary Table' for the information page under review from UKTIS. (Author)
- Undertake a literature search to identify new primary literature which was published since the UKTIS 'Evidence Summary Table' was last updated.
- Use PubMed as the primary database
- Include the following search strategies and MESH search terms:

Pregnancy search
1. [Medicine Name]
2. [Medicine Class]
3. [Medicine Indication]
4. "Medicine Name"[Mesh]
5. "Medicine Class"[Mesh]
6. "Medicine Class"[Pharmacological Action]
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. Pregnancy
9. ("Pregnancy"[Mesh])
10. #8 OR #9
11. #7AND #10

- Apply relevant filters:
  - **Publication year:** Limit the search to include literature published since the review date of the 'Evidence Summary Table' provided by UKTIS.
  - **Species**:
    - For pregnancy information: Include 'Other Animals' when data from humans are limited or when there is a particular concern raised from experimental animal studies
  - **Language**: English
- More complex search terms may be developed in the future or by individual authors. These should be recorded in the 'Evidence Summary Table' document.

- Where searches in PubMed yield an insufficient number of results, or where results are insufficient to inform a risk-benefit recommendation, alternative databases should be searched. This decision is at the discretion of the author. EMBASE is the proposed secondary database.
- At the author's discretion, additional literature of relevance may be identified from conference abstracts and by screening reference lists of available primary literature and review articles.
- Screen secondary literature sources (such as Reprotox, TERIS, Briggs) to identify additional literature of relevance. A list of potential existing/secondary literature sources is provided below. Retrieve and save a copy of existing reference sources in the relevant section of the backend of the KB (Figure A2.5).

Secondary literature sources - Pregnancy	
Resource	**Access**
Lareb TIS	https://www.lareb.nl/tis-knowledge (Dutch) Full text may be requested through ENTIS representative
Janusmed	https://janusmed.sll.se/fosterpaverkan (Swedish) Full text may be requested through ENTIS representative
Embryotox	https://www.embryotox.de/ (German)
Reprotox	Full text may be accessible through ENTIS members
TERIS	Full text may be accessible through ENTIS members
Drugs in Pregnancy and Lactation - GG Briggs (Wolters Kluwer)	Full text may be accessible through ENTIS members
Mother to baby	https://mothertobaby.org/fact-sheets/
Meta-preg	http://metapreg.org/
Le Crat	http://www.lecrat.org (French)

B. Where an existing 'Evidence Summary Table' is not available from UKTIS and where resources/capacity of the KB contributors is limited:

- Identify key literature of relevance using existing information sources (such as existing Teratology Information Specialist (TIS) summaries) or secondary literature sources (such as Reprotox, TERIS, Hale) described above.
- Retrieve and save a copy of existing reference sources in the relevant section of the backend of the KB (Figure A2.5).
- Undertake an updated search of published primary literature as described in A above. Limit the search to include literature published since the review date of existing/secondary reference sources or previous literature search.

C. Where there are no existing sources or references available for a medicine, or where KB contributors have the capacity:

- Undertake a complete review of published primary literature as described in A above. The author may choose to limit by publication year. This may reflect the quality and quantity of initial search results and available literature. (Author)

2.2. For the breastfeeding section of the information page:

- Identify key publications/literature of relevance using secondary literature sources. A list of suggested secondary literature sources is provided below.

Secondary literature sources - Breastfeeding	
Resource	**Access**
UKDILAS	SPS.NHS.UK
Lactmed	https://www.ncbi.nlm.nih.gov/books/NBK501922/
E-lactancia	http://www.e-lactancia.org/
Medications and Mother's Milk – Thomas Hale (Springer)	Full text may be accessible through ENTIS members

- Retrieve and save a copy of existing reference sources in the relevant section of the backend of the KB (Figure A2.5).
- Undertake an updated search of available literature as described for the pregnancy summary above with the following modifications:
- Include the following search strategies and MESH search terms:

Breastfeeding search
1. [Medicine Name]
2. [Medicine Class]
3. [Medicine Indication]
4. "Medicine Name"[Mesh]
5. "Medicine Class"[Mesh]
6. "Medicine Class"[Pharmacological Action]
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. "Milk, Human"[Mesh]
9. "Lactation"[Mesh]
10. "Breast Feeding"[Mesh]
11. "Lactation Disorders"[Mesh]
12. "Milk Ejection"[Mesh]
13. #8 OR #9 OR #10 OR #11 OR #12
14. #7 AND #13

- Apply relevant filters:
  - **Publication year:** The author may choose to limit by publication year. This may reflect the quality and quantity of initial search results, available literature.
  - **Species**: Include 'Human' only; Animal data is not used for risk assessment for medicine use during breastfeeding due to poor applicability of the data to humans. Better animal models are currently in development, and therefore this position will be reviewed if required.
  - **Language**: English

2.3. Record details of the search strategy in the relevant pregnancy or breastfeeding 'Evidence Summary Table' document (Appendix 4).

2.4. Screen abstracts of identified literature and select publications for further review and critical appraisal.

2.5. Keep a record of publications identified above but not selected for critical appraisal in the appropriate section of the relevant 'Evidence summary Table' along with a brief reason for exclusion. Details of excluded publications (e.g. design, population, outcomes) are not required. (Author)

Step 3: Review and critically appraise the literature (Author)

3.1. Review and critically appraise selected publications. Consider potential risk of bias. (Author)

3.2. Extract relevant details from each publication and complete the pregnancy or breastfeeding 'Evidence Summary Table' (Appendix 4). (Author) Extracted information should be completed under the following headings:

Information to be extracted into the evidence summary table	
Pregnancy	**Breastfeeding**
Author	Author
Study details (e.g. design, population, time period)	Study details (e.g. Design, population, time period)
Study population (e.g. Total pregnancies, total number of exposed infants, number of infants exposed in first trimester)	Study population (e.g. number of infants exposed, infant age, length of exposure, dose)
Evidence of increased risk of congenital malformations	Outcomes (e.g. Milk level, infant serum level, infant adverse effects, Relative Infant Dose (RID) calculated, effect on lactation)
Other findings (e.g. Spontaneous miscarriage, stillbirth, low birth weight, preterm birth, other neonatal outcomes neurodevelopmental disorders)	Other findings
Comments	Comments

3.3. Return the pregnancy 'Evidence Summary Table' (Appendix 4a) to UKTIS for review. (Author)

Step 4: Verify the information (UKTIS)

4.1. Verify data extraction and interpretation of published literature in the pregnancy 'Evidence Summary Table' in line with internal procedures. (UKTIS)

4.2. Return the approved 'Evidence Summary Table' to the information page author. (UKTIS)

Note: Step 4 will not be undertaken for the breastfeeding 'Evidence Summary Table'

Step 5: Write the information page (Author)

5.1. Draft the information page using the information page template document. The proposed structure is detailed in Appendix 3.

