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ASSESSMENT OF METHODOLOGICAL CHARACTERISTICS AND QUALITY REPORTING OF CLINICAL TRIALS IN PALLIATIVE CARE

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Orientador: Prof. Doutor Joaquim Ferreira

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Dissertação especialmente elaborada para a obtenção do grau de Mestre em cuidados paliativos.

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Abstract

Background

Over the past decades there has been a significant increase in the number of published clinical trials in palliative care. However, empirical evidence suggests that there are problems with the design of these clinical trials, which in turn raises questions about the validity of their findings and the strength of the available evidence.

Aims

To evaluate the methodological characteristics and assess the quality of reporting of clinical trials in palliative care.

Methods

We performed a systematic review of published clinical trials assessing therapeutic interventions in palliative care. Trials were identified using MEDLINE (from its inception to February 2015). We assessed methodological characteristics and describe the quality of reporting using Cochrane Risk of Bias tool.

Results

We retrieved 107 studies. The most common medical field studied was oncology. Regarding type of intervention 43,93% trials evaluated pharmacological interventions. Symptoms control and physical dimension were the palliative care specific issues most studied. In quality of reporting there is information missing, especially in respect to sequence generation, allocation concealment and blinding.

Conclusions

While the number of clinical trials in palliative care has increased with time, methodological quality remains suboptimal. This compromises the quality of studies. Therefore, a greater effort is needed to enable the appropriate performance of future studies and increase the robustness of evidence-based medicine in this important field.

Key words

Palliative care, methodological quality, risk of bias, clinical trials

Resumo

Contextualização

Os cuidados paliativos têm como objectivo a prestação de cuidados à pessoa como um todo, através do controlo de sintomas e da integração de aspectos psicológicos e espirituais na assistência ao doente, promovendo a qualidade de vida e morte, sem a antecipar ou adiar.

Este conceito foi utilizado pela primeira vez em 1973, por Balfour Mount. Desde então, sofreu uma série de transformações na sua definição e consequentemente na sua área de atuação e objectivos. A Organização Mundial de Saúde, autora das duas definições mais utilizadas, afirmou em 1990, que a população alvo de cuidados paliativos era composta pelos pacientes cujo a doença não respondia ao tratamento curativo e mais tarde, em 2002, a população alvo passou a incluir também os familiares de doentes com uma doença que ameaçasse a vida.

Desde a abertura, em 1969, do St. Christopher Hospice, o primeiro *hospice* sediado em Londres, esteve presente a noção do papel crucial da investigação clínica como forma de demonstrar a eficácia terapêutica dos cuidados paliativos. Segundo uma pesquisa na OVID MEDLINE, entre 1970 e 2005 o número de artigos publicados nesta área quadriplicou. Em 2006, a medicina paliativa foi reconhecida nos Estados Unidos como subespecialidade, tornando-se mandatário a adopção de pontos-chave standard já aplicados noutras especialidades e subespecialidades médicas, tais como: avaliação dos métodos e raciocínio clínico na tomada de decisão, a identificação de obstáculos para execução de uma prática baseada na evidência e desenvolvimento de estratégias para contornar os mesmos e uma atualização da prática clínica e investigacional de forma a coincidir com os parâmetros de alta qualidade da medicina baseada na evidência. Atualmente existe uma vasta gama de intervenções terapêuticas disponíveis, exigindo dos profissionais de saúde a capacidade de avaliar criticamente a evidência e de aplicá-la corretamente na prática clinica.

As revisões sistemáticas são consideradas como o *gold standard* da evidência para orientar a prática clínica, uma vez que agregam de forma metódica, explícita e passíveis de reprodução uma coleção abrangente de estudos relevantes para a questão em estudo.

A forma como um ensaio aleatorizado e controlado é conduzido pode estar sujeita a enviesamentos, isto é, erros sistemáticos que dão origem a desvios da verdade nos resultados ou inferências. Como consequência, é de extrema importância a avaliação da qualidade dos estudos originais, aquando da realização de uma revisão sistemática.

Muitas ferramentas, em diferentes áreas da saúde, têm sido propostos para este fim. Em 2011 a *Cochrane* propôs uma nova abordagem à avaliação da qualidade, associando o conceito de qualidade dos estudos à sua validade interna, ou seja, ao risco de viés. Desenvolveu, desta forma, uma ferramenta com base num crescente corpo de evidência empírica quantificando a associação entre determinadas características do estudo e a estimativa de efeito dos tratamentos. Esta é composta por duas partes e avalia sete domínios: geração da sequência de aleatorização, ocultação da alocação, ocultação de participantes e profissionais, ocultação de avaliadores, resultados incompletos, relato seletivo de resultados e outras fontes de viés . A primeira parte da ferramenta refere-se à descrição do que foi relatado no estudo, detalhado o suficiente para que a avaliação seja tomada com base nesta informação; a segunda parte avalia o risco de viés para cada uma das áreas analisadas atribuindo uma classificação de três níveis: baixo, alto ou risco de viés incerto.

