Abstract
This is the protocol for the systematic review of outcome measures used in early phase critical care trials.
# TABLE OF CONTENTS

1. **BACKGROUND** ........................................................................................................................................... 2  
   DESCRIPTION OF THE ISSUE .......................................................................................................................... 2  
   WHY IT IS IMPORTANT TO DO THIS REVIEW .................................................................................................. 7  

2. **OBJECTIVES** ............................................................................................................................................. 8  
   REVIEW QUESTION(s) ...................................................................................................................................... 8  

3. **METHODS** .................................................................................................................................................. 8  
   CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW ...................................................................... 8  
   Types of study to be included ......................................................................................................................... 8  
   Types of participants ..................................................................................................................................... 8  
   Types of outcome measures .......................................................................................................................... 9  

4. **SEARCH METHODS** .................................................................................................................................. 9  

5. **DATA COLLECTION AND ANALYSIS** ....................................................................................................... 9  
   Study Selection ............................................................................................................................................... 9  
   Data extraction ............................................................................................................................................. 9  
   Assessment of reporting biases ...................................................................................................................... 10  
   Information synthesis .................................................................................................................................... 10  
   Dissemination plans ....................................................................................................................................... 10  

6. **ACKNOWLEDGEMENTS** ............................................................................................................................ 10  

7. **REFERENCES** .......................................................................................................................................... 10  

8. **APPENDIX** ............................................................................................................................................... 10  
   APPENDIX A. SEARCH TERMS ....................................................................................................................... 0  
   APPENDIX B. OUTCOME EXTRACTION FORM FOR SYSTEMATIC REVIEW ....................................................... 0
1. BACKGROUND

Description of the Issue

Clinical trials are planned experiments in human beings. A well conducted randomized controlled trial (RCT) is deemed as the gold standard of clinical trials because RCTs are meticulously planned in order to determine the cause-effect relationship between intervention and outcome. In RCTs, patients who agreed to take part in the experiment are randomly allocated to intervention arm or control arm. An intervention can be described as a process or action which is considered to improve a particular condition or situation. For example drugs, medical devices, procedures, vaccines, education, can be considered as interventions. Archie Cochrane (1972) defined three concepts related to testing healthcare interventions; (i) Efficacy- Does the intervention show benefit under ideal circumstances (“Can it work?”), (ii) Effectiveness- Does the intervention show benefit in usual medical practice (“Does it work in practice?”) and (iii) Efficiency- Effect of the intervention based on resource utilisation (“Is it worth it?”) (Haynes 1999). The efficacy, effectiveness and efficiency of the interventions are measured by the careful selection of outcomes that are influenced by the intervention.

RCTs were developed essentially to test pharmacological interventions or drugs (Boutron, Tubach et al. 2003). Clinical studies can be classified as human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use based on the objectives (Guideline 1997). Purpose of this review is whether the outcome measures in early phase studies can actually predict the late phase trial outcomes. That is, (for example) whether the effect size based on 28 day mortality can actually predict 90 day or long term mortality. Outcome measures generated from the systematic review will be analysed determine whether short term outcomes can predict long term trial outcomes (trial level).

The selection of outcomes measures in a clinical trial is very important because these measures will affect the size of intervention effect, sample size and overall trial. A poorly designed trial can cause two types of errors 1) Type 1 error- showing that the intervention is beneficial when it is not and 2) Type 2 error - showing that the intervention is not beneficial when it is actually beneficial (Rubenfeld, Abraham 2008). Type 1 error is considered very serious as the patients will be exposed to more harm or less effective treatment compared to the standard treatment. The type II error will be serious if there is no treatment available for a
particular condition and an effective treatment was rejected due to the choice of the outcome measure.

Outcome measures used in critical care trials can be broadly classified as clinical endpoints, or surrogate outcome measures. The National Institute of Health (NIH) Definition Working Group defines ‘clinical endpoint’ as “a characteristic or variable that reflects how a patient feels, functions or survives.” and ‘surrogate endpoint’ as “a biomarker intended to substitute for a clinical end point that should predict clinical benefit or harm or lack of both (De Gruttola, Clax et al. 2001). A clinical investigator uses epidemiologic, therapeutic, pathophysiologic, or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or harm (De Gruttola, Clax et al. 2001). A composite outcome measure combines two or more components (surrogate and or clinical endpoint), and patients who experience at least one of the component events are considered to have experienced the composite outcome (Schoenfeld, Bernard 2002).