- For the pregnancy summary, give priority to evidence from comparative studies or meta-analyses. Inclusion will depend on the quality of the individual studies and the quality of the meta-analysis. For meta-analyses, it is at the discretion of the author whether to consider the overall findings from the meta-analysis or whether to consider individual study findings separately. Only include data from case reports or case series when there are insufficient data from comparative studies or where there is a suspected signal. Consider the properties of the medicine itself and pharmacokinetic data when necessary.
- For the breastfeeding summary, where limited published information is available the author should consider the properties of the medicine itself and pharmacokinetic data. The author may also extrapolate from information available on other medicines within the same class. This information should be documented in the breastfeeding 'Evidence Summary Table'.

- Give preference to published data on the specific medicine of interest. Only include information related to the medication class when there is insufficient data available on the specific medicine itself and when information relating to the drug class is relevant.
- It is at the discretion of the author whether to review the full publication or whether the abstract can be considered alone. This may be influenced by the level of detail provided in the abstract and the findings of the study in the context of other published literature.
- Use Standardised writing styles and standardised sentence structures where possible.
- The 'Detailed information' section of the information page should be referenced appropriately. The author should reference the original primary literature where relevant. Secondary literature sources (e.g. Hale, Briggs, etc.) should be referenced directly when including opinion, commentary or advice from the secondary literature resource.
- PubMed ID should be included in the reference list where available. The use of referencing software when drafting the information page is at the discretion of the information page author.
- Where possible a full-text copy of each publication cited in the information page should be saved to the appropriate location in the backend of the KB platform.
- Put questions/comments for the reviewer in the comments section of the KB backend (Figure A2.4)
- Check readability of the summary paragraph using the 'Spelling and Grammar' functionality in Microsoft word (See Appendix 7 for more information). Seek input on from a native English speaker where relevant.

5.2. Notify the reviewer when the draft of the information page is completed. (Author)

Step 6: Review the information page (Reviewer)

6.1. Verify the search strategy documented in the relevant 'Evidence Summary Table' (Appendix 4).
6.2. Consider the totality of evidence presented in the 'Evidence Summary Table' as well as any comments or queries relating to specific studies documented by the author. The level of this review is at the discretion of the reviewer.
6.3. Review and comment on the draft information page using tracked changes and add comments to the KB backend.
6.4. The reviewer should endeavour to complete his/her review of the draft information page within 3 weeks or sooner if a rapid review of the literature is required.
6.5. Notify the author when the review is complete. (Reviewer)
6.6. The author and reviewer should discuss and resolve any outstanding queries or comments in the draft document or the 'Evidence Summary Table' (Author and Reviewer). Use the comment and 'resolve comment' functionality to keep a record of amendments. Where an agreement cannot be reached by the author and reviewer, the KB administrator/manager should assign an independent reviewer to resolve the query. All queries, discussions and resolutions should be documented in the relevant 'Evidence Summary Table' or in the internal comments section of the information page (Figure A2.4.
6.7. Address reviewer's suggestions or comments on the draft information page to produce the pre-approval draft. (Author)
6.8. If relevant, seek clinical input from an appropriate clinician within the KB working group. (Author)

Step 7: Approve the information page (KB Governance structure)

7.1. Disseminate the information page to the appropriate governance structure for review. An appropriate response time should be agreed in advance with the governance structure which is in place. Responses should be requested within a timely manner, especially if a rapid update of the information page is required. (KB Administrator)

7.2. Address suggestions or comments of the approver(s), if any. Use the comment/resolve comment functionality to keep a record of how comments are dealt with. (Author)

7.3. Once approved, generate a clean version of the information page by accepting tracked changes, resolving comment threads and converting references to plain text using Vancouver style. Keep a copy of the working document(s) containing tracked changes and comments/resolved comments for archiving on the KB backend (Figure A2.5). (Author)

7.4. Update the review date and document management system. The following documents should be saved in the backend of the KB for both the pregnancy and breastfeeding summaries: (KB Administrator)

- A copy of the working document(s) used to write and review the current version of the information page (containing tracked changes and comments) (e.g. Version 0.X)
- An updated copy of the approved information page (Version X.0)
- An updated copy of the relevant 'Evidence Summary Table' documents.

Step 8: Publish the information page on the KB website. (KB Administrator and Author)

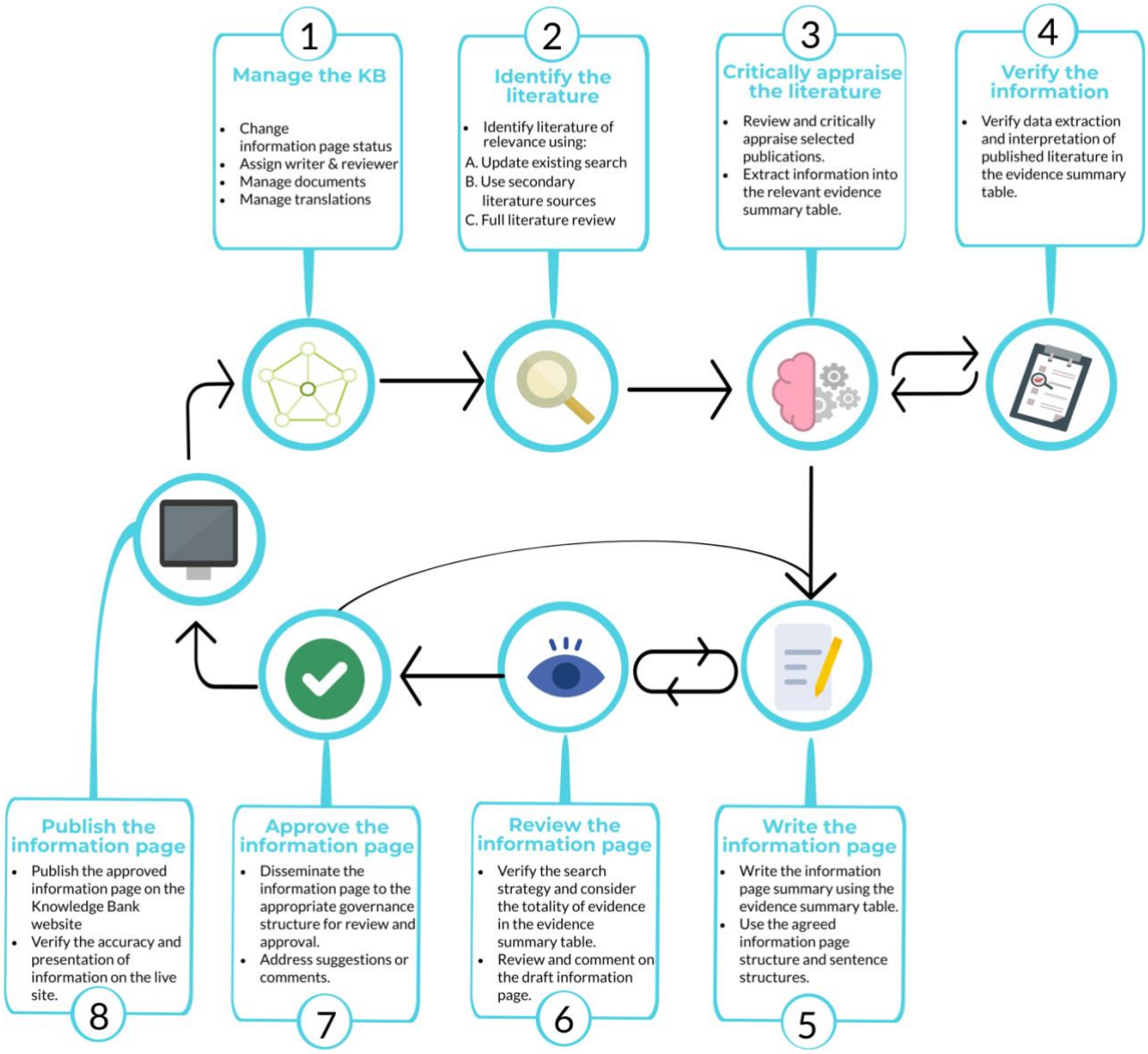
8.1. Publish the information page on the KB website. (KB Administrator and Author) A co-ordinated approach between the author and KB administrator is necessary when publishing the information page to the KB website:

