Executive Summary

Systematic review of diagnostic tests

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☐ Part 1. Systematic review of diagnostic tests

1.1 Developing the topic and key questions

- It is necessary to investigate that the diagnostic test is located in any clinical context and plays an any role in the clinical field as well as the characteristics of a medical test studies when performing a systematic review of diagnostic tests.

- The 'causal pathway' should be taken into account in developing the SR topic of diagnostic and defining the key questions, it is recommended to utilize the analytic framework in order to perform it effectively.

1.2 Developing the study protocol

- An organization of researchers or advisory committee, defining the key questions and pre-reviewing the existing studies performs at the planning stage of a systematic review. The key question should be written clearly and specifically utilizing the P(P)IC(R)O form.

- It writes prior to start of the study and consists of title, background, objectives or key questions, study methods sequentially. The search strategy, selection criteria of literature, assessing method of quality of literatures, data extracting method, data analysis method, assessing method of the level of evidence are described in study methods.

- Protocol will be completed by consultation taken from relevant experts and changes to

methodology during the study progression should be recorded in the original protocol of the review with explicit reasons.

1.3 Searching for studies

- To obtain relevant studies, reviewers search core bibliographic databases such as MEDLINE, EMBASE and The Cochrane library as well as 8 local databases for Korean clinical studies.

- Search strategy should be designed to be highly sensitive, although this is likely to result in low precision.

- The search should adapt subject headings or related text terms according to the index test and target condition as the key concepts of the SR.

- Checking references of relevant studies, the use of the reference tracking function (e.g. 'related articles' etc) in electronic databases, and other sources, are important additional methods for identifying relevant studies.

- Searches is carried out process through repetitive tasks, it can be limited in use of search filter to minimize the risk of missing relevant studies.

1.4 Selecting studies

- Study selection and exclusion criteria should be defined based on the PICO components in the protocol.

- Study selection and classification should be clear and should be performed independently by at least two investigators. If there is a disagreement, it is resolved through agreement between investigators or intervention of third party.

- Based on exclusion of duplicated literature and criteria of study selection, the process of study selection go through the first exclusion after check of title and abstract, the second exclusion after full-text check.

- The excluded studies should be listed with reason for exclusion, the process of study selection should be reported using flow chart.

- Study of diagnostic test is classified as clinical effects study, diagnostic accuracy study depending on outcomes, accordingly, study design and study classification are divided.

1.5 Assessing risk of bias and applicability

- Bias is a systematic error and risk of bias means the degree of risk which can be occurring of bias. The occurring problems in the processes of design, implementation and reporting of diagnostic accuracy test can be lead to the bias.

- The use of checklist for evaluation on quality of the individual item about primary study is suitable when assessing the quality of diagnostic accuracy study. It is recommended to use of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) as an assessment tool.

- Assessing the methodological quality of studies using QUADAS-2 is conducted with the following 4 steps. First, reporting of the review question. Second, developing the review-specific guidance for the application of assessment items. Third, reviewing the flow diagram presented with respect to the primary study if there is no reported, establish a flow diagram. Fourth, determining the bias and applicability.

- The QUADAS-2 is consists of four main domains such as patient selection, index test, reference standard, flow and timing. The signaling questions in each domain can be added or omitted depending on study characteristics and risk of bias and concerns about applicability are evaluated.

- Quality assessment results can be expressed using tabulation or figures and the results can be utilized in meta-regression, sub-group analysis and sensitivity analysis.

1.6 Extracting data

- Data extraction refers to the process of extracting study results reported in included studies of diagnostic test.

- Data collection forms should be designed carefully to target the purposes of the systematic review and should be developed through the pilot test.

- Data may be reported in diverse formats, but can often be converted into a format suitable for meta-analysis.

- For the data extraction of a meta-analysis from studies of diagnostic test should be extracted by the 2x2 table which can calculate diagnostic accuracy. It is essential to know the concept of diagnostic accuracy-related terms and calculation formula.

1.7 Summarizing data and presenting results

- The method of data analysis in a systematic review includes quantitative method and qualitative method, quantitative composition commonly expressed in the meta-analysis.

- In case of reviewing of diagnostic accuracy, analysis of diagnostic accuracy indexes of the included primary studies, coupled forest plot, SROC curve, bivariate meta-analysis, HSROC etc. can be utilized diversly.

- The results presentation of diagnostic accuracy can be presented by tables or graphs such as characteristic table of included studies, table on diagnostic accuracy index of the primary studies, table on quantitative results using bivariate model, HSROC etc.

1.8 Evaluating level of evidence and drawing conclusions

- Evaluating level of evidence is achieved through assessment on risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, dose-response relationship, confounding factor.

- Level of evidence is classified into 4 phases such as high, moderate, low, very low.

- The important things in giving overall level of evidence are that key clinical question relevant to the causal pathway or major clinical outcome given, of these, a determination is needed what should be considered preferentially.

- The study of diagnostic tests constitutes studies about diagnostic accuracy mainly, impact on health outcomes of patient, in other words, studies on the clinical utility is difficult to find out. Therefore, based on the results of diagnostic accuracy should be drawn a conclusion about clinical utility.

1.9 Writing report

- When writing a report on systematic review, it should be written referring to the items of PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses)' s guideline checklist. However, a checklist (Stroup et al, 2000) of the Mosses (Meta-analysis of Observational Studies in Epidemiology) also can refer considering the most of diagnostic test literatures are observational studies.

- Writing a report should be written to be confirmed a clarity and reproducibility of a systematic review. But, if it can not recordable all contents in the body of report, it should be reported the details using appendix.

☐ Part 2. Meta-analysis of diagnostic test

2.1 Meta-analysis of diagnostic test

- Study on diagnostic accuracy simultaneously reports two kinds of measure (ex. sensitivity/specificity, positive predictive value/negative predictive value, positive likelihood ratio/negative likelihood ratio etc.) different with intervention study.

- Diagnostic accuracy study exists threshold-effect and the model of meta-analysis is necessary considering threshold-effect.

2.2 Meta-analysis model on diagnostic test

- Considering relevance of sensitivity and specificity, the Moses-Littenberg SROC model and the hierarchical model (bivariate model, Rutter & Gatsonis HSROC model) are widely utilized in general.

- The Moses-Littenberg SROC model was initially created model and can not grasp heterogeneity as well as the fixed effect model of intervention, and does not provide the summary estimate.

- A bivariate model is able to estimate the summary estimate of sensitivity, specificity and these correlation directly, and provides the SROC curve, confidence region and prediction region. However, if there was a small number of studies, the case occurs that did not converge well compared to the HSROC model.

- The HSROC model does not provide a summary estimate and only provide the SROC curve directly. In case of a small number of studies compared to the bivariate model, it does converge will but review stage of heterogeneity is complicated compared to the bivariate model.

- There are the SAS, R and Stata software for applying these models and the referable instruction was organized and provided when performing the meta-analysis of diagnostic test centering around these software.

- A Bayesian inference method based on the posterior distribution was summarized. This Bayesian model can be applied to another distribution besides assumption of normal distribution of random effect and is effective in case of a small number of studies including a meta-analysis.

2.3 Investigating heterogeneity of meta-analysis on diagnostic test

- The degree of heterogeneity and presence can grasp using a sign of estimated correlation coefficient of bivariate model, comparison of changes in between studies and changes in studies and size of prediction area.

- The cause of heterogeneity can be identified on the basis of the significance of regression coefficient Including covariates that thought to be the cause of the heterogeneity in the models of bivariate model and HSROC model

- In case of the main object of two or more diagnostic test methods for comparing diagnostic accuracy, diagnostic accuracy between diagnostic tests can be compared based on the significance of regression coefficient by adding a covariate of types of diagnostic test in the same way as investigating heterogeneity method of hierarchical model.

☐ Part 3. Special Topics

3.1 Systematic review of prognostic tests

- Clinical utility of a prognostic test depends on the ability to provide accurate prognostic information about patients' likelihood of developing a disease and classify them into various prognostic groups.

- The methods to conduct systematic reviews of a prognostic test are not well established yet and the issues discussed here should be considered when planning and conducting them.

- It is hard to search for the literature about prognostic tests because there is greater likelihood of missing studies which should be included compared to searching for systematic reviews of medical intervention based on randomized clinical trials.

- Prognostic variables should be evaluated from the presentative samples of patients gathered at the same time with respect to the subjects' disease progression state. Ideally, they should be received all the same medical treatments or should be included in randomized clinical trial.

- The standard method for assessing quality of primary study about prognostic test was not firmly established and prognosis tests are often known to be insufficient the methodological validity yet.

- Meta-analysis based on published articles can' t be performed when there are insufficient reports of study design and outcomes or there are large variations between studies and patient characteristics.
- For the systematic review and meta-analysis of prognostic tests, core statistics are various general characteristic, level of risk and predicted outcome probabilities.
- Consideration about relation between a prognostic test and patient outcomes commonly performed can not significantly affect other than determination about need of progress in prognostic test.

3.2 Systematic review of genetic tests

- To understand the purpose of genetic tests must take precedence in order for systematic review on genetic test.
- Genetic test should be assessed in the light of analytical validity, diagnostic accuracy and clinical utility. Also, when drawing conclusions, we should be consider Ethical, social and legal implications.
- It is important to develop the analytic Frameworks that reflect predictive nature of genetic tests and appropriate outcomes
- When evaluating a case-control study, potential selection bias should be considered carefully.
- Additional value of genetic tests over the existing risk models should be confirmed.
- The statistics issues of specifically related to genetic tests study should be understood.
- When assessing associations between a gene function and disease, the risk of potential bias should be taken into account.

diagnostic test, diagnostic accuracy, systematic review, meta-analysis