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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

GUIDELINE

Endpoints used for Relative Effectiveness Assessment

Composite endpoints

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Adapted version (2015)

based on

"Endpoints used for REA of pharmaceuticals : Composite endpoints" – February 2013

The primary objective of EUnetHTA JA1 WP5 methodology guidelines was to focus on methodological challenges that are encountered by HTA assessors while performing a rapid relative effectiveness assessment (REA) of pharmaceuticals.

The guideline "Endpoints used in REA of pharmaceuticals: Composite endpoints" has been elaborated during JA1 by experts from THL and IQWiG, reviewed and validated by all members of WP5 of the EUnetHTA network; the whole process was coordinated by HAS.

During Joint Action 2 the wording in this document has been revised by WP7 in order to extend the scope of the text and recommendations from pharmaceuticals only to the assessment of all health technologies. Content and recommendations remained unchanged.

This guideline represents a consolidated view of non-binding recommendations of EUnetHTA network members and in no case an official opinion of the participating institutions or individuals.

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Acronyms – Abbreviations

CE: Composite endpoint

CI: Confidence intervals

COA: Clinical outcome assessment

HRQoL: Health related quality of life

HTA: Health technology assessment

PRO: Patient reported outcomes

REA: Relative effectiveness assessment

Summary and recommendations

Summary

This guideline provides a set of recommendations and aspects to be considered for the assessment and interpretation of results of composite endpoints while performing relative effectiveness assessments.

A composite endpoint (CE) consists of two or more single events combined in one outcome that should represent an overall clinically relevant and valid measure of clinical benefit due to treatment. It is possible to combine binary or time-to-event endpoints. Either the occurrence of any event from a given set of events is of interest, or the time to the occurrence of the first event. Composite endpoints usually refer to combined morbidity and mortality endpoints, it may also be a combination of objective (e.g. laboratory measurements) and subjective outcomes (e.g. pain); in this case, clinical relevance of overall results can be more difficult to interpret.

The main advantage of composite endpoints is a gain in statistical efficiency of a trial; because they facilitate higher event rates, the sample size needed for a clinical trial can be decreased, and length of clinical studies and costs reduced. In addition, the issue of multiple testing may be avoided.

The major limitation of composite endpoints is that they can be difficult to interpret and their incorrect interpretation may result in an overestimation of the effects of an intervention. In addition, it is often difficult to interpret results of composite endpoints in trials because of poor reporting and uncertain clinical relevance in many cases. The results can be also influenced by one of the components in relation to the other (e.g. in cardiovascular diseases: hospitalisations for an event vs. stroke or death).

The use of composite endpoints as primary endpoints is not recommended if a suitable single primary endpoint is available. A composite endpoint may be appropriate in cases where no single outcome is a suitable primary endpoint (e.g. some events in a given disease are of similar clinical importance), in case of very rare diseases/events, and for example, in the case of use of a combined safety endpoints.

When analysing results from a clinical trial using composite endpoints for a relative effectiveness assessment, assessors should pay close attention to the effects not only on the composite endpoint overall, but also on each component of the composite endpoint. If such data are missing or incomplete, then accurate interpretation of the trial data may be problematic. Assessors should check whether that definition of a composite endpoint is consistent with clinical recommendations and throughout trials, as well as the definitions of each component of a CE; in addition, the choice of components has to be pre-specified and fully justified. This justification should be based on medical grounds. Use of some clinician-reported or patient-reported outcomes that are subjective by nature together with objective measures is repeatedly done in clinical trials, even if it is a matter of debate. Some clinician-reported or patient-reported outcomes such as need for hospitalisation, or dyspnoea, are open for bias if studies are not conducted under double-blind conditions. In addition, use of patient reported outcomes in composite endpoints is more reliable if they have demonstrated content and psychometric validity as well as clinical relevance for the disease studied.

Components of a composite endpoint are considered as secondary endpoints. When assessing the appropriateness of the reporting of results from a clinical trial using composite endpoints, in addition to the effect observed on composite endpoint, effects on each component of composite endpoint should be reported separately in a clear and complete manner. Additionally, influence or effect size of each component of the composite endpoint on the overall treatment effect observed

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on the composite endpoint should be carefully assessed. Even then, the interpretation of the treatment effect may be problematic. In addition, in the context of REA, the same component of a composite endpoint (e.g. duration of hospitalisation) may be differently weighted in different countries.