- The KB administrator should transfer the content of the approved information page onto the relevant sections KB platform. Add or verify ATC code, SNOMED code, keywords and links to other information pages as appropriate (Figure A2.3). (KB Administrator)
- The KB administrator should publish the information page on the KB website (KB Administrator)
- Simultaneously, the author should review and approve the published information page on the live site to verify the accuracy and presentation of information (Author)
- The KB should change the status of the information page once approved. (KB Administrator)

8.2. Notify KB working group/contributors of updated information page and invite translations into local languages. (KB Administrator)

8.3. Publish summary translations once completed and approved by established governance structures (Figure A2.6. (KB Administrator)

Figure: Process for of developing and maintaining information on the Knowledge Bank



6. Updating and maintaining existing information pages

The author of each information page should monitor newly published literature which may be of relevance. This may be achieved by the use of publication alerts. If this is not possible, this responsibility should be assigned to an alternative individual by the KB administrator.

- Information pages should be routinely reviewed and updated every 2-3 years. Information pages may be updated sooner if new information is made available which significantly alters the body of evidence contained in an individual information page.
- When a routine update is being carried out:
  - Follow the 'Procedure for the development of new information pages' outlined above using existing evidence summary tables which are available in the KB backend.

  - The author and reviewer may be alternated on each review cycle.
  - Limit the search strategy to include literature published since the date of the last literature search.
  - Update the relevant 'Evidence Summary Table' with new literature.
  - Where new information is added to the pregnancy 'Evidence Summary Table' this should be sent to UKTIS contributors for verification.
  - Consider the need to update ATC code, SNOMED code, keywords and links to other information pages as appropriate.
  - Once the update has been approved, notify the relevant individuals to update the summary translations.
- In addition, where new evidence is identified which may significantly alter the message of the current version of the information page:
  - The author(s) and reviewer should expedite the updating of this information page. This update should ideally be completed and approved within 2 weeks.
  - Remove the current information page from public view.
  - Consider displaying a message such as: "Update in Progress. There has been significant new information since this information page was published. An updated version of the knowledge page will be available soon. If you have any questions, please contact your doctor or national teratology information service, if available in your country <link to TIS contacts on ENTIS website??> "

7. Maternal medicine condition pages

Purpose and scope: The purpose of a maternal medical condition page is to provide accurate information on the management of specific maternal medical conditions in pregnancy. The information presented is intended to provide context and balance for risk-benefit decision making about medication use in pregnancy. Initial maternal medicine condition pages developed will focus on conditions where there is a clear need for medication in managing the maternal condition.

Target: The target audience of these pages is women who have been diagnosed with the medical condition in question who are considering pregnancy, trying to become pregnant or are pregnant.

Accessibility: These pages are stored and accessible on the KB. These pages may be linked from drug information pages using keywords.

Structure and contents

- Each page will cover a single medical condition or, where relevant group of conditions.
- The maternal condition pages will be developed in combination with individual drug information pages.
- The maternal medicine condition pages should use the following structure:
  - What are the effects of pregnancy on….
  - What are the effects of … on pregnancy
  - General approach to managing … in pregnancy
- Prior to publication, the maternal medical condition page should be reviewed and approved by a specialist in maternal fetal medicine or obstetrics.
- For the purpose of the IMI ConcePTION project, the topics for new maternal medical conditions will be determined by partners involved in WP 5.2. For the purposes of IMI conception, these pages will be assigned to the author of the drug information page. After completion of the IMI ConcePTION project, these processes determined and agreed by an appropriate governance structure.

Discussion

The SOP has been primarily developed by future contributors to the KB, who have extensive experience in the interpretation and communication of information on medication use in pregnancy and breastfeeding. Input was obtained from internal and external stakeholders, as well as potential end-users.

The proposed SOP has been developed to ensure the process of developing and maintaining content on the KB is rigorous and meets the needs and expectations of potential end-users, yet is sustainable within the available resources and includes flexibility to reflect the collaborative, work-sharing approach of the KB and its contributors.

Conclusion

This SOP outlines the collaborative process of KP development within WP 5.2 of the IMI ConcePTION project. The processes outlined in this SOP will inform and support further development and sustainable, collaborative maintenance of the KB in the future.

Appendixes

Appendix 1: Current contributors to the Knowledge Bank for the purpose of IMI ConcePTION

Name	Qualification	Position/Affiliation
Maya Berlin	BSc.Pharm, MSc.Med	Responsible pharmacist, Clinical advisor, Clinical Pharmacology and Toxicology Unit, Drug Consultation Center, Shamir Medical Center (Assaf Harofeh), Israel.
Benedikte Cuppers	MSc RPh	Teratology Information Service, Netherlands Pharmacovigulence Centre Lareb, Netherlands.
Patrik Dreher Sköld	MSc Pharm	Stockholm County Council, Health and Medical Care Administration, Sweden.
Ulrika Nörby	MScPharm, PhD	Stockholm County Council, Health and Medical Care Administration, Sweden.
Alison Oliver	PhD	Senior Medical Information Scientist, UK Teratology Information Service (UKTIS), Newcastle upon Tyne Hospitals NHS Foundation Trust and Public Health England.
Fergal O'Shaughnessy	PhD, MSc, MPharm, BSc (Pharm)	Senior Pharmacist, Rotunda Hospital, Dublin Ireland. Honorary Clinical Lecturer, Royal College of Surgeons in Ireland (RCSI), Dublin, Ireland
Jonathan Luke Richardson	PhD	Senior Medical Information Scientist, UK Teratology Information Service (UKTIS), Newcastle upon Tyne Hospitals NHS Foundation Trust and Public Health England.

