Worksheet for Studies Related to Intervention/Therapy, Prognosis, Diagnosis

Worksheet author(s):	**Date submitted for review:**

Clinical question:

Is this question addressing:

□ Intervention/therapy
□ Prognosis
□ Diagnosis

Search strategy:

Resources	**Deails (please indicate specific names and keywords)**
□ e-databases (e.g. Medline)	
□ References of relevant articles & reviews	
□ Conference Proceedings	
□ Hand-searching unindexed journals	
□ Pharmaceutical & device manuacturers	
□ Experts in the fied	

Inclusion criteria:

Exclusion criteria:

Number of articles/sources meeting criteria for further review:
(Use Citation List and Summary of Evidence for guidance)

Reviewer's final comments and assessment of benefit/risk:

Conclusion:

Consensus on science:

Treatment recommendation (if applicable):

Reviewer's conflicts of interest:

Citation List

Reviewer should select the appropriate columns to fill up as some column(s) may not be applicable to certain types of references.

S/N	Citation	Description of subjects	Study design	Methods	Results	Conclusion & Recommendation	Evidence (use Summary of evidence)	Remarks (if any)
	Include date of publication, name of journal & citation	Include disease groups, sub-groups, population type (e.g. adults/paediatrics)	Include type (e.g. RCT, cohort study, etc)	Include intervention, primary/secondary outcomes, sample size, treatment arms, randomisation, blinding	Include key findings, statistical tests used etc	Authors' conclusion, and recommendations	State summary of evidence based on the below given C2010 Level of evidence table.	

Summary of Evidence

Please fill in the citations of reviewed study in the appropriate cell. You may wish to refer to C2010 Level of Evidence for to guide assessment.

How to grade a study?
Please refer to C2010 Level of Evidence for to the detailed questions asked to assess the quality of evidence. If the scoring criteria were not explicitly mentioned, the following should be used to guide assessment.

- Good studies = have most/all of the relevant quality items
- Fair studies = have some of the relevant quality items
- Poor studies = have few of the relevant quality items (**but** sufficient value to include for further review).

If a study has insufficient relevant quality items to even be classified as "poor" then that study should be excluded from further review.

Evidence SUPPORTING Clinical Question					
GOOD					
FAIR					
POOR					
	1	**2**	**3**	**4**	**5**
Level of Evidence					

Evidence NEUTRAL to Clinical Question					
GOOD					
FAIR					
POOR					
	1	**2**	**3**	**4**	**5**
Level of Evidence					

Evidence OPPOSING Clinical Question					
GOOD					
FAIR					
POOR					
	1	**2**	**3**	**4**	**5**
Level of Evidence					

C2010 Level of Evidence

Adapted from Quality assessment for individual studies to be used for the review of the resuscitation science for 2010 from C2010 Consensus Process
(Available at: http://www.heart.org/idc/groups/heart-public/@wcm/@private/@ecc/documents/downloadable/ucm_308201.pdf)

The Levels that are to be used are divided into three major categories, depending on the type of question being asked: intervention (Section A), diagnosis (Section B), or prognosis (Section C).

(A) Levels of Evidence for studies assessing interventions (LOEs 1 to 5)