Clinical Endpoints

Clinical endpoints are clinically relevant or patient-centred, for example mortality or survival. These endpoint measures often require longer follow-up over time and a larger number of patients to obtain sufficient numbers who meet the endpoint. Thus, the use of a patient-centred outcome can make trials very large, difficult to run, involve a lot of time and financial resource. These endpoints are the ideal primary endpoints of a confirmatory trial or phase III trial (Gluud, Brok et al. 2007). Use of clinical endpoints in early phase trials are generally not feasible due to time and financial limitation pressures which are characteristic of these trials. Therefore in early phase trials surrogate outcome measures are generally used because they can deal with the issue of rejecting an effective intervention and can also speed up the process of drug development.

Surrogate Endpoints

A surrogate outcome is a measurement of a specific outcome which is considered to be a valid predictor (or representative) of the clinical endpoint or final result. It is a factor or a covariate that is known (or highly suspected) in the causal pathway of the long term outcome or clinical endpoint. For example, in heart disease, cholesterol is considered as a surrogate outcome measure and mortality is the clinical endpoint because hypercholesterolemia is
positively associated with mortality. Similarly, in an HIV infection, the CD4 count is a surrogate measure and the clinical endpoint is mortality. Selection of these surrogate outcome measures make trials simpler, faster and cheaper because the response occurs soon after the intervention is delivered compared to clinical endpoint. The term ‘intermediate outcome measure’ is considered as a synonym for surrogate measure; it implies that all the intervention effect on the clinical endpoint should be mediated through the surrogate measure. However surrogate measures may not be an intermediate step in the intervention to disease causal pathway. Hence the term intermediate measure can be misleading (Gøtzsche, Liberati et al. 1996). Because of that reason scientific validity of the estimates based on surrogate measures can be questioned. However, for a surrogate measure to be valid, all the intervention effect on the clinical endpoint should be mediated through the surrogate measure (see figure 1). The terminology of “surrogate endpoint” is avoided here on the basis that they are not endpoints but outcome measures which can predict a clinical endpoint or a true endpoint.

A surrogate measure should aid the diagnosis of the disease, be able to predict the clinical endpoint and also be able to monitor the response to the intervention. Surrogate outcome measures can be useful in early phase screening trials for identifying whether an intervention is biologically active, for guiding decisions and also whether the intervention is promising enough to justify a large definitive trial with clinically meaningful outcomes.

An ideal surrogate outcome measure should mediate all mechanisms of action to the clinical endpoint.

![Figure 1. Surrogate Outcome Measure](adapted from Fleming, DeMets 1996)

Validation of surrogate outcome measures are often overlooked. Use of non-validated outcome measures to inform drug trials, especially in confirmatory trials, can cause serious
ethical issues. For example, the Food and Drug Administration (FDA) approved encainide, flecainide and moricizine drugs as they effectively suppressed cardiac arrhythmias. The Cardiac Arrhythmic Suppression Trial: CAST I in 1989 and CAST II in 1992, hypothesised that suppression of ventricular arrhythmias by antiarrhythmic drugs after myocardial infarction would improve survival". The study looked at the association between arrhythmias (surrogate) and the mortality (clinical endpoint) and confirmed that the drugs effectively suppressed asymptomatic ventricular arrhythmias, but increased arrhythmic deaths (Greene, Roden et al. 1992, Ruskin 1989). This is a case where by the surrogate outcome measure did not mediate the mechanism of action to the clinical endpoint.

Fleming and DeMets (1996) explained four different pathways of an invalid surrogate;

![Diagram of surrogate measures](image)

**Figure 2.** A. The surrogate is not in the causal pathway of the disease process. B. Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate. C. The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect. D. The intervention has mechanisms of action independent of the disease process. Dotted lines = mechanisms of action that might exist. (adapted from Fleming, DeMets 1996)

Figure 2 shows the reasons for the failure of a surrogate measure. Firstly, the surrogate measure may be correlated with the clinical endpoint; however the surrogate outcome
measure might not involve the same pathophysiologic process that results in the clinical endpoint (2A). The other scenario is that the surrogate has a similar pathologic process, but some disease pathways are not mediated through the surrogate outcome measure. The intervention may only affect the pathway mediated through the surrogate endpoint (2B) and in some cases the effect of the intervention is in the pathway or pathways independent of the surrogate outcome measure (2C). The intervention may have several complex pathways to the clinical endpoint and the surrogate endpoint may only be in one of these pathways. The pathways may be poorly understood and the intervention mediated through the surrogate may be significantly affected by other complex mechanisms. Therefore, the same intervention can yield different results at a different time due to the complexity of the pathways (Fleming, DeMets 1996). Proper validation of the surrogates requires an in-depth understanding of the causal pathway of the disease process as well as the intervention mechanisms of actions (Fleming, DeMets 1996).