Appendix 2: Screenshots of the proposed Knowledge Bank

Figure A2.1: Sample information page

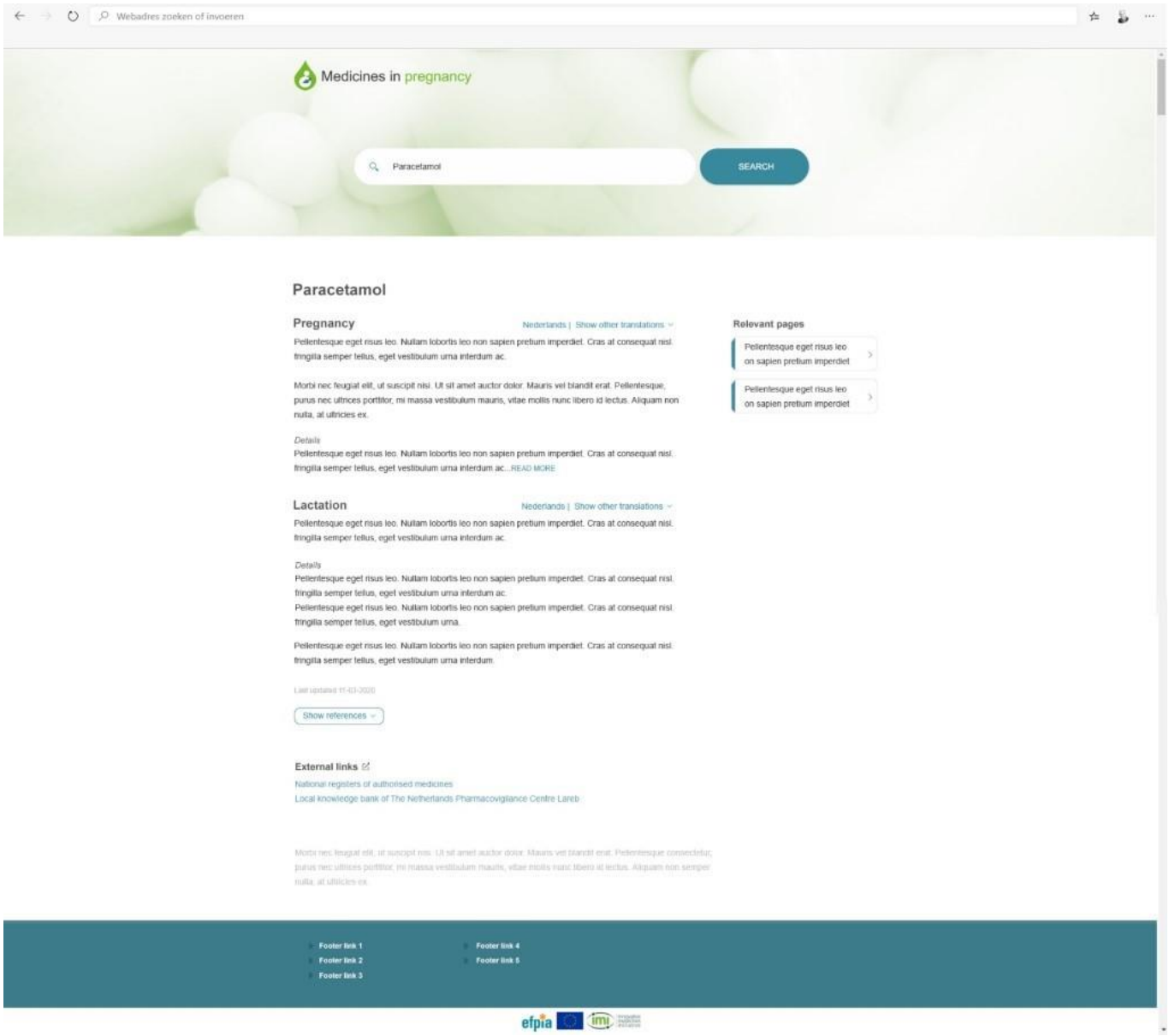


Figure A2.2 Proposed information page structure

Figure A2.3: Information page backend navigation

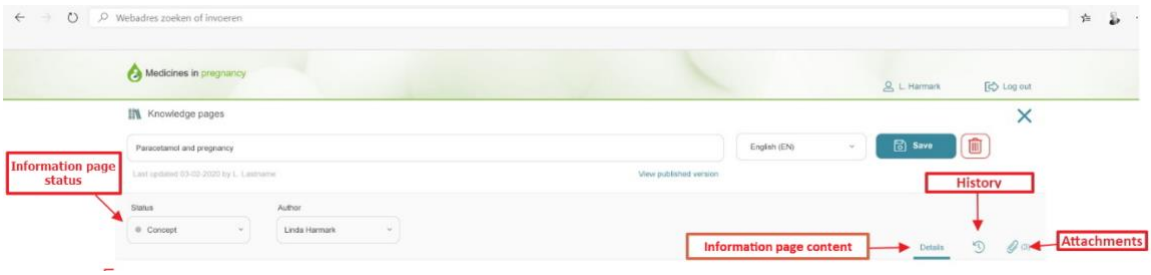