C2010 Levels of Evidence for Studies of Therapeutic Interventions	
LOE 1	**Randomised Controlled Trials (or meta-analyses of RCTs)** These studies prospectively collect data, and randomly allocate the patients to intervention or control groups. <u>7 factors to consider for RCTs</u> *i. Was the assignment of patients to treatment randomised?* *ii. Was the randomisation list concealed?* *iii. Were all patients who entered the trial accounted for at its conclusion?* *iv. Were the patients analysed in the groups to which they were randomised?* *v. Were patients and clinicians "blinded" to which treatment was being received?* *vi. Aside from the experimental treatment, were the groups treated equally?* *vii. Were the groups similar at the start of the trial?* <u>6 factors to consider for meta-analyses of RCTs</u> *i. Were the specific objectives of the review stated [based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were specified]?* *ii. Was the study design defined?* *iii. Were the selection criteria stated for studies to be included (based on trial design and methodological quality)?* *iv. Were inclusive searches undertaken (using appropriately crafted search strategies)?* *v. Were characteristics and methodological quality of each trial identified?* *vi. Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?*
LOE 2	**Studies (including meta-analyses) using concurrent controls without true randomisation (e.g. "pseudo"-randomised)** These studies can be: ▪ Experimental - having patients that are allocated to intervention or control groups concurrently, but in a non-random fashion (including pseudo-randomisation: e.g. alternate days, day of week etc); or ▪ Observational – including cohort and case control studies <u>4 factors to consider for studies (both experimental and observational) using concurrent controls without true randomisation</u> *i. Were comparison groups clearly defined?* *ii. Were outcomes measured in the same (preferably blinded), objective way in both groups?* *iii. Were known confounders identified and appropriately controlled for?* *iv. Was follow-up of patients sufficiently long and complete?* For these studies it would be reasonable to consider the presence of all 4 factors = Good,

	only 3 factors = Fair, and only 2 factors = Poor. A study with only one factor would be considered of insufficient quality to include in the next step of the review. <u>6 factors to consider for meta-analyses of studies using concurrent controls without true randomisation</u> *i. Were specific objectives of the review stated (based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were specified)?* *ii. Was study design defined?* *iii. Were selection criteria stated for studies to be included (based on trial design and methodological quality)?* *iv. Were inclusive searches undertaken (using appropriately crafted search strategies)?* *v. Were characteristics and methodological quality of each trial identified?* *vi. Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?*
LOE 3	**Studies using retrospective controls** These studies use control patients that have been selected from a previous period in time to the intervention group. <u>4 factors to consider for studies using retrospective controls</u> *i. Were comparison groups clearly defined?* *ii. Were outcomes measured in the same (preferably blinded), objective way in both groups?* *iii. Were known confounders identified and appropriately controlled for?* *iv. Was follow-up of patients sufficiently long and complete?* For these studies it would be reasonable to consider the presence of all 4 factors = Good, only 3 factors = Fair, and only 2 factors = Poor. A study with only one factor would be considered of insufficient quality to include in the next step of the review.
LOE 4	**Studies without a control group (e.g. case series)** A single group of people exposed to the intervention (factor under study), but without a control group. <u>3 factors to consider for case studies</u> *i. Were outcomes measured in an objective way?* *ii. Were known confounders identified and appropriately controlled for?* *iii. Was follow-up of patients sufficiently long and complete?* For these studies it would be reasonable to consider the presence of all 3 factors = Good, only 2 factors = Fair, and only 1 factor = either Poor or of insufficient quality to include in the next step of the review.
LOE 5	**Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.)** LOE 5 to refer to studies that are not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.), and should have their methodological quality allocated to the methodology of the study. The suggested relevant quality criteria are: *i. Good = randomised controlled trials (equivalent of LOE 1)* *ii. Fair = studies without randomised controls (equivalent of LOE 2-3)*

	iii. Poor = studies without controls (equivalent of LOE 4) This would mean that a randomised controlled trial performed in a related population (e.g. stroke patients or animals), would be categorised as good quality LOE 5 study.

(B) Levels of Evidence for studies assessing prognosis (LOEs P1 to P5)