Composite Outcome Measures

Composite outcome measures have a median (range) of 3 (2-9) components (Cordoba, Schwartz et al. 2010). If a patient experiences one of the component events, he/she is considered to have experienced the event of interest, which means an increased event rate. For example, consider that event of death or myocardial infarction is the components of the composite outcome measure. A patient experiencing myocardial infarction or death or both is considered to have the events. This will increase the event rate and reduce the sample size required to detect a significant difference between groups. For example, ventilator-free days (VFD) score is a popular outcome measure used in the critical care setting. VFD combines duration of ventilation (surrogate) and mortality (clinical endpoint) and produces a score based on days alive and free from mechanical ventilation typically recorded within a defined time period such as 28-days (Yudkin, Lipska et al. 2011). If the patients comes off the ventilator at day 10 and was alive at day 28, the patient gets a score of VFD score 18. One of the issue with the VFD score is that it gives a similar score (0) for reduced duration of mechanical ventilation in patients with early deaths and patients with prolonged ventilation. There are instances when the composite endpoint and clinical endpoint can give contradictory results. For example, Willson (2005) evaluated the effect of calfactant in paediatric acute lung injury. Mortality and VFD scores were considered as the main clinical endpoints. There was a significant reduction in hospital mortality in the intervention arm (19% vs. 36%,
p=0.03). However, VFD scores were not significantly different (13.2 (10) vs. 11.5 (10.5), p-value=0.21).

**Challenges**

Some challenges are anticipated in relation to the variability of the patients’ requiring intensive care. One-day point prevalence study involving 1638 patients in 412 medical-surgical ICUs from North America, South America, Spain, and Portugal showed that common indications for requiring mechanical ventilation are acute respiratory failure (66%), acute exacerbation of chronic obstructive pulmonary disease (13%), coma (10%), and neuromuscular disorders (10%) (Esteban, Anzueto et al. 2002). This implies that additional measures may be required based on the condition the patients’ required intensive care. The second issue is in relation to the variability in the definition of the outcome measures. Contentin (2014) reviewed 128 trials reports, 55 (43.0%) reported VFDs. VFD score was defined in 13 different ways in 34 articles which provided one. The variability in the definition of surrogate measures is suspected in this review. Third issue is that, categorization of the variables as surrogates or clinical endpoint can be difficult because outcome measures which is considered as surrogates in a particular trial can be clinical endpoint in some other trial. For example, the endpoints pharmacodynamics & pharmacokinetics studies are clinically important. But these endpoints will be considered as a surrogate measures in later phase studies.

**Why it is important to do this review**

The ICUs treat the sickest patient and critical care research is very important in saving patient lives. Mortality is considered as the most important outcome measure in critical care research. But mortality rates in the ICU are reported to be on decline (Young, Hodgson et al. 2012). That implies that the difference in the mortality rates between the treatment arms is becoming smaller and the sample size required to detect clinically meaningful reductions are increasing. So it is important to determine whether there are any mechanistically compelling surrogate measures to critical care trials rather than more inefficient studies with a clinical endpoint. Many phase III clinical trials in critical care show no effect; one reason for this is that beneficial effects of surrogate outcomes in early phase clinical trials are used to inform the design of subsequent phase III trials and they may not be good representatives of the real clinical outcome. This implies that there are no valid surrogate measures in critical care.
There are several issues that can affect the validation of surrogate measures in this particular population. The first issue is that probability of death is high in this patient population. The second issue is the presence of competing risk which further increases the probability of the event of death in the intensive care setting. Probability of death is high in intensive care setting and the presence of competing risk further increases the probability. The International study of the prevalence and outcomes of infection in intensive care units (EPIC II) (Vincent, Rello et al. 2009) showed that intensive care unit mortality rates were 18.2%, but the rate in infected patients was 25.3% compared to 10.7% in non-infected patients. ICU-acquired infection and related sepsis remain the leading cause of mortality and morbidity in hospitals and ICUs. Therefore, competing risk needs to be accounted for during the validation of surrogate measures.

There is overwhelmingly large amount of literature already available and millions are being added to it each year. So it is very important to do a systematic review to determine different outcome measures used in critical care trials. This review intends to determine the definitions of the outcome measure with the aim of standardising them.

2. OBJECTIVES

Review question(s)

Which are the putative surrogate outcome measures used in critical care trials, to determine the efficacy of an intervention? How are the outcome measures defined in critical care trials?