Figure A2.4: Information page content editor

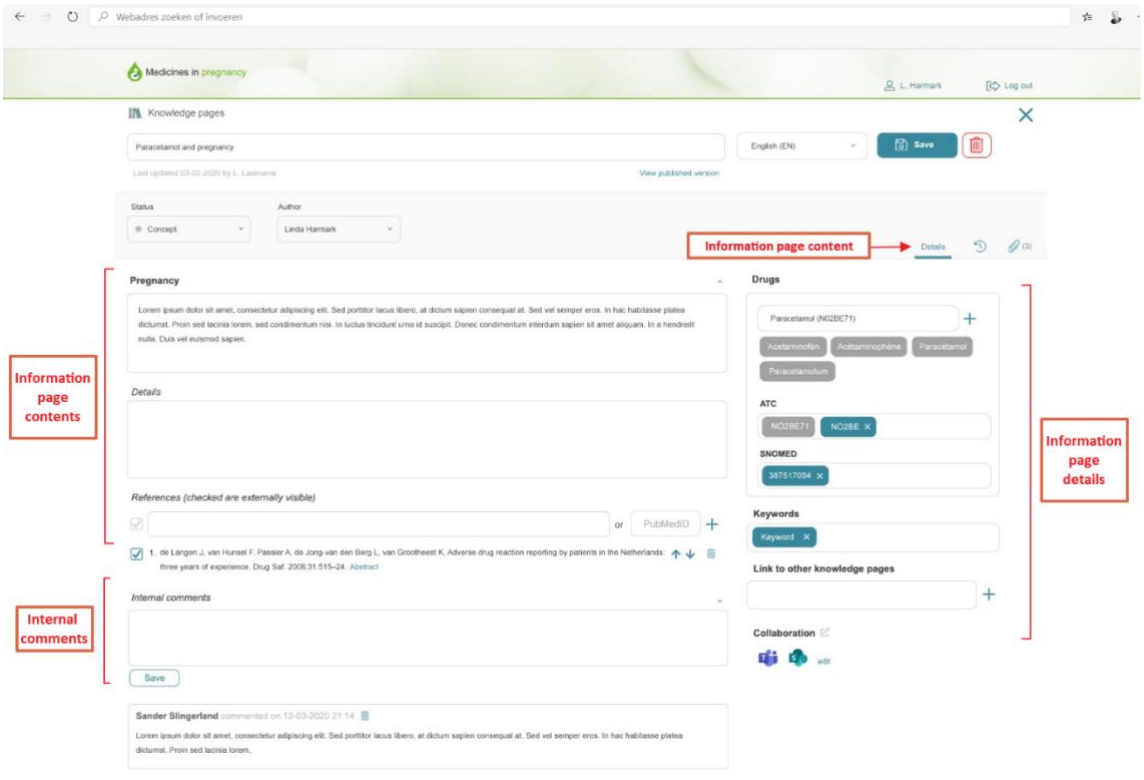


Figure A2.5: Information page attachments

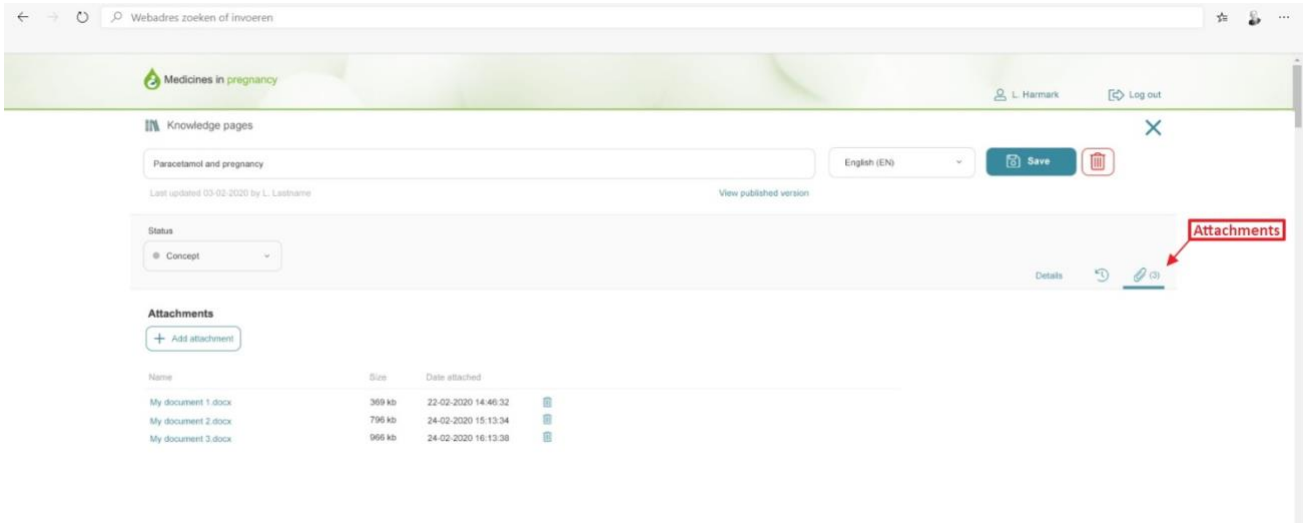


Figure A2.6: Information page history

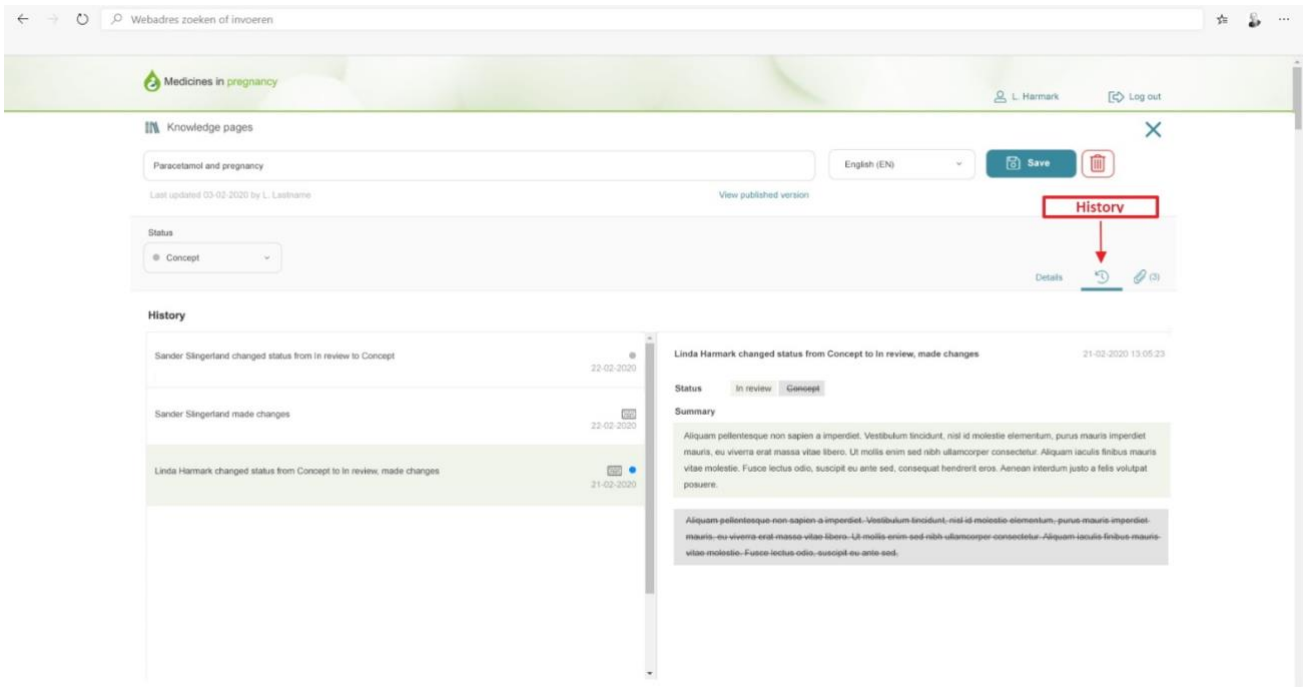
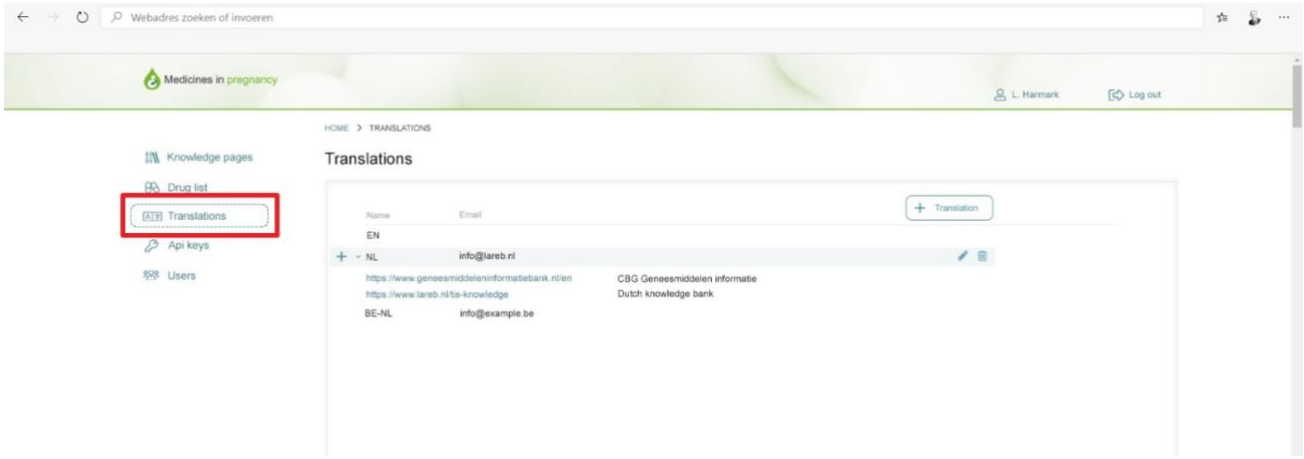