C2010 Levels of Evidence for Prognostic Studies	
LOE P1	**Inception (prospective) cohort studies (or meta-analyses of inception cohort studies), or validation of Clinical Decision Rule (CDR)** In a cohort study, outcomes for groups of people observed to be exposed to an intervention, or the factor under study, are compared to outcomes for groups of people not exposed. For a cohort study to be considered LOE P1, it should be an inception/prospective cohort study. In these studies, at study inception, the group of people (cohort) is either non-diseased or all at the same stage of the disease or where cohorts are observed at a point in time to be exposed or not exposed to an intervention (or the factor under study) and are followed prospectively with further outcomes recorded as they happen. Clinical Decision Rules (CDRs) are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category. For a study to be considered LOE P1, the CDR should be validated using a completely separate population (single or multiple) to that in which it was derived. <u>4 factors to consider for inception/prospective cohort studies, or for studies validating a Clinical Decision Rule</u> *i. Were comparison groups clearly defined?* *ii. Were outcomes measured in the same (preferably blinded), objective way in both groups?* *iii. Were known confounders identified and appropriately controlled for?* *iv. Was follow-up of patients sufficiently long and complete (e.g. >80%)?* For these studies it would be reasonable to consider the presence of all 4 factors = Good, only 3 factors = Fair, and only 2 factors = Poor. A study with only one factor would be considered of insufficient quality to include in the next step of the review. <u>6 factors to consider for meta-analyses of inception/prospective cohort studies</u> *i. Were specific objectives of the review stated (based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were specified)* *ii. Was study design defined?* *iii. Were selection criteria stated for studies to be included (based on trial design and methodological quality)?* *iv. Were inclusive searches undertaken (using appropriately crafted search strategies)?* *v. Were characteristics and methodological quality of each trial identified?* *vi. Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?*
LOE P2	**Follow-up of untreated control groups in RCTs (or meta-analyses of follow-up studies), or derivation of CDR, or validated on split-sample only**

	Clinical Decision Rules (CDRs) are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category. For a study to be considered LOE P2, the CDR can be either derived from a population, or validated using a split-sample (derived from part of population, and validated on rest of population). <u>4 factors to consider for studies involving follow-up of untreated control groups in RCTs, studies deriving a Clinical Decision Rule or studies validating a Clinical Decision Rule using a split sample</u> *i. Were comparison groups clearly defined?* *ii. Were outcomes measured in the same (preferably blinded), objective way in both groups?* *iii. Were known confounders identified and appropriately controlled for?* iv. *Was follow-up of patients sufficiently long and complete (e.g. >80%)?* For these studies it would be reasonable to consider the presence of all 4 factors = Good, only 3 factors = Fair, and only 2 factors = Poor. A study with only one factor would be considered of insufficient quality to include in the next step of the review. <u>6 factors to consider for meta-analyses of follow-up studies</u> *i. Were specific objectives of the review stated (based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were specified)* *ii. Was the study design defined?* *iii. Were the selection criteria stated for studies to be included (based on trial design and methodological quality)?* *iv. Were inclusive searches undertaken (using appropriately crafted search strategies)?* *v. Were characteristics and methodological quality of each trial identified?* vi. *Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?*
LOE P3	**Retrospective cohort studies** Where the cohorts (groups of people exposed and not exposed) are defined at a point of time in the past and information collected on subsequent outcomes. <u>4 factors to consider for retrospective cohort studies</u> *i. Were the comparison groups clearly defined?* *ii. Were outcomes measured in the same (preferably blinded), objective way in both groups?* *iii. Were known confounders identified and appropriately controlled for?* *iv. Was follow-up of patients sufficiently long and complete (e.g. >80%)?* For these studies it would be reasonable to consider the presence of all 4 factors = Good, only 3 factors = Fair, and only 2 factors = Poor. A study with only one factor would be considered of insufficient quality to include in the next step of the review.
LOE P4	**Case series** A single group of people exposed to the intervention (or factor under study). Only outcomes after the intervention (or factor under study) are recorded in the series of people, so no comparisons can be made. <u>3 factors to consider for case series</u> *i. Were outcomes measured in an objective way?* *ii. Were known confounders identified and appropriately controlled for?*

	iii. Was follow-up of patients sufficiently long and complete (e.g. >80%)? For these studies it would be reasonable to consider the presence of all 3 factors = Good, only 2 factors = Fair, and only 1 factor = either Poor or of insufficient quality to include in the next step of the review.
LOE P5	**Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.)** LOE 5 to refer to studies that are not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.), and should have their methodological quality allocated to the methodology of the study. The suggested relevant quality criteria are: *i. Good = randomised controlled trials (equivalent of LOE 1)* *ii. Fair = studies without randomised controls (equivalent of LOE 2-3)* *iii. Poor = studies without controls (equivalent of LOE 4)* This would mean that a randomised controlled trial performed in a related population (e.g. stroke patients or animals), would be categorised as good quality LOE 5 study.

(C) Levels of Evidence for studies assessing diagnosis (LOEs D1 to D5)

C2010 Levels of Evidence for Diagnostic Studies	
LOE D1	**Validating cohort studies (or meta-analyses of validating cohort studies), or validation of Clinical Decision Rule (CDR)** Validating cohort (prospective, observational) studies test the quality of a specific diagnostic test, based on prior evidence. Validation of a CDR (algorithms or scoring systems) leads to a prognostic estimation or a diagnostic category. For a study to be considered LOE D1, the CDR should be validated using a completely separate population (single or multiple) to that in which it was derived. <u>3 factors to consider for validating cohort (prospective, observational) studies, or studies involving validation of a Clinical Decision Rule</u> *i. Was the diagnostic test evaluated in an appropriate spectrum of patients (e.g. in those in whom it would be used in practice)? (Minimising "spectrum bias")?* *ii. Was there an independent, blind comparison with a reference ("gold") standard of diagnosis? (Minimising "review bias")* *iii. Was the reference standard applied regardless of the test result? (Minimising "verification bias")* For these studies it would be reasonable to consider the presence of all 3 factors = Good, only 2 factors = Fair, and only 1 factor = either Poor or of insufficient quality to include in the next step of the review. <u>6 factors to consider for meta-analyses of validating cohort studies</u> *i. Were specific objectives of the review stated? (Based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were specified)* *ii. Was study design defined?* *iii. Were selection criteria stated for studies to be included (based on trial design and methodological quality)?* *iv. Were inclusive searches undertaken (using appropriately crafted search strategies)?* *v. Were characteristics and methodological quality of each trial identified?*

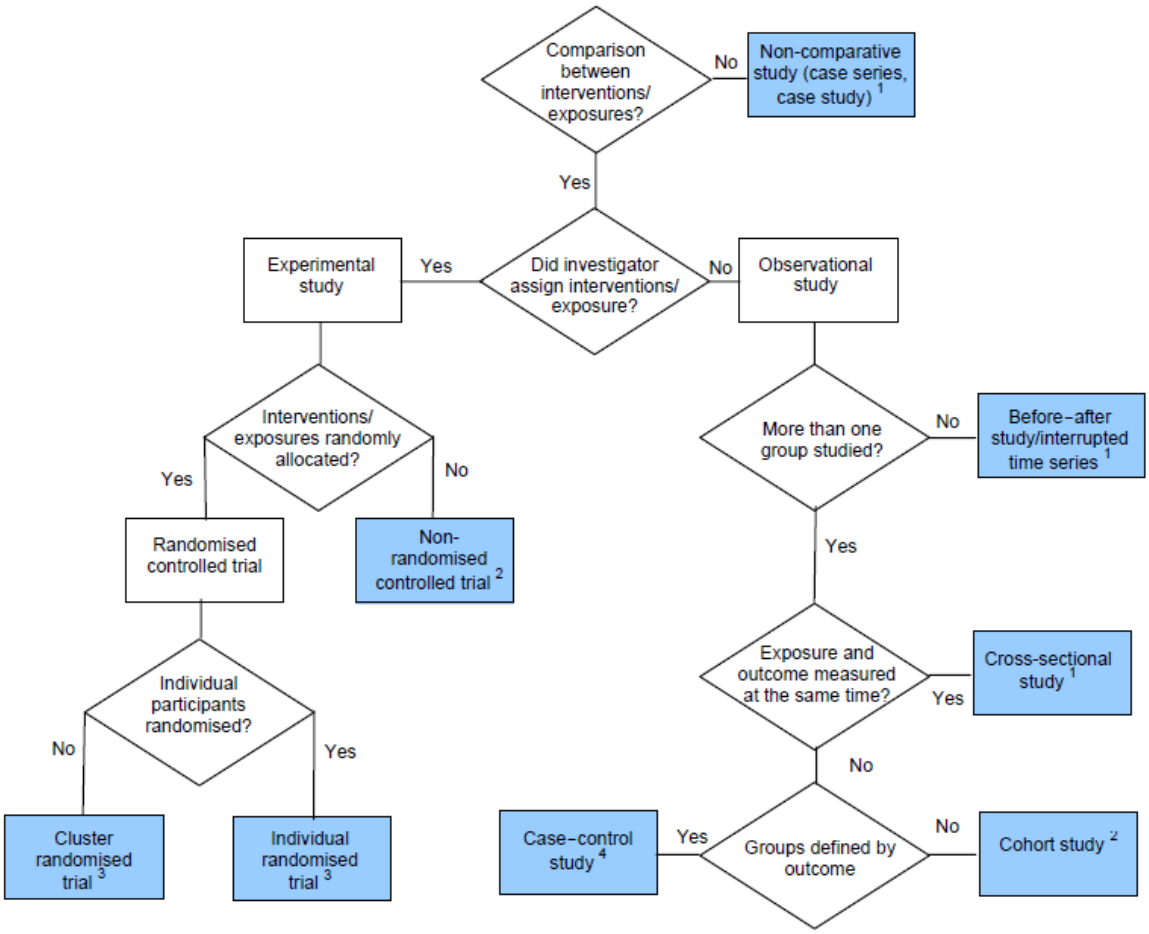
	vi. *Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?*
LOE D2	**Exploratory cohort study (or meta-analyses of follow-up studies), or derivation of CDR, or a CDR validated on a split-sample only** An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are "significant". A meta-analysis of such follow-up studies would also be considered LOE D2. Clinical Decision Rules (CDRs) are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category. For a study to be considered LOE D2, the CDR can be either derived from a population, or validated using a split-sample (derived from part of population, and validated on rest of population). <u>3 factors to consider for exploratory cohort studies, studies deriving a Clinical Decision Rule or studies validating a Clinical Decision Rule using a split sample</u> i. *Was the diagnostic test evaluated in an appropriate spectrum of patients (eg. in those in whom it would be used in practice)? (Minimising "spectrum bias")?* ii. *Was there an independent, blind comparison with a reference ("gold") standard of diagnosis? (Minimising "review bias")* iii. *Was the reference standard applied regardless of the test result? (Minimising "verification bias")* For these studies it would be reasonable to consider the presence of all 3 factors = Good, only 2 factors = Fair, and only 1 factor = either Poor or of insufficient quality to include in the next step of the review. <u>6 factors to consider for meta-analyses of follow-up studies</u> i. *Were specific objectives of the review stated? (Based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were specified)* ii. *Was study design defined?* iii. *Were selection criteria stated for studies to be included (based on trial design and methodological quality)?* iv. *Were inclusive searches undertaken (using appropriately crafted search strategies)?* v. *Were characteristics and methodological quality of each trial identified?* vi. *Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?*
LOE D3	**Diagnostic case control study** Diagnostic case-control study is a case control study that involves identifying patients who have the outcome of interest (cases) and patients without the same outcome (controls), and looking back to see if they had the exposure of interest. For a case control study to be considered as LOE D3, it must be a diagnostic case control study. In these studies, the index test results for a group of patients already known to have the disease (through the reference standard) are compared to the index test results with a separate group of normal/healthy people known to be free of the disease (through the use of the reference standard). In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called "spectrum bias" because the spectrum of study participants will not be representative of patients seen in practice.

	3 factors to consider for diagnostic case-control studies *i. Was the diagnostic test evaluated in an appropriate spectrum of patients (eg. in those in whom it would be used in practice)? (Minimising "spectrum bias")?* *ii. Was there an independent, blind comparison with a reference ("gold") standard of diagnosis? (Minimising "review bias")* *iii. Was the reference standard applied regardless of the test result? (Minimising "verification bias")* For these studies it would be reasonable to consider the presence of all 3 factors = Good, only 2 factors = Fair, and only 1 factor = either Poor or of insufficient quality to include in the next step of the review.
LOE D4	**Study of diagnostic yield (no reference standard)** These studies provide the yield of diagnosed patients, as determined by the index test, without confirmation of the accuracy of the diagnosis (i.e. whether the patient is actually diseased) by a reference standard test (index test). These may be the only alternative when there is no reliable reference standard. 3 factors to consider for studies of diagnostic yield *i. Were outcomes measured in an objective way?* *ii. Were known confounders identified and appropriately controlled for?* *iii. Was follow-up of patients sufficiently long and complete?* For these studies it would be reasonable to consider the presence of all 3 factors = Good, only 2 factors = Fair, and only 1 factor = either Poor or of insufficient quality to include in the next step of the review.
LOE D5	**Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.)** LOE 5 to refer to studies that are not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.), and should have their methodological quality allocated to the methodology of the study. The suggested relevant quality criteria are: *i. Good = randomised controlled trials (equivalent of LOE 1)* *ii. Fair = studies without randomised controls (equivalent of LOE 2-3)* *iii. Poor = studies without controls (equivalent of LOE 4)* This would mean that a randomised controlled trial performed in a related population (e.g. stroke patients or animals), would be categorised as good quality LOE 5 study.

These are all based on the principle that higher levels of evidence are allocated to studies that minimise the risk of bias, and all offer the opportunity to include studies that are not directly related to the question being asked (allowing extrapolation of information from different populations, animal studies etc).

Algorithm for classifying study design for questions of effectiveness

Taken from The Guidelines Manual 7 – Reviewing and grading the evidence by National Institute for Health and Clinical Excellence (April 2007) (Available at: http://www.nice.org.uk/niceMedia/pdf/GuidelinesManualChapter7.pdf)



Glossary

Adapted from Levels of Evidence used for the review of Resuscitation science for 2010 from C2010 Consensus Process
(Available at: http://www.heart.org/idc/groups/heart-public/@wcm/@private/@ecc/documents/downloadable/ucm_308199.pdf)

Case control study:
A case control study involves identifying patients who have the outcome of interest (cases) and patients without the same outcome (controls), and looking back to see if they had the exposure of interest.

Case series:
A single group of people exposed to the intervention (factor under study). Only outcomes after the intervention (factor under study) are recorded in the series of people, so no comparisons can be made.

Clinical Decision Rule
These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category. These can be derived, validated using a split-sample only (derived from part of population, and validated on rest of population), or validated using a separate population (single or multiple).

Cohort study
Outcomes for groups of people observed to be exposed to an intervention, or the factor under study, are compared to outcomes for groups of people not exposed.

Diagnostic case-control study:
The index test results for a group of patients already known to have the disease (through the reference standard) are compared to the index test results with a separate group of normal/healthy people known to be free of the disease (through the use of the reference standard). In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice. (Note: this does not apply to well-designed population based case-control studies.)

Exploratory study:
Collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

Inception/prospective cohort studies
At study inception the cohort is either non-diseased or all at the same stage of the disease or where groups of people (cohorts) are observed at a point in time to be exposed or not exposed to an intervention (or the factor under study) and then are followed prospectively with further outcomes recorded as they happen.

Randomised Controlled Trials:
These studies prospectively collect data, and randomly allocate the patients to intervention or control groups.

Retrospective cohort studies
Where the cohorts (groups of people exposed and not exposed) are defined at a point of time in the past and information collected on subsequent outcomes (e.g. the use of medical records to identify a group of women using oral contraceptives five years ago, and a group of women not using oral contraceptives, and then contacting these women or identifying in subsequent medical records the development of deep vein thrombosis).

Studies using concurrent controls without true randomisation:
These studies can be:

- experimental - having patients that are allocated to intervention or control groups concurrently, but in a non-random fashion (including pseudo-randomisation: e.g. alternate days, day of week etc), or
- observational – including cohort and case control studies

Studies using retrospective controls:
These studies use control patients that have been selected from a previous period in time to the intervention group.

Study of diagnostic yield:
These studies provide the yield of diagnosed patients, as determined by the index test, without confirmation of the accuracy of the diagnosis (ie. whether the patient is actually diseased) by a reference standard test (index test). These may be the only alternative when there is no reliable reference standard.

Validating cohort (prospective, observational) studies:
Test the quality of a specific diagnostic test, based on prior evidence.