Recommendations

Number	CE construction	References
1	Composite endpoints should generally not be used, if a suitable single primary endpoint is available. If a single primary endpoint is not available or if a composite endpoint can be justified to be more suitable (e.g. rare disease/event), it may be chosen instead.	1
2	There should be prior empirical and clinical evidence of the value of each chosen component for the composite outcome.	
3	The number of components of the composite endpoint should be limited to 3 or 4 in order to avoid problems in the analysis and interpretation.	
4	Trials using composite endpoints should follow CONSORT guidelines and report pre-specified primary and secondary endpoints to allow appropriate interpretation. Changes in the definition of a composite endpoint should not occur during the trial.	1,6,10,15,24
5	All components of a composite endpoint should be separately defined as secondary endpoints and reported with the results of the primary analysis.	10
6	Components of similar clinical importance and sensitivity to intervention should preferably be combined. Heterogeneity (mix of subjective and objective endpoints) should be avoided.	1,6, 11, 17
7	Inclusion of components in which influence of the intervention is known to be small or unlikely should be avoided. If adequate, mortality should however be included if it is likely to have a censoring effect on the observation of other components.	6
8	Composite endpoints can be used to assess not only effectiveness but also harms of a health technology.	3
	CE reporting	
9	Treatment effects should be reported on the CE at the first place. Results should also be reported for each component of a composite endpoint; in the way it contributed to the result within the composite endpoint. All results should be reported separately even if they lack statistical power. A list of results for all components should be provided in a table with confidence intervals.	1, 10
10	Separate components can be reported according to hierarchical levels, for example L1, all- cause mortality, L2, cause-specific mortality, L3, nonfatal clinical events, L4, symptoms.	2
11	In cases where the composite endpoint includes fatal and non-fatal events, it is recommended to report results on relevant combinations of components of the CE.	2
12	All data should be reported. The number of patients with partially missing values on some components should be reported in detail.	1
13	If there are relevant subgroups or special patient populations at risk (such as elderly, or patients with renal failure), results should be provided for these subgroups.	
	Analysis and synthesis of the evidence from CE studies in REA	
14	Treatment effects should be interpreted based on the CE at the first place. However, treatment effect on teach component of a composite endpoint in the way it contributed to the result within the composite endpoint should also be analyzed to assess whether an intervention had similar effects on all endpoint components.	
15	It is recommended to check that clinically important components of the	17

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	composite endpoint are not affected negatively by the treatment, as some treatments may have negative effect on one component which can be masked by a large beneficial effect of the remaining components. In these cases it may not be possible to conclude that the treatment has a clinically relevant effect on the composite endpoint as a whole. It should be stated and/or identified by the REA process which component is mainly responsible for the overall effect	
16	If valid and comparable composite endpoints from several studies are available, consider basing the overall conclusion on a meta-analysis.	
17	If – according to this table there is a single relevant problem or a significant accumulation of problems associated with a given CE, considerable uncertainty concerning the validity of study results has to be concluded. The position of this study in the hierarchy of evidence and its usefulness for REA will have to be downgraded.	

1. Introduction

1.1. Definitions and general information

Composite endpoints (CE) combine two or more single endpoints in one outcome to demonstrate overall treatment effects. Patients who have experienced any of the events specified by the components are considered to have experienced the composite endpoint (1, 2). Composite endpoint usually refers to combined morbidity and mortality endpoints; it may also be a combination of patient-reported, observer reported or clinician reported measures. Patient-reported outcomes are collected directly from the patient, by using simple scales or multi-domain questionnaires (3, 4).

1.2. Context

1.2.1. Problem statement

What are the advantages and limitations of composite endpoints from the standpoint of relative effectiveness analysis (REA)? How can methodological pitfalls related to the use, interpretation and assessment of composite endpoints be minimized?

1.2.2. Discussion

The main reason for use of composite endpoints is to increase event rate and decrease sample size so that trials can be conducted in a timely fashion. A recent systematic review showed that individual components of composite endpoints are often unreasonably combined, inconsistently defined and inadequately reported (1).

Since composite endpoints are increasingly used in clinical trials; assessors dealing with such research findings should be aware of both the advantages and limitations of using composite endpoints**.** Special attention should be paid to the definition of composite endpoints and of each of the individual components; results for each component should also be reported separately.

The methodological issues related to the use of composite endpoints are discussed.

1.3. Scope/Objective(s) of the guideline

This guideline is intended to describe the advantages and disadvantages of the use of composite endpoints as opposed to single endpoints and offer guidance for assessors with regard to construction, reporting and interpretation of the results of composite endpoints in the context of REA. The guideline has been developed during Joint Action 1 for REA of pharmaceuticals. During Joint Action 2 the wording of this document has been slightly changed by WP7 to extend the scope of text to non-drug interventions.

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The guideline is based on systematic review of the literature and on assessors experience while performing REA.

1.4. Related EUnetHTA documents

This guideline should be read in conjunction with the following documents:

EUnetHTA guideline on Endpoints used in REA: Clinical endpoints
EUnetHTA guideline on Endpoints used in REA: HRQoL
EUnetHTA guideline on Endpoints used in REA: Surrogate endpoints

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2 Analysis and synthesis of literature

2.1 Characteristics

Composite endpoints combine two or more single events in one outcome showing the overall treatment effects. The number of components of the composite endpoint is recommended to be limited to 4 in order to avoid difficulties in the interpretation of the results.

The choice of components will depend on the main characteristics of a disease (life-threatening or non life-threatening, type of occurring events) and the main objective of a trial.

In general, the components of composite endpoints may be clinical events (such as birth, death, stroke, convulsions) or different types of measures presented as events (binary variables) or measures reported by clinicians (clinician-reported outcomes, ClinRO), patients (patient-reported outcomes, PRO), or caregivers (observer reported outcomes, ObsRO), that may be either subjective (e.g. symptoms such as pain, pruritus, insomnia), or objective in nature (laboratory tests/measurements, clinical events). In this context, the assessment of some clinician-reported or patient-reported outcomes (such as need for hospitalisation or dyspnoea) may be open for bias if studies are not conducted under double-blind conditions.

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Patients who have experienced any one of the single events specified as the components are considered to have experienced the composite endpoint (1, 2). Nevertheless, patients should be monitored until the end of the follow-up period to determine whether they experience other components of the composite endpoint or the qualifying event for the second time.

Composite endpoints are increasingly used in clinical trials, especially in cardiovascular trials; in a systematic review 73% of the trials reporting composite endpoints were related to cardiovascular interventions (1,5). For example, in trials assessing treatment effects on the reduction of major cardiovascular events, the commonly used composite endpoint includes all-cause mortality, non-fatal myocardial infarction, stroke, hospitalizations and revascularization procedures. In addition, composite endpoints have been used in rare diseases where single endpoints are too rare or occur too late and therefore are not sufficiently informative. The use of composite endpoints can be considered if it allows for better assessment of overall benefit of the intervention than a single endpoint.

2.2 Why are composite endpoints used?

Composite endpoints are used to increase the overall event rates, reduce the sample size of the trials, achieve desired power, shorten the study duration and thereby obtain timely answers to clinically important questions (6, 7). Reduction in the number of patients necessary in a study to detect a significant treatment effect is a major advantage. For example, if an outcome is expected to occur at a 5% annual rate and the trial is planned to last five years, more than 2500 patients are needed to show a statistically significant hazard ratio of 0.75 with $p<0.05$ (8). But if single outcomes can be combined into a composite endpoint that has an annual rate of 20%, fewer than 800 patients will provide adequate power. Furthermore, there is less need for adjustment for multiple comparisons than is usually necessary when several single endpoints are studied.

The number of single events appears to decline due to improved treatments of a disease and better health of the population in general. Therefore trials including very large number of patients are needed in order to identify small differences between treatments (9). Composite endpoints help overcome this problem by combining a number of different events. Furthermore, trials are

becoming increasingly difficult to conduct due to competition for resources. It is also important that results are available for clinical use without much delay so that effective treatments become available within a reasonable time frame.

Composite endpoints may be suitable in cases when no single event is an adequate primary endpoint by itself (10). Furthermore, the use of composite endpoints avoids the problem caused by arbitrary selection of a primary endpoint in cases where there are a number of equally important endpoints (e.g. cardiovascular death/myocardial infarction/stroke in trials of antiplatelet drugs; deep venous thrombosis/pulmonary embolism in trials of anticoagulants). Selection of the primary endpoint depends on the assessed health technology, clinical relevance of the outcome and in some cases costs and convenience. In some cases composite endpoints are used to balance the positive and negative effects of an intervention (e.g. reduction of cardiovascular events and increase in bleeding events). In such cases it is of special interest to assess whether the single events are of comparable clinical importance.

A general health technology assessment (HTA) process during REA may be supported through the conduct of meta-analyses of treatment effects based on single components of CEs for which individual clinical trials are not powered. This of course requires consistent definitions and the reporting of the single component's results.

Advantages of using composite endpoints	References
Statistical efficiency, reduced sample size requirements.	7,9,11,12,13
Increased events rates.	7,9,12,13
Resource implications.	8,9
Avoiding arbitrary choice of a single outcome when many may be of equal importance.	7,9,11
Avoiding adjustments for multiple comparisons.	7,11,14
Estimates the net clinical benefit of the health technology.	7,13
Effective treatments will be made available in a timely manner.	14

2.3 Drawbacks of composite endpoints for relative effectiveness assessment

Clinical relevance of a treatment effect estimated using a composite endpoint may be difficult to interpret. The most frequently quoted problem is the risk of misinterpretation when there is heterogeneity of response among components of composite endpoints (3, 4, 7). In some situations the overall positive effect may be related to the less clinically relevant component(s) of the composite measure (i.e. less important outcomes may account for the majority of events). It has been shown that the effect is often much lower for the most relevant components (such as death) and larger for the less important components (such as distal thrombosis rate in trials with anti-thrombotic drugs) or potentially biased clinician-driven events (such as revascularization or hospitalization) (1). Therefore, the interpretation of composite endpoints currently used in some cardiovascular trials may lead to inadequate conclusions (15).

The selection and interpretation of some components of a composite endpoint has been shown to be problematic and methodologically flawed (7, 14, 15, 16) as studies are frequently not powered to show differences in individual components of a composite endpoint. On the other hand, if the effect on a composite endpoint is mostly driven by an effect on one of the components, it is not admissible to conclude that the treatment has an equal or important effect on all the components. This has been demonstrated by several systematic reviews of studies using CEs (1, 7). Meta-analyses have increased importance in demonstrating significant treatment effects on components.

If the effects of treatment on the individual components differ either quantitatively (i.e. size of effects) or qualitatively (i.e. the direction of effects), treatment effect based on a composite

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endpoint will be difficult to interpret (11,19). One concern is that the treatment under study may have adverse effect on one or more components which are not shown by the composite endpoint due to large "masking" beneficial effects on the remaining components (17). For this reason, it is recommended that each individual component be analyzed separately as secondary endpoint to ensure that the effects on one component is not negating the effects of another (18).

In addition, it often is difficult to give a definition of "responder" based on a composite endpoint, as responder definitions are usually validated for single endpoints.

There may be a different importance to each component of a composite endpoint. Clinician-driven endpoints such as elective revascularization are easy to measure, and frequently preferred as components of a composite endpoint, but might not be very relevant for patients, and prone to bias if study is not double-blind (4,9). In some cases, patient-reported outcomes, assessed by validated tools (such as VAS for pain), may be useful in the interpretation of the overall effect observed on a composite endpoint. HRQoL, a multi-dimensional multi-item concept assessing different aspects of patients' QoL, is not an appropriate component of a composite endpoint.

In general, the combination of objective and subjective components should be avoided (see recommendation6) to minimize problems with the interpretation of results. In some rare diseases (e.g. pulmonary arterial hypertension), use of such combined endpoints could be justified but has to be done in an explicit manner.

A systematic literature review showed that changes in the definition of composite endpoints during a trial are common and are a source of biased reporting (1). It is recommended that trials using composite endpoints follow CONSORT guidelines and report pre-specified primary and secondary endpoints to allow appropriate interpretation. Changes in the definition of composite endpoints during a trial should not occur. These changes may only be justified in rare and pre-specified circumstances, e.g. for trials running over many years in case of a new evidence showing that a chosen endpoint is no longer appropriate. Then changes are only possible before interim analyses or unblinding of the trial.

Another disadvantage of dealing with composite endpoints in systematic reviews arises when the components of composite endpoints of reviewed trials vary for the same disease and similar intervention. In this case a meta-analysis might not be possible. This also applies to indirect comparisons when two health technologies are compared for their therapeutic value in absence of a head-to-head trial. When definitions of individual components of the composite endpoints are not identical, the results of such analysis could be biased. A possible solution might be the use of the individual components of the composite endpoint to compare the treatments. However, there may be issues associated with statistical power (if the number of events is too low).

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Disadvantages of composite endpoints for the interpretation of study results	References
Components are often unreasonably combined, inconsistently defined and give opportunity for post-hoc changes.	1
Improvement can be driven by less important component(s) of the composite endpoint and this would not support a claim based on the whole composite endpoint.	4,7
Effects observed on separate components of a composite endpoint may not be in the same direction. In this case, it will be difficult to explain the overall effect observed on the composite endpoint.	1,7
Inclusion of unresponsive components may reduce the effect of the composite outcome.	9
Clinician driven endpoints may be prone to bias (e.g. elective revascularization, admission to a hospital).	1
Possible lack of relevance of some components of a composite endpoint for patients, since not all patients attach similar importance to each component.	9,19
Alpha error must be adjusted to perform statistical inference on the components.	7

2.4 Statistical considerations related to the use of composite endpoints

Multiplicity: Composite endpoints have been used to reduce the multiplicity problems related to multiple separate endpoints (4, 17). The need to adjust for multiple comparisons is removed (7, 11).

Missing data considerations:

If a patient has missing data on some of the components but not all, according to the intention-to-treat principle this patient should be included in the analysis of the composite endpoint. The intent-to-treat analysis may therefore be a flawed estimation of the true effect of the treatment. Exclusion due to missing data may lead to inconsistent estimates of the true effect (20). There is therefore no single way to analyze the data in the presence of patients with partially missing data. The chosen approach should match the type of data and therapeutic area. But even if it becomes more complicated in the case of composite endpoints, the general principles are the same as for single endpoint studies. The situation is frequently encountered when mortality is included in a composite endpoint, because mortality can be assessed through administrative inquiry at study endpoint, which is not the case for non-fatal components.

Statistical analysis:

Besides the main statistical analysis of the composite endpoint, studies involving CEs that are most useful for REA include

- the analysis of each component as it counts in the composite endpoint (first event of the composite for a given patient), which may require methods for competing risks (23)
- the analysis of each component independently of its role in the component (notwithstanding a previous occurrence of another component)

If valid results on comparable composite endpoints from several studies are available, assessors could handle this information in the following ways:
- if reported composite endpoints are defined in the same way, an overall conclusion, e.g. drawn by means of meta-analytic approaches, can be considered.
- if the definitions of the composite endpoints are different, one can either assess components of the composite endpoints that are defined in the same way, or, if this is not possible, assess each composite endpoint individually.

Some additional aspects have to be considered, for example, results for individual components of the composite endpoints might be negligible when no events, or only a few, are recorded. This has to be judged separately for each assessment.

In case of heterogeneity (e.g. the effect on the composite is driven by the effect on one of its components), it may be very difficult, or impossible to interpret the results. It is tempting then to draw conclusions based on the component which dominates (i.e. is associated with the largest treatment effect), but there is a risk that the power is insufficient for that component alone.

3. Discussion

If composite endpoints are used while performing REA, each of the individual components should be clinically relevant to the disease and health technology being assessed. When composite endpoints are used as primary outcomes, the overall effect of treatment should be first interpreted based on CE (11, 21). Nevertheless, the results for each individual component

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should also be analysed to check whether treatment effects are consistent. This might also allow the use of components in meta-analyses. It is advisable to report pre-specified descriptive and inferential statistics and it is also recommended to report results for combinations of components of a composite endpoint considered to be clinically relevant (e.g. stroke and myocardial infarction). Reporting of all possible combinations of components of a composite endpoint is inappropriate and confusing (12) (for example, with a composite of 4 events, it is possible to define 10 partial combinations of 2 or 3 events).

There are differing points of view as to whether or not composite endpoints should be composed of equally important components. Usually the necessity of equal importance is emphasised (1, 6, 11, 17). Evidence shows that the way results are reported can mislead readers into believing that all components are equally important, even though they may range from events such as dyspnoea or hospitalisation to death (1, 2). It has been argued that it would be clearly unrealistic to expect each component to occur at the same rate or to be equally severe (8, 14). Further, less severe events may carry information for a more severe one that has not yet been observed. Composite endpoints can provide a valuable holistic measure of outcome in that they can incorporate relevant clinical and patient-based aspects of a disease process.

Death is usually considered as the most important event and should therefore be included in a composite endpoint where relevant (i.e. life-threatening diseases). However this might cause problems in some diseases if it occurs relatively infrequently and is associated with the smallest treatment effects (1, 2).

4. Conclusion

When there is no one primary endpoint that can adequately reflect the overall effect of a treatment, the use of composite endpoints in clinical trials can prove helpful in the evaluation of health technologies. However, the measurement properties of each component should be taken into account as well as their relative influence on the composite endpoint itself. The problem of appropriate reporting and interpretation of results remains (7, 12, 15, 22). The greatest risk for assessors when composite endpoints have been used is the conclusion that a treatment confers a greater benefit than it is really the case, as can occur when a large effect on a relatively minor component dominates (1, 6). It should also be noted that a large effect on a composite endpoint does not imply that similar large effects are to be expected on each component separately

In the selection of the primary composite endpoint for a study, it is important that the composite endpoint is capable of providing the most clinically relevant evidence of treatment effect directly related to the primary objective of the trial (10).

Death has been usually considered to be the most important outcome and therefore should be included in composite endpoint when relevant (in life-threatening diseases). However, issues such as predicted event rate have to be taken into account, (24) and therefore some form of weighting of components might be necessary.

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Annexe 2: Methods and results of literature search (conducted during JA 1)

Keywords for search

Keywords that were used for the bibliographic search: * represents a truncation of the respective search term

Composite endpoint(s) Endpoint Determination
Endpoint Determination/methods, standards*
Randomized controlled trials as topic
"Outcome Assessment (Health Care)"
Epidemiologic study characteristics as topic

Sources of information

Data-bases

Ovid Medline (including Medline),
Cochrane Database of Systematic Reviews,
Cochrane Methodology Register,
Cochrane Central Register of Controlled Trials,
University of York Centre for Reviews and Dissemination (CRD) databases)

Websites

European Medicines Agency, EMA
Food and Drug Administration, FDA
National Institute for Health and Clinical Excellence, NICE
Pharmaceutical Benefits Advisory Committee, PBAC.

Bibliographic search strategy

The search was limited to studies in English published between January 1st 2000 and August 3rd 2010. The following strategy was applied for Medline but modified for other sources:

1 endpoint determination/mt
2 endpoint determination/st
3 *Endpoint Determination/
4 OR/1-3
5 (composite adj2 endpoint*).ti.
6 (composite adj2 end point*).ti.
7 (composite adj2 outcome*).ti.
8 OR/5-7

In Medline search also:

9 randomized controlled trials as topic/

10 exp "Outcome Assessment (Health Care)"/
11 exp epidemiologic study characteristics as topic/
12 or/9-11
13 8 AND 12
14 4 AND 12
15 OR/13-14
16 (news or letter or comment or editorial or interview).pt.
17 15 not 16
18 limit 17 to yr="2000-current"

Selection criteria

In the selection of relevant literature an emphasis was put on guidelines and studies including methodological aspects. Letters, editorials and comments were accepted. The Medline search provided 342 references of which 53 included “composite endpoint” or “composite outcome” and out of those 40 were found to be relevant for the outcomes. Cochrane Methodology Register provided another 3 relevant publications.

Drug or disease specific studies and guidelines were excluded if they did not include methodological aspects.

Literature search results

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