Figure A2.7 Information page translations



Appendix 3: Information Page Template

<DRUG NAME>

Version:

Date:

Pregnancy

Summary:

<Summary of the literature to go here >

A concluding statement or key/take home message should be included in the opening sentence e.g. 'Azithromycin can be used in pregnancy if there is an infection which could affect the health of the mother or the baby.'

Consider structuring the remainder of the summary section by following the BRAN structure:

- *Benefits: Potential benefits of taking the medicine*
- *Risks: Potential risks associated with taking the medicine*
- *Actions or Alternatives: Alternative treatment options or actions*
- *Nothing: Possibility and consequences of doing nothing*

It is not necessary to reference the summary section.

Detailed information

<First few lines of text shown with …..'Show more' link to dropdown >

Suggested structure of 'Detailed information'

1. A concluding statement on use of medicine in pregnancy (if appropriate include specific information on benefit of the medication to the maternal condition or risk-benefit of medication exposure and untreated medical condition).
2. A brief summary about the medicine (For example, what is it or what is it used for. This may be excluded information if variable or too detailed.
3. A summary about the quality and/or quantity of data which was considered when writing the information page. For example: "Data from x studies describing n exposed pregnancies were reviewed".

4. A summary of animal data may be included if human data is limited or when there is a possible risk reported in animal studies or mentioned in the Summary of Medicinal Product Characteristics (SmPC).
5. Summarised information about specific endpoints, where appropriate using the following sub-headers:
    - miscarriage
    - congenital malformation
    - intrauterine death
    - low birth weight
    - preterm delivery
    - neonatal complications
    - neurodevelopment
    - Other outcomes of interest

    Where data are not available for specific endpoints the subheader 'Other outcomes' can be used and this can be summarised in a single statement, for example: "No studies have been located which have investigated the risk of intrauterine death, neurodevelopmental impairment or neonatal / infant complications following maternal azithromycin use in pregnancy."

The 'Detailed information' section should be referenced. Including appropriate references after the statement "The available data consist of x studies describing n exposed pregnancies" will allow a single reference list to be used for the 'Detailed information' section of the KB.

References:

Click here to see references

Lactation

Summary

<Summary of the literature to go here >

A concluding statement or key/take home message should be included in the opening sentence e.g. 'Azithromycin can be used during breastfeeding if there is an infection which could affect the health of the mother.' Note: avoid using the term 'safe' as this implies a level of assurance that we can rarely give.

Consider structuring the remainder of the summary section by following structure:

- *What evidence is available*
- *How much will the infant be exposed to*
- *Have any adverse effects been reported*
- *Monitoring advice*

It is not necessary to reference the summary section.

Detailed information

<First few lines of text shown with …..'Show more' link to dropdown >

Suggested structure of 'Detailed information'

1. A concluding statement on use of medicine in breastfeeding
2. A summary about the quality and/or quantity of data. If there is no data, this should be stated and the following statement used: 'there is no evidence for the use of xxx in breastfeeding. The risk assessment has therefore been made based on the properties of the medicine itself and extrapolation from information available from other medicines within the same class'.
3. Summary about drug properties and pharmacokinetic data. The extent this is utilised will depend on the evidence base available. Consider using the following (not exhaustive) and others may need to be considered depending on the situation:
    - Half-life (to predict infant accumulation and side-effects)
    - Protein binding (to predict how much might get across into breast milk)
    - Oral bioavailability (once in milk, how much will the infant absorb)
    - Metabolites. Consider whether there are active metabolites—these may also have extended half-lives and need to be considered in the overall assessment.
4. Summarised information about the following sub-headers:
    - Amount found in milk
        - Include relative infant dose where available
        - If it not known, a best-case prediction should be made on the drug properties information, but the descriptors will be qualitative, e.g. very small amounts are likely to be found in milk
    - Infant serum levels
    - Adverse effects reported. If none have been reported, state this as the case.
    - Longer term exposure and outcome

The 'Detailed information' section should be referenced.

References:

Click here to see references

Appendix 4a: Pregnancy 'Evidence Summary Table' template

Literature search:

Information Page Details:			
Information page name:			
Version:			
Date of update:			
Author(s):			
Reviewer(s):			
Literature Search			
Date literature search undertaken:			
Completed by:			
Search terms used:			
Filter: Species (Human / Other animal)			
Filter: Language			
Filter: Publication dates (if filters applied):			
PubMed search results (N):			
EMBASE search results (if used) (N):			
Results selected for critical appraisal (N):			
Secondary literature sources reviewed			
Source	Date of last update	Date of last update	Date of last update
Lareb TIS			
Janusmed			
Toxbase (UKTIS)			
Embryotox			
Reprotox			
TERIS			
Drugs in Pregnancy and Lactation - Briggs			
Mother to baby			
Meta-preg			
Le Crat			

Included studies:

Author	Design	Study population	Increased risk of Congenital Malformations?	Other findings	Comments
E.g. Author, Year	*E.g. Study design, population, time period*	*E.g. Total pregnancies, total number of exposed infants, number of infants exposed in first trimester*		*E.g. Spontaneous miscarriage, stillbirth, low birth weight, preterm birth, other neonatal outcomes neurodevelopmental disorders)*	

Excluded studies:

Author	*Comments* / Reasons for exclusion

Appendix 4b: Breastfeeding 'Evidence Summary Table' template

Literature search:

Information Page Details:			
Information page name:			
Version:			
Date of update:			
Author(s):			
Reviewer(s):			
Literature Search			
Date literature search undertaken:			
Completed by:			
Search terms used:			
Filter: Species (Human / Other animal)			
Filter: Language			
Filter: Publication dates (if filters applied):			
PubMed search results (N):			
EMBASE search results (if used) (N):			
Results selected for critical appraisal (N):			
Secondary literature sources reviewed			
Source	Date of last update	Date of last update	Date of last update
UK Drugs in Lactation Advisory Service			
Lactmed			
E-lactancia			
Reprotox			
Medications and Mother's Milk – Thomas Hale (Springer)			

Included studies:

Author	**Design**	**Study population**	**Outcomes**	**Other findings**	**Comments**
E.g. Author, Year	*E.g. Study design, population, time period*	*E.g. Number of infants exposed, infant age, length of exposure, dose*	*E.g. Milk level, infant serum level, infant adverse effects, Relative Infant Dose (RID) calculated, effect on lactation*		

Excluded studies:

Author	***Comments* / Reasons for exclusion**

Appendix 5a: Procedure for extracting information into UKTIS – Evidence Summary Table

- Published studies on **human** exposure in pregnancy identified in the literature search should be tabulated in Word format following the guidance contained in table 1.
- Studies should be added to the table in chronological date order.
- It should be made clear in the title of the table/s if inclusion/exclusion criteria has been applied i.e. only controlled studies have been included (see titles provided for example evidence summary tables below). This may be particularly relevant for medicines that have a large body of data available. In the example given, a second table is populated to include studies that investigate a specific association (atopy) that has a significant body of data.
- A list of excluded studies and a brief description of the reasons for exclusion should be provided with the table when it is returned to UKTIS for reference checking.
- The table/s can be adapted to suit the available data (see example populated tables) but where a UKTIS table already exists for a medicine, the original format should be maintained where possible.
- The key to the table should be populated appropriately.

Table 1: Format of the evidence summary table and guidance on populating the table with data

Author	**Design**	**Study population**	**Overall increased risk of CMs?**	**Increased risk of specific CMs and other findings?**	**Increased risk of fetal loss SA / SB / IUD?**	**Any other findings**	**Comments**
Authors name et al. year	Retrospective or prospective? Cohort/case report/case control/case series? Include the country of data origin and the years the data was collected	How many women/pregnancies/ infants/cases/ controls were included	Include the overall incidence of CMs, with numbers of affected infants and stats if available Relevant headings include but are not limited to: • Yes • -No • -Not investigated • No statistical analysis • Unable to comment	Include data for specific CMs with statistics if available Same headings as previously	Include data r.e. fetal loss, with stats if available. Same headings as previously	Findings relevant to the monograph's sub headings (*Preterm delivery*, *LBW/SGA*, neonatal complications/*neurodevelopment* etc should be discussed here Same headings as previously	Include study limitations Any other relevant information and/or comments

T1= first trimester, T2= second trimester, T3= third trimester, SA= spontaneous abortion, ETOP= elective termination of pregnancy, CM= congenital malformation, OR= odds ratio, RR= relative risk, aOR= adjusted odds ratio, CI= confidence interval, LBW = low birth weight, SGA=small for gestational age

Appendix 5b: Example of populated evidence summary tables

In this example, two evidence summary tables are used.

Table 1: Studies investigating exposure to PPIs either as a group or singularly in pregnancy. Only studies that have been peer reviewed and include a comparison group have been included in this review.

Author	*Design*	*Study population*	*Increased risk of CMs?*	*Increased risk of other pregnancy outcomes?*	*Comments*
Lalkin et al, 1998	Multi centre prospective cohort study Using data from the Canadian, Italian and French TIS'	113 women exposed to **omeprazole** vs. 113 women exposed to histamine blockers (disease controls) and 133 women exposed to non-teratogenic drugs	**Omeprazole** **NO:** No significant increased risk of MCM was observed in women exposed to omeprazole (in T1), compared to those exposed to histamine blockers or non-teratogenic drugs: 4/78 (5.1%) vs. 3/98 (3.1%) vs. 2/66 (3.0%), p>0.05	***Spontaneous abortion*** **Omeprazole** **NO:** No significant increased risk for SA was observed between groups: 16/113* (14%) vs. 9/113 (8%) vs. 9/113 (8%), p>0.05 ***Preterm delivery*** **Omeprazole** **NO:** No significant differences in the incidence of preterm delivery was observed between groups: 8/84* (9.5%) vs. 16/101 (15.8%) vs. 8/99 (8.1%), p>0.05 ***Mean birth weight*** **Omeprazole** **NO:** No significant differences between groups; 3,325g ± 573g vs. 3,397g ± 653g vs. 3,403g ± 632g, p>0.05	Cases were matched to controls for maternal age, (±2 years) smoking and alcohol consumption, but not matched by TIS location (all controls were Canadian – although maternal characteristics were shown to be similar for all which the authors claim excludes the potential for bias) *Authors stated that women in the omeprazole group had a non-significant tendency towards more SAs, however when women with underlying medical conditions that may predispose them to SA were excluded (along with a case exposed to cytotoxics) the trend was nullified

				Neonatal problems **Omeprazole** **NO:** Authors stated that no differences observed (data was not presented)	
Kallen et al, 1998	Population-based cohort study Using data from the Swedish Medical Birth Registry collected between 1995-1997	275 women exposed to a **PPI** in T1 (of whom 262 were omeprazole-exposed and 13 were lansoprazole-exposed) vs. 255 women exposed to H2As in T1	**PPIs as a group** **NO:** No difference in the proportion of CMs in PPI vs. H2A groups (crude OR 0.86; 95% CI 0.33 to 2.23) **Omeprazole** **Not statistically analysed:** There were 8/262 (3.1%) CMs in lansoprazole-exposed pregnancies, compared to 8/255 (3.1%) in H2A-exposed pregnancies **Lansoprazole** **Not statistically analysed:** There were 2/13 (15%) CMs in lansoprazole-exposed pregnancies, compared to 8/255 (3.1%) in H2A-exposed pregnancies Specific CMs reported were: 3 VSD* (all omeprazole-exposed) 1VSD* (lansoprazole-exposed_ 1 PDA* (omeprazole-exposed) 1 Unspecified CVM* (omeprazole-exposed) 1 Urethral valve CM (omeprazole-exposed) 1 undescended testes (lansoprazole-exposed) 1 Facial anomaly (omeprazole-exposed) 1 Trisomy 21 (omeprazole-exposed)	**Not investigated**	CM analysis assessed major and minor CMs as single group *Authors reported that while the incidence of CVMs seemed high, none of these infants had been reported to the Child Cardiac Register suggesting that they were minor conditions No statistical analysis of PPI subgroups carried out, and conclusions regarding lansoprazole exposure limited by small sample size

Table 2. Studies investigating associations between *in utero* exposure to acid suppressive drugs (including PPIs) and atopy in the offspring.

