1.0 Aim: To critically and comprehensively evaluate the evidence for mean progression of periodontitis and associated determinants of progression

2.0 Objectives:
   2.1 To investigate the evidence for progression of periodontitis – What is the evidence for different mean values of progression?
   2.2 Which risk factors are associated with different mean values of progression of periodontitis?
   2.3 Which aetiological factors are associated with different mean values of progression of periodontitis?

3.0 Focussed question: In adults, what is mean progression of periodontitis in terms of clinical attachment loss, radiographic bone loss and tooth loss?

4.0 Methods
4.1 Systematic review registration
Once the protocol has been signed off, we will register the review prior to commencing the study on the PROSPERO database (www.crd.york.ac.uk/PROSPERO).

4.2 Population
Periodontally untreated adults will be recognised as 18 years or older. Studies which include both adults and younger individuals without distinction will be included and stratified for this criterion. Populations will include those previously ‘diagnosed’ with periodontitis as well as those without or a mix. Data will be stratified into studies on periodontitis populations, non-periodontitis populations and mixed/unclear populations. No subjects who are in continuous periodontal maintenance after periodontal therapy will be included.

4.3 Exposure
Since case definition for periodontitis remains unclear at earliest stages of initiation of the condition, all definitions will be included. These will be stratified according to definition.

4.4 Primary outcome measure
The primary outcome will be clinical attachment loss (or variants including relative attachment loss). All probing methods (manual, controlled force etc.) will be included. All definitions of ‘change’ in attachment level will be included. Change of probing depth will be not considered.

4.5 Secondary outcome measures. These will be included only for studies presenting attachment level change
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Radiographic bone loss. All radiographic methods (film, digital, subtraction customised film holders) will be included. All definitions of ‘change’ in marginal bone level will be included although stratified into whether based on prior determination of measurement error or not.

Tooth loss. All types of data will be included whether reporting cause of the tooth loss or not. Clearly, tooth loss might be related to factors other than periodontitis and this limitation will be considered in the data interpretation.

4.6 Disease determinants, risk factors and aetiological agents:
The association of disease progression with disease determinants will be recorded including gender, SES, genetic, lifestyle, health behaviours, nutritional and microbiological factors, and number of teeth present at baseline. The measure of association e.g. relative risk will be recorded. The quality of measurement of the determinant/exposure will be assessed (see below).

4.7 Study duration of follow-up
Any study duration will be included or interval of follow-up. Studies will be grouped for best similarity of follow-up as available.

4.8 Types of studies
Any prospective longitudinal study. These are likely to be of two main types; population-based and institution-based. The former will likely be on large populations with field-study characteristics and the latter, smaller, more controlled institution-based environments. Both offer strengths and limitations to addressing the research questions.

4.9 Inclusion criteria
- Prospective, longitudinal studies. It is anticipated that most will be cohort studies.
- Duration of follow-up: at least 12 months.
- Adults, 18 years of age or greater. Studies where participants younger than 18 years are included without subgrouping will be included and stratified separately.
- Study reporting progression of periodontitis using attachment level assessments.
- Periodontally healthy, untreated periodontitis or participants not part of periodontitis treatment investigations. We anticipate that population studies will not report detailed periodontal treatment status of participants.

4.10 Exclusion criteria
- Studies investigating solely specific systemic disease populations e.g. diabetes.
- Experimental studies testing the effect of interventions on periodontitis.
- Cross-sectional or retrospective studies.
- Studies only recruiting participants previously treated for periodontitis

4.11 Search
A sensitive search will be conducted. Electronic databases (MEDLINE, EMBASE, LILACS) will be searched using a string of medical subject heading and free-text terms. Open Grey will be searched for unpublished, grey literature. The search strategy will be developed with Anna Di Iorio, Head Librarian, UCL Eastman Dental Institute, who has extensive experience in designing searches for systematic reviews. There will be no language restrictions. Reference
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Lists of eligible studies and previous reviews will be searched for missing records. In addition, the final list of eligible studies will be circulated to workshop chairman for evaluation for possibly missing studies. The search results will be downloaded to a bibliographic database and duplicate records will be removed.

4.12 Screening for eligibility
Titles (and abstracts if available) will be screened by NG and FM in duplicate and independently. Disagreement will be resolved by discussion or if not achieved, by arbitration by a third reviewer (IN), an experienced systematic reviewer. The full text of all possibly eligible records will be obtained for the next stage of eligibility assessment which will also be conducted in the same manner as that for titles. Reasons for exclusion of full-text studies will be recorded. Agreement between reviewers will be assessed using Kappa statistics.

4.13 Risk of bias will be assessed using the Newcastle-Ottawa scale as it is the mostly widely used tool for epidemiologic studies (Appendix).

4.14 Other domains of methodological quality will include and methodological quality.
- Security of measurement of attachment level. Studies will be assessed as secure if the method involved appropriate training and calibration of examiners, insecure if training was absent or inadequate or unclear if unreported
- Security of assessment of bone level change. Studies will be assessed as secure if the method involved standardised positioning of the radiographs e.g. cephalostat or customised film holders, insecure if standardisation was absent or inadequate or unclear if unreported.
- Power calculation. If meta-analysis is not possible, assessment of the potential of individual studies to demonstrate statistically significant differences will become important. Therefore, presence of a power calculation will be assessed
- Periodontal assessment: Full mouth or partial mouth assessment

4.15 Data abstraction
Data will be abstracted from eligible articles by two reviewers (NG & FM) independently and in duplicate. Disagreement will be resolved by discussion or if not achievable by reference to a third reviewer (IN). A specially designed abstraction template will be produced and piloted on 10 articles prior to commencing data abstraction.

4.16 Unclear or missing data
Wherever possible, authors of paper will be contacted for clarification of missing or unclear data with two attempts at contact one, month apart.

4.17 Key characteristics for abstraction
- Study design: Type of study
- Setting: Community, institution, country etc.
- Sample: Random sample, referred patients, periodontal status, systemic health status. numbers starting study, number completing study, drop-outs/withdrawals (with reasons)
- Disease determinants, risk factors etc.
- Method for assessing periodontitis: CAL, RAL etc, type of probe, thresholds
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- Progression data: CAL, bone loss and tooth loss
- Risk of bias and methodological quality

4.20 Data synthesis
4.20.1 Data will first be entered into evidence tables stratified by study design. Decisions on meta-analysis will be made depending on similarity of chief study characteristics related to each research question i.e. mean progression of periodontitis and association of progression with disease determinants.

4.20.2 If meta-analysis is appropriate, an overall measure of mean progression with 95% confidence interval at a given time point and for strata of interest (e.g., for smokers and non-smokers, for different age groups) but stratification will depend on the information provided in the papers. It may be possible to obtain an overall measure of the difference in the mean LOA for various factors. Analytic statistics will be conducted by Dr Aviva Petrie, a biostatistician experienced in systematic reviews and meta-analysis.

4.20.3 Heterogeneity will also be assessed using both chi-square and I² measures. I² will be interpreted according to the guidance of the Cochrane Handbook:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

4.20.4 If there are sufficient studies, we will plan to investigate heterogeneity using meta-regression including risk of bias, security of disease progression method, type of population i.e. initially healthy or periodontitis. Similar methods will be employed to assess association between mean progression and risk/aetiological factors. It should be noted that the ecological fallacy may be a problem in the meta-regression, resulting in the relationship at the study level not being true at the subject level.

4.21 Protocol amendments
Protocol amendments made following initiation of review will be reported in the review document.

4.22 Timescale
Completion of review protocol: 15 February 2016
First draft of review to working group chairs: 27 June 2016
Final draft of review submitted: 9 January 2017

4.23 Authorship. All named reviewers on page 1 will be co-authors of the final publication.

4.24 Contribution. A statement of contribution by the authors report will be presented in the review report and publication

4.25 Conflicts of interest. A statement of conflicts of interest will be presented in the review report and publication
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Appendix

Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)

**Cohort studies** (A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability)

**Selection**

1) Representativeness of the exposed cohort
   - a) truly representative of the average in the community
   - b) somewhat representative of the average in the community
   - c) selected group of users e.g. nurses, volunteers
   - d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   - a) drawn from the same community as the exposed cohort
   - b) drawn from a different source
   - c) no description of the derivation of the non-exposed cohort

3) Ascertaintment of exposure
   - a) secure record (e.g. surgical records)
   - b) structured interview
   - c) written self-report
   - d) no description

4) Demonstration that outcome of interest was not present at start of study
   - a) yes
   - b) no

**Comparability**

1) Comparability of cohorts on the basis of the design or analysis
   - a) study controls for (select the most important factor)
   - b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor)

**Outcome**

1) Assessment of outcome
   - a) independent blind assessment
   - b) record linkage
   - c) self-report
   - d) no description

2) Was follow-up long enough for outcomes to occur
   - a) yes (select an adequate follow up period for outcome of interest)
   - b) no

3) Adequacy of follow up of cohorts
   - a) complete follow-up - all subjects accounted for
   - b) subjects lost to follow-up unlikely to introduce bias - small number lost (<20%, or description provided of those lost
   - c) high lost to follow-up rate and no description of those lost
   - d) no statement