# Systematic Review Protocol for Animal Intervention Studies

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**Version 2.0 (December 2014)**

<table>
<thead>
<tr>
<th>Item #</th>
<th>Section/Subsection/Item</th>
<th>Description</th>
<th>Check for approval</th>
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<tbody>
<tr>
<td>A. General</td>
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<tr>
<td>1.</td>
<td>Title of the review</td>
<td>Systemic factor effects on orthodontically induced inflammatory root resorption: A systematic literature review [provisional title].</td>
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</tbody>
</table>
| 2. | Authors (names, affiliations, contributions) | Linn Haugland, DMD. Department of Orthodontics, University of Bergen and Specialist Oral Health Center for Western Norway Department: Rogaland. Norway haug.linn@gmail.com  
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| 3. | Other contributors (names, affiliations, contributions) | | |
| 4. | Contact person + e-mail address | Linn Haugland, DMD Department of Orthodontics, University of Bergen, Årstadveien 19, 5009 Bergen Telephone: +47 55 58 66 00 haug.linn@gmail.com | |
| 5. | Funding sources/sponsors | Remaining authors had no financial support for the submitted work | |
| 6. | Conflicts of interest | Authors affirm that we have no financial affiliation or involvement with any commercial organization that has a direct financial interest in any matter included in this research. | |
| 7. | Date and location of protocol registration | December, 2015 | |
### B. Objectives

#### Background

10. What is already known about this disease/model/intervention? Why is it important to do this review?

   Systemic factors are shown to affect the degree of orthodontically induced inflammatory root resorption (OIIRR). However, a systematic overall assessment of their impact on OIIRR has not yet been reported. We aimed to systematically assess the risk of any intervention(s) that could induce systemic effect on OIIRR in human or animal subjects.

#### Research question

11. Specify the disease/health problem of interest

   Orthodontically induced inflammatory root resorption (OIIRR)

12. Specify the population/species studied

   Patients and animals with fixed orthodontic appliances

13. Specify the intervention/exposure

   Systemic factor intervention defined as: systemic or hormonal disorders, specific diet regimen, LLLT, ultrasound therapy and any systemic or local administration of substances that might interfere directly or indirectly with bone physiology.

14. Specify the control population

   A matched control group with fixed appliance and without intervention (placebo, sham treatment)

15. Specify the outcome measures

   OIIRR quantitatively measured on histological sections, by radiographs or tomographic imaging

16. State your research question (based on items 11-15)

   How do systemic factors affect the degree of OIIRR in animal and human subjects?

### C. Methods

#### Search and study identification

17. Identify literature databases to search (e.g. Pubmed, Embase, Web of science)

   - MEDLINE via PubMed
   - Web of Science
   - SCOPUS
   - EMBASE

   Others, namely:
   - Cochrane Central Register of Controlled Trials,
   - EBM Reviews (Cochrane database of systematic reviews),
   - LILACS (Latin American and Caribbean Center on Health Sciences),
   - Grey literature (Google Scholar)
   - Unpublished literature (ClinicalTrials.gov)

   - Specific journal(s), namely:

18. Define electronic search strategies (e.g. use the step by step search guide and animal search filters) The search terms were developed for MEDLINE and modified to operate in all of the selected databases. Search terms included root resorption, orthodontics and tooth movement.
|   |   | MEDLINE search:  
|   |   | (("root resorption"[All Fields] OR "root resorption"[MeSH Terms])  
|   |   | (("orthodontics"[MeSH Terms] OR "tooth movement"[All Fields]) OR ("orthodontics"[MeSH Terms] OR "orthodontics"[All Fields])))  
|   |   | NOT ("endodontics"[MeSH Terms] OR ("endodontics"[MeSH Terms] OR "endodontics"[All Fields])))  
| 19. | Identify other sources for study identification | ☑Reference lists of included studies  
|   |   | ☑Reference lists of relevant reviews  
|   |   | ☐Conference proceedings, namely:  
|   |   | ☑Contacting authors/ organisations, namely: Corresponding author will be contacted whenever there is a need for additional or clarifying information.  
| 20. | Define search strategy for these other sources | Google Scholar, Google.  
| Study selection |   |  
| 21. | Define screening phases (e.g. pre-screening based on title/abstract, full text screening, both) | 1. Title/abstract screening.  
|   |   | 2. Full text screening  
| 22. | Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved | a. Per phase, two of the reviewers (VVR) and (LH) will independently screen for relevant studies.  
|   |   | b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers).  
|   | Define all inclusion and exclusion criteria based on: | Inclusion criteria: Randomized and controlled clinical trials, cohort studies, case control studies and animal experiments, with split-mouth design included.  
| 23. | Type of study (design) | Exclusion criteria: Studies with fewer than five animals/subjects in each group  
|   |   | Inclusion criteria: Patients and animals with fixed orthodontic appliance  
| 24. | Type of animals/population (e.g. age, gender, disease model) | Exclusion criteria: Patient and animals without fixed appliance  
| 25. | Type of intervention (e.g. dosage, timing, frequency) | Inclusion criteria: Systemic factor intervention defined as: systemic or hormonal disorders, specific diet regimen, LLLT, ultrasound therapy and any systemic or local administration of substances that might interfere directly or indirectly with bone physiology.  