Author	*Design*	*Study population*	*Increased risk of atopy in offspring*	*Comments*
Dehlink et al, 2009	Population-based observational cohort study Using data from the Swedish national healthcare registers: the Medical Birth Register, the Hospital Discharge Register, and the Swedish Prescribed Drug Register Children born in Sweden between 1995 and 2004	585, 716 children 29,490 (5.03%) children had a discharge diagnosis of allergy or prescriptions for allergy medications 5,645 children were born to mothers who took acid suppressing medications 405 children with *in utero* exposure to acid suppressing drugs had allergy (**220 exposed to PPIs**)	Allergic Disease ***YES: All acid suppressive drugs** Maternal use of acid-suppressive drugs at any stage of pregnancy significantly increased the odds for developing childhood allergic diseases (OR 1.43, 95% CI 1.29 to 1.59) **YES: PPIs only** Maternal use of PPIs at any stage of pregnancy significantly increased the odds for developing childhood allergic diseases (OR 1.46, 95% CI 1.27 to1.66) Asthma **YES: All acid suppressive drugs** Maternal acid-suppressive drug use at any stage of pregnancy significantly increased the risk for developing childhood asthma (OR 1.51, 95% CI 1.35 to 1.69)	Exposure identified by prescription *Secondary analysis did not change the odds for developing allergy in allergic mothers ?depending upon acid-suppressive treatment, or the timing of the exposure The authors concluded that 'a history of maternal allergy itself is likely such a strong predictor for allergy that intake of acid blocking drugs during pregnancy has no additional effect.' The number of cases for the sub-analysis might have been too small to reach statistical significance The study was not able to control for postnatal risk factors for allergy, such as living in small households environmental exposure to tobacco smoke and air pollutants or allergic sensitizations Subgroup analysis of exposures in T1 and those later in pregnancy produced very similar ORs
Andersen et al, 2012	Population-based cohort study Using data from the Danish Medical Birth Registry collected between 1996-2008	197,060 children: **2,238 prenatally exposed to PPIs (1,238 in T1)** And 1,605 prenatally exposed to H2RA (disease control group) Vs. 194,822 prenatally unexposed children	*Asthma* ***YES: PPIs** 381/2,238, 17% (PPI-exposed) vs. 24,125/194,822, 12.3% (non exposed) aIRR of asthma 1.41; 95% CI 1.27 to 1.56* The observed association was not drug-specific. An effect was also observed for H2RAs (315/1605, 19.6%; aIRR of asthma 1.47, 95% CI 1.32 to 1.65) and maternal postnatal use	Exposure identified by prescription Adjusted for year of birth, county, gender of child, gestational age, birth order, mother's age, maternal smoking during pregnancy, maternal asthma, mode of delivery, and maternal use of antibiotics during pregnancy *The association did not vary by trimester of exposure

Appendix 6: Proposed structure of Knowledge Bank 'Backend Summary'

Note: In future, a more detailed structured summary and analysis of the available pregnancy literature may be uploaded to the backend of the KB for use by TIS centres and KB contributors. The proposed structure of this 'Backend Summary' is provided below.

Summary of available literature:

Background to underlying illness and medicine (e.g. medicine type, agree to omit indication and dosing)

Preclinical (animal) data

< Summary line of Preclinical (animal) data to go here >

Available evidence:
<Details of Preclinical (animal) data to go here >

Human data
< Summary line of Human data to go here >

Available evidence:
<Details of human data to go here >

- **Miscarriage**
  < Summary line of miscarriage to go here >
  Available evidence:
  <Details of miscarriage to go here >

- **Congenital malformations/anomalies**
  < Summary line of Congenital malformations/anomalies to go here >
  Available evidence:
  <Details of Congenital malformations/anomalies to go here >

- **Intrauterine death**
  < Summary line of Intrauterine death to go here >
  Available evidence:
  <Details of Intrauterine death to go here >

- **Low birth weight/SGA**
  < Summary line of low birth weight to go here >
  Available evidence:
  <Details of low birth weight to go here >

- **Preterm delivery**
  < Summary line of preterm delivery to go here >
  Available evidence:
  <Details of preterm delivery to go here >

- **Neonatal or infant complications**
  < Summary line of neonatal complications to go here >
  Available evidence:
  <Details of neonatal complications to go here >

- **Neurodevelopment**
  < Summary line of neurodevelopment to go here >
  Available evidence:
  <Details of neurodevelopment to go here >

- **Other outcomes of interest**
  < Summary line of other outcomes of interest to go here >
  Available evidence:

  <Details of other outcomes of interest to go here >

ENTIS/ConcePTION data (if available in the future)

References:

Appendix 7: Guidelines Writing for the General Public

Writing the summary

Include the *who*, *what*, *where*, *when*, *why*, and *how* of the subject

- Start with your conclusion
- Specify your conclusion if applicable, for example safety in specific stages of pregnancy, or specific patient populations
- Continue with supporting information which on what this conclusion is based.

Writing the detail for healthcare professionals

- Start with an overall conclusion
- Continue with an overview of what has been found in literature
- Specify important studies
- If needed, explain something about the indication for which the drugs is being used and described if there is a relationship between the indication and possible negative pregnancy outcomes

General writing appointments

- Always spell out abbreviations in the summary. For the details section, spell out abbreviations the first time you use them.
- Use generic drug names instead of brand names. The exception is when the information page is about a specific brand drug

General tips for writing for the general public

For more information, also see: https://www.usability.gov/how-to-and-tools/methods/writing-for-the-web.html

- Include one message per sentence
- Use short sentences and paragraphs. Preferably not more than 12-20 words per sentence and 5 sentences per paragraph.
- Try to use a 'point' where you would like to use a 'comma' or the word 'and'
- Start with the conclusion and then provide additional details (inverted pyramid)
- Try to use no more than 160 words
- Write in active voice
- Be concrete
- Avoid jargon and difficult words
- Use non-directive, non-judgemental language
- Use bullets and numbered lists
- Use clear headlines and subheads
- Use white space
- Use standard statements and sentence structures to ensure the information page is accessible to all users.
- Use Microsoft Word's Readability Statistics feature—part of the Spelling & Grammar check—to measure your progress as you write and edit copy.
    - To enable readability statistics in Microsoft Word: File > Options > Proofing > Check "Show readability statistics"
    - To check readability statistics: Review > Spelling and Grammar > Once any Spelling and Grammar issues are addressed the Flesch-Kincaid Grade level and Flesch Reading Ease will

be displayed. The inclusion of medication names and other terms may necessitate acceptance of a higher score than those cited below.

- Flesch Reading Ease: The higher the score, the easier it is to understand. Aim between 60-70.
- Flesch-Kincaid Grade level test: Aim between 7.0 – 8.0.

- Use preferred terms, see table

Preferred term	**Less preferred**
Baby	Infant, newborn
Medicine	Drug, medication
Breastfeeding	Lactation, nursing
Birth defect	Malformation,
Risk of (malformation)	Chance of (malformation)
Preterm birth	Preterm delivery/Preterm Labour
Healthcare professional	Healthcare provider/clinician
COVID-19	Coronavirus, COVID

From a ConcePTION poll with 152 responses