
A review of developments in the evidence base: in which topic areas are new clinical trials being registered?

1. Introduction

Cochrane reviews include evidence from clinical trials on the effectiveness of treatments, and in some cases, diagnostic tests. Cochrane Oral Health wanted to find out where there were new clinical trials being registered or where there might be emerging areas of evidence, to inform our work going forwards. This is an important part of priority setting, as we need to ensure that we are addressing the most up-to-date questions in future, and not commissioning research where there is no evidence to include.

The process of examining the evidence base can be very time consuming, as it involves searching the literature for new trials and then screening the results. This is labour intensive, especially in areas where there is complexity (Welsh, *et al*, 2015). As well, as looking for new clinical trials, this research also addressed the question of whether text mining packages could be applied to assist with this process by easing the burden involved in screening. Therefore, the two aims of the review of the evidence base were to find out if there was a substantive “direction of travel” in oral health clinical trials registered or reported between 2014 and 2017; and to examine whether these trials could be identified in a less labour intensive way.

Text mining, otherwise known as semantic searching, has been used in information retrieval to identify papers for inclusion in systematic reviews (O’Mara-Eves *et al*, 2015). It has been defined as “the process of discovering knowledge and structure from unstructured data (i.e., text)” (O’Mara-Eves *et al*, 2015). It has been most notably used in the systematic review context for screening studies for inclusion in reviews, but to date it has not been used to assist in the priority setting process. It can be helpful in this context because it is designed to read and analyse a large volume of texts and data in a short amount of time. Text mining makes use of Natural Language Processing (NLP) algorithms, which can pull together similar ideas and concepts, however differently they are expressed (Linguamatics, 2017). It can identify relationships and patterns across a dataset, and make these visible as structured data. This is commonly done as a “visualisation”, which can take the form of a graph, map or table (Linguamatics, 2017). Text mining should make the process of identifying new evidence from a volume of literature in a particular topic less time consuming.

2. Methods

2.1. Searching for clinical trials

Cochrane Oral Health’s scope was broken down into 33 conditions or diseases (see Table 1), and a search strategy was developed for each. A search was then conducted for each topic area across those databases where there were likely to be randomized controlled or controlled

clinical trials. The Cochrane Central Register of Controlled Clinical Trials (CENTRAL), the WHO International Clinical Trials Registry Platform (WHO ICTRP) and the US National Institutes of Health Trials Registry (ClinicalTrials.gov) were searched. CENTRAL is part of the Cochrane Library, and is produced from several sources, including records from PubMed, Embase and from Cochrane review groups' individual clinical trials registries (Cochrane Library, 2017). The only studies eligible for publication in CENTRAL are randomised controlled trials, controlled clinical trials, controlled before and after studies and interrupted time series (Cochrane Library, 2017). WHO ICTRP is a single point of access to identify clinical trials, and is made up of trials registry records from various countries, including Australia, New Zealand, Brazil, China, South Korea, India, Cuba, Germany, the EU, Iran, Japan, Thailand, Peru and the Netherlands (WHO ICTRP, 2017). ClinicalTrials.gov is a resource which was created through the requirement for all clinical trials in the US to be registered (ClinicalTrials.gov, 2017). Although none of these three databases claims to be exhaustive, taken together they are a reasonable reflection of the evidence base in terms of clinical trials. It is a mandatory requirement for a Cochrane review to search all three (Cochrane, 2017). As the last prioritization exercise took place in 2014, the searches undertaken for this study were limited by date: 1 January 2014 to 1 May 2017.

For each topic area, the number of hits was recorded (see Table 1). If the combined total was over 500, the results from each database were imported into the reference management software EndNote. 13 of the topics met this criteria, and 13 EndNote Libraries were created.

The results of each search were checked for duplicated records, and records which were obviously not about the topic. At this stage, the records retrieved on the xerostomia topic area were excluded, as the trials identified by the search were found to be less about interventions to treat or prevent xerostomia, but more about reporting it as a side effect of a drug intervention which may have nothing to do with oral health. After excluding the trials which were only about xerostomia as a side effect, the number of remaining trials on this topic did not meet the threshold for including in the study.

Table 1: Topic areas explored for clinical trials, 2014-2017 with number of results returned

| Topic | CT.gov | WHO ICTRP | CENTRAL | TOTAL |
|----------------------------------|--------|--------------|---------|-------|
| Periodontal disease | 582 | 1246 | 2033 | 3861 |
| Oral cancer | 97 | 220 | 2425 | 2742 |
| Partial / full edentulousness | 290 | 574 | 1338 | 2202 |
| Caries management | 270 | 760 | 1020 | 2050 |
| Xerostomia | 130 | 40 | 1760 | 1930 |
| Malocclusion | 46 | 171 | 1034 | 1251 |
| Gingivitis | 83 | 415 | 437 | 935 |
| Temporomandibular joint disorder | 88 | 262 | 394 | 744 |
| Oral mucositis | 124 | 50 | 508 | 682 |
| Root canal therapy | 18 | 24 | 639 | 681 |
| Impacted / unerupted teeth | 111 | 38 | 442 | 591 |
| Wisdom tooth extraction | 71 | 108 | 338 | 517 |
| Traumatized teeth | 93 | 20 | 399 | 512 |
| Tooth discolouration | 28 | 39 | 428 | 495 |
| Herpes simplex virus | 60 | 25 | 388 | 473 |
| Recurrent mouth ulcers | 16 | 79 | 370 | 465 |
| Hypersensitive teeth | 137 | 4 | 194 | 335 |
| Cleft lip and palate | 41 | 50 | 204 | 295 |
| Dental anxiety | 22 | 71 | 129 | 222 |
| BRONJ | 7 | 24 | 180 | 211 |
| Sialorrhea | 10 | 33 | 146 | 189 |
| Oral lichen planus | 20 | 82 | 65 | 167 |
| Jaw fractures | 10 | 26 | 123 | 159 |
| Non-cariou tooth lesions | 14 | 5 | 104 | 123 |
| Oral candidiasis | 9 | 45 | 53 | 107 |
| Periimplantitis | 32 | 4 | 47 | 83 |
| Dry socket | 4 | 16 | 58 | 78 |
| Toothache | 37 | 3 | 35 | 75 |
| Burning mouth syndrome | 6 | 10 | 44 | 60 |
| Fluorosis | 2 | 13 | 29 | 44 |
| Oral submucous fibrosis | 4 | 16 | 24 | 44 |
| Odontogenic cysts | 1 | 5 | 23 | 29 |
| Noma | 0 | 0 | 2 | 2 |

2.2. Text mining packages

The titles and abstracts from each of the other 12 searches were then exported from EndNote and uploaded to three text mining packages: Voyant, VOSViewer and TerMine. These three text mining packages were chosen because they are free of charge and because they have been put forward as examples in training courses for Cochrane Information Specialists. They have therefore already been made available to staff at Cochrane, and have been used in the systematic review process already, albeit with different aims (Glanville, 2016). As these are new technologies with regard to priority setting, three different packages were chosen in order to crosscheck that the results were consistent.

Voyant was originally developed for the digital humanities. It is a web-based text reader, which can produce word-clouds of the most commonly used words in a text (Voyant, 2017). VOSViewer is a tool developed at the Centre for Science and Technology at Leiden University. It produces textual maps, and can create a network of most frequent terms used (Levallois, 2017). These can be displayed in the form of “heat maps”, with areas of colour density showing where terms occur together. TerMine is a service provided by the UK’s National Centre for Text Mining (NaCTeM), based at the University of Manchester. It uses linguistic analysis to find all “candidate terms” in a text, and extracts word sequences, so that you can see the keywords in context. These can then be produced in a tabulated list (NaCTeM, 2012).

For each of the twelve eligible topics, a Word cloud was produced using Voyant. This was limited to interventions only by adding other terms as stop words, meaning that they would not appear in the Word Cloud. A heat map was produced using VOSViewer, and a table of key words in context was produced using TerMINE.

The different results were then analysed for common themes which provide a snapshot of the recent evidence from clinical trials in oral health. The themes were then mapped against Cochrane Oral Health’s existing reviews portfolio, to see where there might be scope for new reviews.

3. Results

The evidence base was reviewed by an analysis of clinical trials in a total of 12 topic areas. The analysis was completed by utilizing text mining software. The table shows the number of trials analysed and the most commonly mentioned interventions or themes in each of the topic areas.

Table 2: Results of the Clinical Trials Survey in Oral Health, 2014-2017

| Topic | Number analysed | Interventions from clinical trials registered or reported 2014-2017 |
|----------------------------------|------------------------|---|
| Periodontal disease | 3,675 | Root planing, oral hygiene interventions, non-surgical treatments |
| Oral cancer | 2,592 | Radiation therapy, induction chemotherapy, cisplatin and fluorouracil, prevention (tobacco use, diet) |
| Caries management | 2,050 | Fluoride (especially varnish), restoration materials, sealants |
| Partial / full edentulousness | 1,981 | Implant stability, surgery to prevent implant failure |
| Malocclusion | 1,153 | Oral hygiene in orthodontic patients, bonding of braces, rapid expansion |
| Gingivitis | 825 | Oral hygiene, toothbrushing, mouthrinse, chlorhexidine |
| Temporomandibular joint disorder | 630 | Occlusal splints, laser therapy |
| Root canal therapy | 623 | Filling materials, bond strength, anesthesia |
| Oral mucositis | 578 | Lasers, honey, caphosol, palifermin |
| Impacted / unerupted teeth | 528 | Surgery |
| Traumatised teeth | 475 | Restoration, filling materials, surgery |
| Wisdom tooth extraction | 444 | Pain relief, side effect reduction |

4. Discussion

The survey of the evidence base did not reveal any substantive new areas of upcoming clinical trials for Cochrane Oral Health to use in evidence synthesis, although there may be scope in some very defined areas. Clinical trials identified and analysed since the last prioritization exercise were mostly on topics that would fit into the existing reviews produced by the Group. In terms of the volume of clinical trials currently underway in oral health, periodontics, oral cancer, caries management and partial or full edentulousness are the areas with most commissioned research.

Cochrane Oral Health's current portfolio of reviews and protocols was mapped against the emerging themes and interventions from the clinical trials. The mapping exercise (see Table 3) produced some evidence that there may be scope for new reviews in some narrowly defined areas. In the topic of oral mucositis, there are no Cochrane reviews on three interventions which came out as having some registered clinical trials: honey, caphosol and laser therapy. There may also be some scope for commissioning reviews looking at periodontal diseases, particularly non-surgical interventions, and technique, duration and frequency of toothbrushing. A further highlighted area was tobacco cessation for the prevention of oral cancer. However, this topic will fall under the scope of a different Cochrane group (Tobacco Addiction).

Table 3: Areas of research mapped against current Cochrane Oral Health reviews

| THEME/INTERVENTION | IS THERE A COCHRANE REVIEW? |
|----------------------------|---|
| Root planing | <ul style="list-style-type: none"> • Full-mouth treatment modalities (within 24 hours) for chronic periodontitis in adults • Treating periodontal disease for preventing adverse birth outcomes in pregnant women • Treatment of periodontal disease for glycaemic control in people with diabetes mellitus • Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis • Routine scale and polish for periodontal health in adults |
| Oral hygiene interventions | <ul style="list-style-type: none"> • Psychological interventions for improving adherence to oral hygiene instructions in adults with periodontal diseases • Powered versus manual toothbrushing for oral health • Chlorhexidine mouthrinse as an adjunctive treatment for gingival health • Flossing for the management of periodontal diseases and dental caries in adults • Routine scale and polish for periodontal health in adults • Interdental brushing for the prevention and control of periodontal diseases and dental caries in adults • Supportive periodontal therapy (SPT) for maintaining the dentition in adults treated for periodontitis • Treatment of periodontal disease for glycaemic control in people with diabetes mellitus • Triclosan/copolymer containing toothpastes for oral health |
| Non-surgical treatments | <ul style="list-style-type: none"> • Full-mouth treatment modalities (within 24 hours) for chronic periodontitis in adults • POSSIBLE SCOPE FOR SPECIFIC NON-SURGICAL INTERVENTIONS - e.g laser therapy |
| Radiation therapy | <ul style="list-style-type: none"> • Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy |
| Induction chemotherapy | <ul style="list-style-type: none"> • Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy |
| Fluoride therapy | <ul style="list-style-type: none"> • Fluoridated milk for preventing dental caries • Fluoride gels for preventing dental caries in children and adolescents • Fluoride mouthrinses for preventing dental caries in children and adolescents • Fluoride supplementation in pregnant women for preventing dental caries in the primary teeth of their children • Fluoride supplements (tablets, drops, lozenges or chewing gums) for preventing dental caries in children • Fluoride toothpastes for preventing dental caries in children and adolescents • Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents • Fluoride varnishes for preventing dental caries in children and adolescents • Fluorides for the prevention of early tooth decay (demineralised white lesions) during fixed brace treatment • Water fluoridation for the prevention of dental caries |

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| | <ul style="list-style-type: none"> • Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents • One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents • Slow-release fluoride devices for the control of dental decay • Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents • Topical fluoride as a cause of dental fluorosis in children |
| Fluoride varnish | <ul style="list-style-type: none"> • Fluoride varnishes for preventing dental caries in children and adolescents • Pit and fissure sealants versus fluoride varnishes for preventing dental decay in the permanent teeth of children and adolescents |
| Restoration materials | <ul style="list-style-type: none"> • Direct composite resin fillings versus amalgam fillings for permanent or adult posterior teeth • Replacement versus repair of defective restorations in adults: amalgam • Replacement versus repair of defective restorations in adults: resin composite • Dental filling materials for managing carious lesions in the primary dentition • Adhesive restorations for the treatment of dental non-carious cervical lesions • Antibacterial agents in composite restorations for the prevention of dental caries |
| Sealants | <ul style="list-style-type: none"> • Sealants for preventing dental caries in primary teeth • Pit and fissure sealants for preventing dental decay in permanent teeth • Pit and fissure sealants versus fluoride varnishes for preventing dental decay in the permanent teeth of children and adolescents |
| Implant stability | <ul style="list-style-type: none"> • Interventions for replacing missing teeth: different times for loading dental implants • Interventions for replacing missing teeth: different types of dental implants • Interventions for replacing missing teeth: dental implants in fresh extraction sockets • Interventions for replacing missing teeth: 1- versus 2-stage implant placement |
| Surgery to prevent implant failure | <ul style="list-style-type: none"> • Interventions for replacing missing teeth: management of soft tissues for dental implants • Interventions for replacing missing teeth: alveolar ridge preservation techniques for dental implant site development • Interventions for replacing missing teeth: augmentation procedures of the maxillary sinus • Interventions for replacing missing teeth: horizontal and vertical bone augmentation techniques for dental implant treatment |
| Oral hygiene in orthodontics | <ul style="list-style-type: none"> • Interdental cleaning in patients with fixed orthodontic appliances • Fluorides for the prevention of early tooth decay (demineralised white lesions) during fixed brace treatment |
| Bonding of braces | <ul style="list-style-type: none"> • Adhesives for bonded molar tubes during fixed brace treatment • Adhesives for fixed orthodontic bands |

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| | <ul style="list-style-type: none"> • Adhesives for fixed orthodontic brackets |
| Rapid expansion | <ul style="list-style-type: none"> • Surgical adjunctive procedures for accelerating orthodontic treatment • Non-surgical adjunctive interventions for accelerating tooth movement in patients undergoing fixed orthodontic treatment |
| Toothbrushing for gingivitis | <ul style="list-style-type: none"> • Powered versus manual toothbrushing for oral health • Different powered toothbrushes for plaque control and gingival health • POSSIBLE SCOPE FOR REVIEWS ON TECHNIQUES, DURATION, FREQUENCY |
| Mouthrinses for gingivitis | <ul style="list-style-type: none"> • Chlorhexidine mouthrinse as an adjunctive treatment for gingival health • Chlorhexidine mouthrinse versus other potentially active mouthrinses as an adjunctive treatment for gingival health |
| Chlorhexidine for gingivitis | <ul style="list-style-type: none"> • Chlorhexidine mouthrinse as an adjunctive treatment for gingival health • Chlorhexidine mouthrinse versus other potentially active mouthrinses as an adjunctive treatment for gingival health |
| Occlusal splints | <ul style="list-style-type: none"> • Occlusal interventions for managing temporomandibular disorders |
| Laser therapy | <ul style="list-style-type: none"> • Covered by planned review on physical therapy |
| Filling materials in root canal therapy | <ul style="list-style-type: none"> • Materials for retrograde filling in root canal therapy • Single crowns versus conventional fillings for the restoration of root-filled teeth • Endodontic procedures for retreatment of periapical lesions |
| Bonding in root canal therapy | <ul style="list-style-type: none"> • Materials for retrograde filling in root canal therapy |
| Anaesthesia | <ul style="list-style-type: none"> • Injectable local anaesthetic agents for dental anaesthesia (not OH review), • Intraoperative local anaesthesia for reduction of postoperative pain following general anaesthesia for dental treatment in children and adolescents • Sedation versus general anaesthesia for provision of dental treatment to patients younger than 18 years (not OH review) • Sedation of children undergoing dental treatment |
| Laser therapy for mucositis | <ul style="list-style-type: none"> • SCOPE FOR NEW REVIEW |
| Honey for mucositis | <ul style="list-style-type: none"> • SCOPE FOR NEW REVIEW |
| Caphosol for mucositis | <ul style="list-style-type: none"> • SCOPE FOR NEW REVIEW |
| Palifermin for mucositis | <ul style="list-style-type: none"> • Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors |
| Surgery for impacted teeth | <ul style="list-style-type: none"> • Surgical removal versus retention for the management of asymptomatic disease-free impacted wisdom teeth |
| Restoration for traumatised teeth | <ul style="list-style-type: none"> • Interventions for treating traumatised permanent front teeth: avulsed (knocked out) and replanted |
| Filling materials for traumatised teeth | <ul style="list-style-type: none"> • Interventions for treating traumatised permanent front teeth: avulsed (knocked out) and replanted |
| Surgery for traumatised teeth | <ul style="list-style-type: none"> • Interventions for treating traumatised permanent front teeth: luxated (dislodged) teeth • Interventions for treating traumatised ankylosed permanent front teeth |