### Exclusion criteria:

**26. Outcome measures**
- Inclusion criteria: OIIRR quantitatively measured on histological sections, by radiographs or tomographic imaging
- Exclusion criteria: Studies that do not measure OIIRR quantitatively

**27. Language restrictions**
- Inclusion criteria: No restrictions
- Exclusion criteria: N/A

**28. Publication date restrictions**
- Inclusion criteria: Studies published up to search date
- Exclusion criteria: No past date restriction

**29. Other**
- Inclusion criteria: N/A
- Exclusion criteria: Double publications (e.g. reviews, thesis).

### Selection phase: Title and abstract screening.
1. Type of study.
2. Type of intervention.

### Selection phase: Full text screening.
1. Type of study.
2. Type of subjects
3. Type of intervention.
4. Outcome measures.

### Study characteristics to be extracted (for assessment of external validity, reporting quality)

**31. Study ID (e.g. authors, year)**
Authors, title, year, language, contact author e-mail

**32. Study design characteristics (e.g. experimental groups, number of animals)**
Experimental groups, number of subjects per group.

**33. Animal model characteristics (e.g. species, gender, disease induction)**
Animal species, strain, age, weight, gender

**34. Intervention characteristics (e.g. intervention, timing, duration)**
Type of systemic factor, route of administration, dose, frequency, duration of systemic factor, timing relative to fixed appliance, duration of fixed appliance, timing of fixed appliance, type of experimental group, type of control group

**35. Outcome measures**
Measurement of orthodontically induced inflammatory root resorption (OIIRR) by histological sections, radiographs or tomographic

**36. Other (e.g. drop-outs)**
Number of teeth
OIIRR assessment method

### Assessment risk of bias (internal validity) or study quality

**37. Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved**
- a. Two reviewers will independently assess risk of bias of included studies.
- b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers).
| 38. | Define criteria to assess (a) the internal validity of included studies (e.g. selection, performance, detection and attrition bias) and/or (b) other study quality measures (e.g. reporting quality, power) | ☑️By use of SYRCLE's Risk of Bias tool⁴  
☐By use of SYRCLE’s Risk of Bias tool, adapted as follows:  
☐By use of CAMARADES' study quality checklist, e.g.²²  
☐By use of CAMARADES' study quality checklist, adapted as follows:  
☒Other criteria, namely: the Cochrane Collaboration risk of bias tool for human studies |
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<td>39.</td>
<td>For each outcome measure, define the type of data to be extracted (e.g. continuous/dichotomous, unit of measurement)</td>
<td>For all outcome measures (mentioned at 35) we are only interested in continuous data for OIIRR.</td>
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<td>40.</td>
<td>Methods for data extraction/retrieval (e.g. first extraction from graphs using a digital screen ruler, then contacting authors)</td>
<td>Data will be extracted preferably from published data (explicit numeral). If data is not available in the text we will extract data from graphs (if available) by using special designed software (<a href="http://avpsoft.com/products/udruler/">http://avpsoft.com/products/udruler/</a>). Whenever necessary, an electronic mail will be send to the correspondent author for further information. If no answer is obtained within a week or there is no contact information, other authors will be randomly contacted. After five weeks, if no answer is received, the study will be excluded from analysis.</td>
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</table>
| 41. | Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved | a. Two reviewers will independently extract data from included studies.  
b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers). |
| 42. | Specify (per outcome measure) how you are planning to combine/compare the data (e.g. descriptive summary, meta-analysis) | To all systemic factors meta-analysis is intended. |
| 43. | Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed | A minimum of 2 articles per outcome measure is required  
No restrictions in terms of heterogeneity will be applied, instead, sources of heterogeneity will be investigated through sensitivity and subgroup analysis. If a meta-analysis seems feasible/sensible, specify (for each outcome measure): |
| 44. | The effect measure to be used (e.g. mean difference, standardized mean difference, risk ratio, odds ratio) | To all systemic factors:  
- Standardized Mean Difference and 95% confidence intervals will be calculated for all the variables. |
| 45. | The statistical model of analysis (e.g. random or fixed effects model) | To all systemic factors:  
- Random effects model |
| 46. | The statistical methods to assess heterogeneity (e.g. I², Q) | I-square |
| 47. | Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis) | Animal species.  
Gender  
Administration method.  
Dose, duration and timing of systemic factor  
Duration and timing with fixed appliance  
Outcome assessment method |
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<th>Outcome measure</th>
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<td>48.</td>
<td>Any sensitivity analyses you propose to perform</td>
<td>Effect of possible interactions by species, gender, administration method, dose, duration, and timing of drug</td>
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<td>49.</td>
<td>Other details meta-analysis (e.g. correction for multiple testing, correction for multiple use of control group)</td>
<td>Correction for multiple time points, Correction for multiple use of control group</td>
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<td>50.</td>
<td>The method for assessment of publication bias</td>
<td>Funnel plot, if applicable</td>
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Final approval by (names, affiliations):   
Date: