First author_____

Title:_____

Journal_____

Year:_____

Volume:_____

Issue:_____

First page:_____

Last Page:_____

1. Type of study

❑ Controlled trial without randomization ⇨ Section B
❑ Observational cohort study ⇨ Section B
❑ Case-control study ⇨ Section C
❑ Cross-sectional study (*exposure and outcome measured simultaneously*) ⇨ Section C
❑ Case series
❑ Case report
❑ Ecological study
❑ Other_____

2. Type of report

❑ Full paper in peer reviewed journal
❑ Full paper in book or other type of report
❑ Abbreviated paper in meeting proceedings or similar publication
❑ Abstract only
❑ Other_____

3. Language

❑ English
❑ Scandinavian
❑ German
❑ French
❑ Other _____

Sektion B 2-6
Sektion C 7-13
Sektion E 14-15

Section B (observational cohort study or controlled clinical trial without randomization)

External validity

Short form answer:

❑ Clear external validity *(0)*
❑ Probable external validity *(1)*
❑ Uncertain external validity *(3)*
❑ External validity cannot be assessed *(5)*

If uncertain, answer questions under Item 1.
Otherwise go to Internal validity (after Item 1)

1. Accrual / selection of study subjects

a. Was the studied exposure well defined (e.g., if follow-up of a specified disease, is the definition of the disease acceptable)?
❑ Yes = 0
❑ No = 2

b. Eligibility / inclusion criteria clearly stated?
❑ Yes = 0
❑ No = 1

c. Consecutive eligible subjects included?
❑ Yes = 0
❑ No = 1
❑ Not stated = 1

d. Numbers and reasons for non-participation given?
❑ Yes = 0
❑ No = 1

e. Exclusion criteria clearly stated and acceptable?
❑ Yes = 0
❑ No = 1

f. Are numbers of excluded persons given by reason (as prescribed in the CONSORT statement)?
❑ Yes = 0
❑ No = 1

Total sum of section 1:
0 = Clear external validity
1 = Probable external validity
2-3 = Uncertain external validity
≥ 4 = External validity cannot be assessed

Internal validity

Short form answer:

- ❑ Excellent internal validity *(0)*
- ❑ Good internal validity *(1)*
- ❑ Acceptable internal validity *(2)*
- ❑ Uncertain internal validity *(4)*
- ❑ Uninformative due to flawed internal validity *(10)*

If uncertain, answer questions under Items 2-6. Otherwise go to Precision (after Item 6)

2. Exposure assessment

a. Was the studied exposure satisfactorily measured / recorded?
- ❑ Yes = 0
- ❑ Yes, with minor criticism = 1
- ❑ No = 3

b. Were *all* in the exposed group really exposed?
- ❑ Yes = 0
- ❑ Yes, probably = 1
- ❑ No, probably not = 2
- ❑ No = 2

c. Were *all* in the reference category really unexposed?
- ❑ Yes = 0
- ❑ Yes, probably = 1
- ❑ No, probably not = 2
- ❑ No = 2

3. Comparability of groups / selection bias / confounding

   a. Was there an account of the comparability of groups with regard to factors that might conceivably affect the outcome (potential confounding factors)? *(If only one cohort was studied and compared with the background population or historical controls – was there data to support the comparability with the reference category).*

❑ Yes = 0
❑ No = 3

   b. Did the investigators consider all <u>important</u> potential confounding factors (*potential confounding factors = factors that are independent causes of / risk factors for / protective factors against the outcome, AND not a link in the causal chain between the studied exposure and the outcome*)?

❑ Yes = 0
❑ Probably = 1
❑ No = 3
❑ No data given = 0 (already scored under 3a)

   c. Were the relevant confounding factors satisfactorily measured / recorded?

❑ Yes = 0
❑ Yes, with minor criticism = 1
❑ No = 3

   d. Were the potential confounding factors unevenly distributed among exposed and /non-exposed/ reference group (*confounding arises if factors described under 3b are unevenly distributed among exposed and unexposed [i.e., linked to the exposure]*)?

❑ Yes = 2
❑ No = 0
❑ No data given = 0 (already scored under 3a)

   e. Were attempts in the analysis to adjust for imbalances between exposure groups with regard to potential confounding factors (e.g., through restriction, stratified analyses, or multivariate modelling)?

❑ Not needed (no important imbalances) = 0
❑ Yes = -2 (subtract 2 if you scored 2 under 3d)
❑ No, despite a need = 2

4. Evaluation of outcome, ascertainment / detection bias

   a. Was there an acceptable definition of the outcome?

❑ Yes = 0
❑ No = 3

   b. Was the outcome clinically relevant?

❑ Yes = 0
❑ Of questionable relevance = 2
❑ Irrelevant ➔ **study is deemed uninformative, excluded**

c. Were the evaluators of the outcome aware of exposure status of the cohort members?

❑ Yes = 1
❑ Probably = 1
❑ No = 0

d. Was there any reason to believe that there was important ascertainment / detection bias (*e.g., exposure linked to smoking, and smoking, in turn, linked to higher frequency of health care visits, and thus a more intense surveillance*)?

❑ Yes = 2
❑ No = 0

5. Losses to follow-up

a. Was there an account of the numbers of subjects who were lost to follow-up?

❑ Yes = 0
❑ No = 3

b. What proportion was lost to follow-up?

❑ <10% = 0
❑ 10-19% = 1
❑ 20-29% = 2
❑ 30-39 = 3
❑ ≥ 40% ➔ **study is deemed uninformative, excluded**
❑ Proportion not stated = 0 (scored under 5a)

6. Analysis

a. Was the main outcome variable defined in advance and was the conclusion of the study based on the analysis of this variable?

❑ Yes = 0
❑ No (or not mentioned in the report) = 1

b. Was there a prior hypothesis?

❑ Yes = 0
❑ No (or not mentioned in the report) = 1

c. Was the statistical method adequate?

❑ Yes = 0
❑ No = 3

<u>Total sum of Items 2-6 (internal validity)</u>:
0-1= Excellent internal validity
2-3 = Good internal validity
4-6 = Acceptable internal validity
7-9 = Uncertain internal validity
≥ 10 = Uninformative due to flawed internal validity

Precision

Short form answer:

❑ Premeditated and sufficient study size *(0)*
❑ Sample size of uncertain adequacy *(2)*
❑ Probably underpowered study *(4)*

If uncertain, answer questions under Items 7-8

7. Smallest clinically relevant effect

   a. Was the smallest clinically relevant effect defined?
   ❑ Yes = 0
   ❑ No = 1

   b. Was the stated smallest clinically relevant effect reasonable?
   ❑ Yes = 0
   ❑ No = 1
   ❑ Not defined = 0 (scored under 10a)

8. Study power

   a. Were the deliberations behind the sample size decision clearly described?
   ❑ Yes = 0
   ❑ No = 2

   b. What was the power to detect a reasonably-sized smallest clinically relevant effect?
   ❑ Not stated because there was a strong and statistically significant effect = 0
   ❑ ≥ 90% = 0
   ❑ 80-89% = 1
   ❑ 70-79% = 2
   ❑ <70% = 3
   ❑ Not stated despite a non-significant finding = 4

Total sum of Items 7-8 (precision)
0-1 = Premeditated and sufficient study size
2-3 = Sample size of uncertain adequacy
≥ 4 = Probably underpowered study

Section C (case-control or cross-sectional studies)

External validity

Short form answer:

❑ Clear external validity *(0)*
❑ Probable external validity *(1)*
❑ Uncertain external validity *(3)*
❑ External validity cannot be assessed *(5)*

If uncertain, answer questions under Item 1.
Otherwise go to Internal validity (after Item 1)

1. Type of cases studied

   a. Was there an acceptable definition of the outcome (*that rendered subjects case/control status*)?
   ❑ Yes = 0
   ❑ No = 2

   b. Did the studied cases correspond to cases <u>in the population to which the investigators wished to generalize their findings</u>?
   ❑ Yes = 0
   ❑ Yes, probably = 1
   ❑ No, probably not = 2
   ❑ No, definitely not = 3

<u>Total sum of section 1</u>:
0 = Clear external validity
1 = Probable external validity
2-3 = Uncertain external validity
≥ 4 = External validity cannot be assessed

Internal validity

Short form answer:

- ❑ Excellent internal validity *(0)*
- ❑ Good internal validity *(1)*
- ❑ Acceptable internal validity *(2)*
- ❑ Uncertain internal validity *(4)*
- ❑ Uninformative due to flawed internal validity *(10)*

If uncertain, answer questions under Items 2-6. Otherwise go to Precision (after Item 6)

2. Study base (*NOTE, not relevant to cross-sectional studies; if so, skip 2-3*)

The study base is defined as the group of people [the "virtual cohort"] who – if they developed the outcome condition – would necessarily have become cases in the study.

a. Was the study base (*the "virtual cohort" [a defined source population followed for a defined time period] that generated the cases*) well defined (geographically, age-wise, gender, other characteristics)?

- ❑ Yes, quite clear (*e.g., an already established cohort, or definition through an existing, well-functioning population register*) = 0
- ❑ Yes, reasonably (*e.g., hospital-based study with strict catchment areas and no important selections of cases or controls*) = 1
- ❑ Yes, probably (*e.g., hospital-based study without clear catchment areas, and/or inability to rule out some less important selection among cases and/or controls; control selection via random digit dialing or through neighbourhood controls whereupon some minor mismatch [for instance socioeconomic] between cases and controls might have occurred*) = 2
- ❑ No, it is impossible to tell if the cases and controls come from the same study base and if there are important selection mechanisms for either of these categories = 4

b. Are the cases representative of all cases <u>in the study base</u>?

- ❑ Yes, they represent all or virtually all new (incident) cases of the outcome that occurred in the study base = 0
- ❑ Yes, although it is difficult to tell if they represent *all* cases, there is no reason to suspect that they are unrepresentative of all cases in the study base = 1
- ❑ Yes, they represent prevalent cases in the study base, but there is no reason to suspect that they are unrepresentative = 1
- ❑ No, there are reasons to suspect that they are unrepresentative of all cases in the study base = 3
- ❑ No, definitely unrepresentative ➔ **study is deemed uninformative, excluded**

c. Do the control subjects come from the very same study base as the cases?

- ❑ Yes, definitely = 0
- ❑ Yes, probably = 1
- ❑ Uncertain = 3
- ❑ Probably not = 4
- ❑ No, definitely not ➔ **study is deemed uninformative, excluded**

d. Were the control subjects representative of the entire study base?

- ❑ Yes, they were selected randomly from a defined sampling frame (*note that stratified random sampling in order to achieve frequency matching is acceptable*) = 0
- ❑ Yes, probably, but they were selected in some other way = 1
- ❑ Uncertain = 3
- ❑ Probably not = 4
- ❑ No, the probability of being selected as control is linked to the subjects' exposure status ➔ **study is deemed uninformative, excluded**

3. Non-participation

a. Were *all* eligible cases occurring in the study base identified and enumerated?

- ❑ Yes = 0
- ❑ Yes, probably = 1
- ❑ No = 3

b. What was the participation rate among all eligible <u>cases</u>?

- ❑ ≥ 90% = 0
- ❑ 80-89% = 1
- ❑ 70-79% = 2
- ❑ 60-69% = 3
- ❑ 50-59% = 4
- ❑ <50% ➔ **study is deemed uninformative, excluded**
- ❑ Proportion not stated ➔ **study is deemed uninformative, excluded**

c. Was anything done to insure that major selection bias was not introduced through non-participation among cases?

- ❑ Not needed because participation among cases was >80% = 0
- ❑ Participation ≤ 80%, but authors provide data about non-participants that seem to rule out important selection bias = -1 (*subtract from sum*)
- ❑ Participation ≤ 80%, and no data is given about non-participants = 0

d. What was the participation rate among all selected <u>controls</u>?

- ❑ ≥ 90% = 0
- ❑ 80-89% = 1
- ❑ 70-79% = 2
- ❑ 60-69% = 3
- ❑ 50-59% = 4
- ❑ <50% ➔ **study is deemed uninformative, excluded**
- ❑ Proportion not stated ➔ **study is deemed uninformative, excluded**

e. Was anything done to insure that major selection bias was not introduced through non-participation among controls?

❑ Not needed because participation among controls was >80% = 0
❑ Participation ≤ 80%, but authors provide data about non-participants that seem to rule out important selection bias = -1 (*subtract from sum*)
❑ Participation ≤ 80%, and no data is given about non-participants = 0

4. Participation in <u>cross-sectional study</u> (*skip if regular case-control study*)
   ❑ ≥ 90% = 0
   ❑ 80-89% = 1
   ❑ 70-79% = 2
   ❑ 60-69% = 3
   ❑ 50-59% = 4
   ❑ <50% ➔ **study is deemed uninformative, excluded**
   ❑ Proportion not stated ➔ **study is deemed uninformative, excluded**

5. Exposure assessment

   a. How was exposure information collected?

   ❑ From existing databases with data obtained before cases developed outcome = 0
   ❑ Face-to-face or telephone interviews with interviewers blinded to case/control status = 0
   ❑ Face-to-face or telephone interviews where interviewers were aware of case/control status = 1
   ❑ Postal questionnaire = 2
   ❑ Other ways or not stated = 3

   b. Use of substitute responders

   ❑ No = 0
   ❑ ≤ 20% = 1
   ❑ >20% = 3

   c. Are there good reasons to suspect biased recall (*i.e., cases remember/report exposures systematically different compared to controls*)

   ❑ No = 0
   ❑ No, probably not = 1
   ❑ Uncertain = 2
   ❑ Yes, recall bias likely = 4
   ❑ Yes, high probability of recall bias ➔ **study is deemed uninformative, excluded**

6. Confounding

    a. Did the investigators consider all <u>important</u> potential confounding factors (*potential confounding factors = factors that are independent causes of / risk factors for / protective factors against the outcome, AND not a link in the causal chain between the studied exposure and the outcome*)?

❑ Yes = 0
❑ Probably = 1
❑ No = 3
❑ No data given = 4

    b. Were the relevant confounding factors satisfactorily measured / recorded?

❑ Yes = 0
❑ Yes, with minor criticism = 1
❑ No = 3

    c. Were attempts in the study design or analysis to identify and handle confounding factors (e.g., through matching, restriction, stratified analyses, or multivariate modelling)?

❑ Yes, adequately = 0
❑ Yes, but not sufficiently = 2
❑ No ➔ **study is deemed uninformative, excluded**

7. Ascertainment / detection bias

    a. Was there any reason to believe that there was important ascertainment / detection bias (*e.g., exposure linked to smoking, and smoking, in turn, linked to higher frequency of health care visits, and thus a more intense surveillance*)?

❑ Yes = 2
❑ No = 0

8. Rare disease assumption

    a. Was the rare disease assumption fulfilled (*the outcome affected less than 10% of the population in the study base*)?

❑ Yes = 0
❑ Unknown = 1
❑ No or probably not = 3 (*effects are likely exaggerated!*)

9. Analysis

    a. Was there a prior hypothesis?

❑ Yes = 0
❑ No (or not mentioned in the report) = 1

b. Was the statistical method adequate?
❑ Yes = 0
❑ No = 3

Total sum of Items 2-9 (internal validity) – CASE-CONTROL STUDY:
0-2= Excellent internal validity
3-4 = Good internal validity
5-7 = Acceptable internal validity
8-10 = Uncertain internal validity
≥ 11 = Uninformative due to flawed internal validity

Total sum of Items 2-9 (internal validity) – CROSS-SECTIONAL STUDY:
0-1= Excellent internal validity
2-3 = Good internal validity
4-5 = Acceptable internal validity
6-8 = Uncertain internal validity
≥ 9 = Uninformative due to flawed internal validity

Precision

Short form answer:

❑ Premeditated and sufficient study size *(0)*
❑ Sample size of uncertain adequacy *(2)*
❑ Probably underpowered study *(4)*

If uncertain, answer questions under Items 10-11

10. Smallest clinically relevant effect

a. Was the smallest clinically relevant effect defined?
❑ Yes = 0
❑ No = 1

b. Was the stated smallest clinically relevant effect reasonable?
❑ Yes = 0
❑ No = 1
❑ Not defined = 0 (scored under 10a)

11. Study power

a. Were the deliberations behind the sample size decision clearly described?

❑ Yes = 0
❑ No = 2

b. What was the power to detect a reasonably-sized smallest clinically relevant effect?

❑ Not stated because there was a strong and statistically significant effect = 0
❑ ≥ 90% = 0
❑ 80-89% = 1
❑ 70-79% = 2
❑ <70% = 3
❑ Not stated despite a non-significant finding = 4

Total sum of Items 10-11 (precision)
0-1 = Premeditated and sufficient study size
2-3 = Sample size of uncertain adequacy
≥ 4 = Probably underpowered study

Sektion E Diagnostiska studier

VALIDATION OF DIAGNOSTIC TEST (adapted from Whiting P et al BMC Med Res Methodology 2003)

A. External validity

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
   - ❑ Yes = 0
   - ❑ No = 1
   - ❑ Not stated / Unclear = 1

2. Were selection criteria clearly described?
   - ❑ Yes = 0
   - ❑ No = 1
   - ❑ Not stated / Unclear = 1

B. Internal validity

3. Is the reference standard likely to correctly classify the target condition?
   - ❑ Yes = 0
   - ❑ No = 1
   - ❑ Not stated / Unclear = 1

4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
   - ❑ Yes = 0
   - ❑ No = 1
   - ❑ Not stated / Unclear = 1

5. Did the whole sample or a random selection of the sample, receive verification using a reference standard?
   - ❑ Yes = 0
   - ❑ No = 1
   - ❑ Not stated / Unclear = 1

6. Did patients receive the same reference standard regardless of the index test result?
   - ❑ Yes = 0
   - ❑ No = 1
   - ❑ Not stated / Unclear = 1

7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
   - ❑ Yes = 0
   - ❑ No = 1
   - ❑ Not stated / Unclear = 1

8. Was the execution of the index test described in sufficient detail to permit replication of the test?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1

9. Was the execution of the reference standard described in sufficient detail to permit its replication?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1

10. Were the index test results interpreted without knowledge of the results of the reference standard?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1

11. Were the reference standard results interpreted without knowledge of the results of the index test?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1

12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1

13. Were uninterpretable/ intermediate test results reported?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1

14. Were withdrawals from the study explained?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1

C. Precision

15. Were the deliberations behind the sample size decision clearly described?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1

16. Was some measure of the variability given (e.g. 95% confidence intervals)?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1

17. Were the estimates reasonably precise?
- ❑ Yes = 0
- ❑ No = 1
- ❑ Not stated / Unclear = 1