3. METHODS

Criteria for considering studies for this review

Types of study to be included

This is a systematic review of outcome measures reported in clinical trials in adult intensive care patients. All the interventions and comparators will be included in the review.

Types of participants

The target population is critically ill adult patients in intensive care units. This review includes trials involving adult critical care patients (16 years and older) and excludes
paediatric and non-invasively ventilated trials. It also excludes end of life trials and trials in transplant patients.

Types of outcome measures

All the listed primary and secondary outcome measures used to inform the efficacy of interventions in the critical care setting will be included in the review. This review will exclude safety and feasibility endpoints.

4. SEARCH METHODS

Searches will include trial registries (2010 onward) including WHO International Clinical Trial Registry Platform (www.who.int/trialsearch/), Clinical Trials (www.clinicaltrials.gov) and Current Controlled Trials (http://www.controlled-trials.com/isrctn/). In addition the following electronic databases will be searched; MEDLINE (2010-present), Excerpta Medica Database (EMBASE) (2010-present), CINAHL via EBSCO host (2010-present). We plan to include articles published in American Journal of Respiratory and Critical Care Medicine, Lancet Respiratory Medicine, Chest, Critical Care Medicine, Intensive Care Medicine and Critical Care. Key search words include intensive care unit, critical care and randomised controlled trials

5. DATA COLLECTION AND ANALYSIS

Study Selection

One reviewer will conduct the search. Two reviewers will review the title and abstract of articles identified by the search. Full text of the articles deemed potentially suitable will be retrieved and read to ascertain inclusion. The retrieved references will then be assessed against the inclusion and exclusion criteria and try to resolve any disagreements. A third reviewer will settle any unresolved issues. Reasons for exclusion will be recorded.

Data extraction

Data extraction will be carried out by two reviewers. Two reviewers will independently extract relevant information from included studies. The data extraction form (Appendix B) designed for a similar review (Blackwood, Clarke et al. 2014) will be used. We will record
key features of each trial including details of: aims, outcome measures, units of measure, definitions, and phases of the study

**Assessment of reporting biases**

We will assess the risk of bias in selectively reporting outcome measures. We will do this by searching all relevant clinical trial registries and or protocol publications and supplement information.

**Information synthesis**

A list of outcome measures used in early phase trials will be generated. Outcome measures will be categorized as clinical endpoint, surrogate outcome measure and composite endpoint. This will be tabulated according to condition and intervention.

**Dissemination plans**

The results of the review will be published. The findings will be used in a future study to develop a core outcome set for early phase trials in mechanically ventilated patients ([http://www.cometinitiative.org/studies/details/709?result=true](http://www.cometinitiative.org/studies/details/709?result=true)).

**6. ACKNOWLEDGEMENTS**

We would like to thank Dr. Daniel Hadfield, Kings College, London for agreeing to be an independent data extractor during the review. We would like to thank the subject librarian Richard Fallis, Medical Library, Queen’s University Belfast for his support in devising the search strategy. We would like to acknowledge the support of the Northern Ireland Clinical Trials Unit for funding a PhD Fellowship to support this work.

**7. REFERENCES**


literature: XIX. Applying clinical trial results A. How to use an article measuring the effect of an intervention on surrogate end points. *Jama, 282* (8), pp. 771-778.


8. APPENDIX

Appendix A. Search Terms

**Medline**
1. Randomized Controlled Trial/
2. exp Randomized Controlled Trial/
3. randomized controlled trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. Random Allocation/
5. Double-Blind Method/
6. Clinical Trial/
7. clinical trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. exp Clinical Trial/
9. (clinical trial, phase ii or clinical trial, phase iii or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.
10. (Randomized controlled trial$ or RCT or Random allocation or Randomly allocated or Randomly allocated or (allocated adj2 random)).tw.
11. ((clinical adj trial$) or (singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)) or Single blind or Double blind$ or Placebo$).tw.
12. Placebos/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
15. lancet respiratory medicine.jn.
16. chest.jn.
17. critical care medicine.jn.
18. intensive care medicine.jn.
19. 14 or 15 or 16 or 17 or 18
20. Critical Care/
21. Intensive Care Units/
22. Pneumonia/ or Critical Illness/ or Anti-Bacterial Agents/ or Cross Infection/ or Aged/ or Gastric Mucosa/ or Intensive Care Units/ or Middle Aged/ or Critical Care/ or Cefotaxime/
23. (intensive care unit or critical care or critically ill or ICU).tw.
24. Intensive Care Units.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
25. Critical Care.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26. Critically Ill.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
27. 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 13 and 19 and 27

**Embase**
1. clinical trial/
2. randomized controlled trial/
3. randomization/
4. single blind procedure/
5. double blind procedure/
6. triple blind procedure/
7. crossover procedure/
8. placebo effect/ or placebo/
9. (((Randomi?ed controlled trial$ or Rct or Random allocation or Randomly allocated or Allocated randomly).tw. or allocated.mp.) adj2 random.tw.) or Single blind$.tw. or Double blind$.tw. or ((treble or triple) adj blind$).tw. or Placebo$.tw. or Case report.tw. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
10. clinical trial/
11. randomized controlled trial/
12. randomization/
13. single blind procedure/
14. double blind procedure/
15. triple blind procedure/
16. crossover procedure/
17. placebo effect/ or placebo/
18. (((Randomi?ed controlled trial$ or Rct or Random allocation or Randomly allocated or Allocated randomly).tw. or allocated.mp.) adj2 random.tw.) or Single blind$.tw. or Double blind$.tw. or ((treble or triple) adj blind$).tw. or Placebo$.tw. or Case report.tw. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. Critical Care.jn.
22. chest.jn.
23. intensive care medicine.jn.
24. intensive care/
25. intensive care/ or intensive care unit/
26. bacterial infection/ or intensive care unit/ or intensive care/ or pneumonia/
27. critical illness/
28. (Critical Care or critical care unit or intensive care or critical illness).tw.
29. Intensive care.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
30. intensive care unit/ or patient/ or critically ill patient/ or critical illness/ or intensive care/
31. 24 or 25 or 26 or 27 or 28 or 29 or 30
32. 20 or 21 or 22 or 23

CINAHL for EBSCO
# Query
S46  S38 OR S39 OR S40
S45  JN Intensive Care Medicine
S44  JN Critical Care Medicine
S43  JN Lancet Respiratory Medicine
S42  JN Chest
S41  JN Critical Care
(MH "Critical Illness") OR (MH "Polyneuropathies") OR (MH "Critically Ill Patients")

MH "Intensive Care Units"

MH "Critical Care" OR (MH "Critical Care Nursing")

S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36

S36 MH "Clinical Trials+"

S35 PT Clinical trial

S34 TX Clinic* n1 trial

S33 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))

S32 TX randomi* control* trial*

S31 MH Random Assignment

S30 TX random* allocat*

S29 TX placebo*

S28 MH Placebos

S27 MH Quantitative Studies

S26 TX allocat* random*

S25 S12 AND S16 AND S21

S24 S12 AND S17 AND S21

S23 S12 AND S19 AND S21

S22 S12 AND S20 AND S21

S21 S13 OR S14 OR S15

S20 JN Intensive Care Medicine

S19 JN Critical Care Medicine

S18 JN Lancet Respiratory Medicine

S17 JN Chest

S16 JN Critical Care

S15 (MH "Critical Illness") OR (MH "Polyneuropathies") OR (MH "Critically Ill Patients")

S14 (MH "Intensive Care Units")

S13 (MH "Critical Care") OR (MH "Critical Care Nursing")

S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11

S11 MH "Clinical Trials+"

S10 PT Clinical trial

S9 TX Clinic* n1 trial

S8 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))

S7 TX randomi* control* trial*

S6 MH Random Assignment

S5 TX random* allocat*

S4 TX placebo*

S3 MH Placebos

S2 MH Quantitative Studies

S1 TX allocat* random*
Appendix B. Outcome extraction form for Systematic Review

**Basic Information**

<table>
<thead>
<tr>
<th>Full Paper Reference</th>
<th>Design</th>
<th>Patient Group</th>
<th>Aim/Objective</th>
<th>Trial Registration Number</th>
</tr>
</thead>
</table>

Record outcomes and how they were measured (add rows as necessary)

<table>
<thead>
<tr>
<th>PRIMARY OUTCOME</th>
<th>UNIT OF MEASUREMENT</th>
<th>Pre-specified</th>
<th>TYPE (Clinical, Surrogate, Composite)</th>
<th>Data Collected</th>
<th>Reported</th>
<th>DEFINITION</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>SECONDARY OUTCOME</th>
<th>UNIT OF MEASUREMENT</th>
<th>Pre-specified</th>
<th>TYPE (Clinical, Surrogate, Composite)</th>
<th>Data Collected</th>
<th>Reported</th>
<th>DEFINITION</th>
</tr>
</thead>
</table>

Primary outcome based on the publication
Unit of measurement based on the publication
Pre-specified objective based on the Trial Registration
Categorisation as Surrogate, clinical or composite
Data collected based on the publication
Reported days reported, summary measure used to report (Mean ± SD … etc).