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| | <ul style="list-style-type: none"> • Interventions for treating traumatised permanent front teeth: avulsed (knocked out) and replanted |
| Pain relief in wisdom tooth extraction | <ul style="list-style-type: none"> • Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth • Paracetamol for pain relief after surgical removal of lower wisdom teeth |
| Reduction of side effects in wisdom tooth extraction | <ul style="list-style-type: none"> • Surgical techniques for the removal of mandibular wisdom teeth • Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth • Paracetamol for pain relief after surgical removal of lower wisdom teeth |

A second aim of this part of the research was to see whether text mining could introduce efficiencies into surveying the evidence base. The text mining element of the research did not prove to be labour intensive. The screening involved in the process was minimal, as records were only screened to see whether they were about the topic or not before being included in the research. Even using three packages, the analysis of the text after uploading to the three tools took less than 10-15 minutes per topic area. The three packages also produced remarkably consistent results.

There were limitations in using this technique. Clinical trials were analysed in bulk across topic areas, so although there is a sense of a direction of travel in terms of interventions, any nuance is lost. This approach to the data may also hide some new and upcoming interventions which have only been tested in a few trials, although arguably if the research is at this stage then it may not be suitable for inclusion in a systematic review in any case. There was also no attempt to find clinical trials outside of the trials registries that were searched, and so any unregistered trials, or trials registered outside ClinicalTrials.gov or not included in the WHO International Trials Registry Platform portal dataset, were not included. The most that this survey can give is an impression of where the volume of evidence is leading in a particular topic area.

5. References

ClinicalTrials.gov (2017). ClinicalTrials.gov background. Available at:

<https://clinicaltrials.gov/ct2/about-site/background>, (Accessed 22 December 2017).

Cochrane. (2017). *Editorial and publishing policy resource: Cochrane review updates*. Available at: <http://community.cochrane.org/editorial-and-publishing-policy-resource/cochrane-review-development/cochrane-review-updates>, (Accessed 28 July 2017).

Cochrane Library (2017). *Access options for the Cochrane Library*. Available at:

<http://www.cochranelibrary.com/help/access-options-for-cochrane-library.html>, (Accessed 28 July 2017).

Glanville, J., (2016). *Cochrane training 2*. Available at:

http://community.cochrane.org/sites/default/files/uploads/inline-files/Glanville%202016_Cochrane%20text%20mining%20webinar_session%202.pdf,

(Accessed 14 December 2017).

Levallois, C. (2017). *A tutorial for VOSViewer*. Available at: <https://seinecle.github.io/vosviewer-tutorials/generated-pdf/importing-en.pdf>, (Accessed 6 October 2017).

Linguamatics (2017). *What is text mining?* Available at: <https://www.linguamatics.com/what-is-text-mining-nlp-machine-learning>, (Accessed 14 December 2017).

NaCTeM (2012). *TerMine*. Available at: <http://www.nactem.ac.uk/software/termine/>, (Accessed 6 October 2017).

O'Mara-Eves, A., Thomas, J., McNaught, J., Miwa, M. and Ananiadou, S. (2015). Using text mining for study identification in systematic reviews: a systematic review of current approaches, *Systematic Reviews*, 4, Article no: 5

Voyant (2017). *About*. Available at: <https://voyant-tools.org/docs/#!/guide/about>, (Accessed 6 October 2017)

Welsh, E., Stovold, E., Kamer, C. and Cates, C. (2015). Cochrane Airways Group reviews were prioritized for updating using a pragmatic approach, *Journal of Clinical Epidemiology*, 68, pp. 341-346

WHO ICTRP (2017). *Search portal*. Available at: <http://apps.who.int/trialsearch/default.aspx>, (Accessed 22 December 2017).