Objectivos

Avaliar as características metodológicas e qualidade do reportar nos ensaios clínicos na área dos cuidados paliativos.

Métodos

Ensaios clínicos de intervenções na área dos cuidado paliativos foram procurados por pesquisa electrónica através da base de dados OVIDMEDLINE, desde o início até Fevereiro de 2015. Para tal foi utilizada uma estratégia pré-definida pelos autores em conjunto com o filtro da *Cochrane*, *The Cochrane Collaboration's highly sensitive search strategy.*

Na seleção de artigos foram considerados os seguintes critérios de inclusão: intervenção paliativa em doentes e/ou familiares/cuidadores, acesso ao resumo e versão integral do artigo e a presença de um grupo de controlo.

Com base nas versões integrais dos artigos selecionados, dois autores de forma independente, procederam à recolha dos dados. Para tal, foi construída uma grelha de

recolha de dados composta por 43 itens, baseada no consenso dos autores sobre os tópicos que consideravam relevante. Seis domínio foram tidos em conta: informação geral (título, nome e país do autor de correspondência, língua de publicação, ano e jornal de publicação, factor de impacto do jornal, área e tipo de intervenção, dimensão da pessoa e aspecto chave da prática dos cuidados paliativos, aprovação ética e consentimento informado), métodos (critérios de elegibilidade, tipo de desenho do estudo, método de randomização, presença de ocultação da aleatorização, tipo de ocultação e duração do *follow-up*), amostra (intervenção, número total de doentes aleatorizados e por grupo, duração e *timming* da intervenção, desistências e cálculo da amostra), análise dos dados (tipo de análise, métodos estatísticos utilizados, objetivos pré-definidos, instrumentos de avaliação e comparabilidade dos grupos), resultados.

Os artigos incluídos foram divididos em domínio clínicos e tipos de intervenção. Foram considerados quatro tipos de intervenção: farmacológica, não farmacológica, não farmacológica – terapias complementares (tais como fisioterapia, musicoterapia, aromoterapia) e cuidado no domicílio (podendo este incluir intervenções farmacológicas e não farmacológicas).

Dividimos também os estudos de acordo com pontos-chave da prática dos cuidados paliativos. Numa primeira divisão, tendo em conta a abordagem holística da pessoa, dividimos os estudos de acordo com as dimensões da pessoa: física, psicológica, social, espiritual, mais relacionada com a intervenção em estudo. A segunda divisão foi feita com base nos restantes pilares da prática dos cuidados paliativos: comunicação, controlo de sintomas, apoio à família e cuidadores e trabalho em equipa.

Resultados

A pesquisa electrónica identificou 939 citações, das quais 120 potencialmente elegíveis. A aplicação dos critérios de inclusão resultou na exclusão de 13 estudos. As principais razões de exclusão foram: repetição na lista de referências (n=3), dupla publicação (n=8) e a língua de publicação (n=2).

Os resultados revelaram que os CT continuam a ser uma minoria na área dos cuidados paliativos. No entanto verificou-se um aumento do seu número ao longo dos anos, sendo a maioria dos Estados Unidos e Reino Unido (26,2% e 21,5%, respectivamente). A oncologia foi a área médica com mais estudos (56,1%, n=60) e

43,9% (n=47) avaliam intervenções farmacológicas. A dimensão física e o controlo sintomático foram os temas específicos da área dos cuidados paliativos mais estudados. O tipo de comparador mais usado foi a não intervenção/melhor cuidado de suporte (46.7%, n=50), usado maioritariamente em estudos com intervenções não farmacológicas. Em estudos de intervenções farmacológicas o comparador utilizado com maior frequência foi outra intervenção (droga ativa já testada e usada na prática clínica; 88,9%).

O cálculo da amostra não foi reportado em 46,7% dos estudos incluídos e taxa de desistências foi superior a 20% do total da amostra em 40,2% dos estudos.

Na análise da qualidade do reportar há uma percentagem significativa de informação em falta, especialmente nos domínios do geração da sequência, ocultação da distribuição, ocultação dos doentes, investigadores e avaliadores.

Conclusões

Nas últimas décadas a esperança média de vida aumentou e com ela o número de pessoas que sofrem de doenças crónicas. Isto torna a investigação na área dos cuidados paliativos ainda mais necessária. Não basta publicar mais, a qualidade da evidência deve acompanhar este crescimento.

Os estudos observacionais são de grande utilidade na identificação, por exemplo, da relação entre características do doente e sintomas. No entanto, estudos experimentais e de alta qualidade como os RCT, com menor risco de viés e de fatores de confundimento, melhoram o nível da evidência.

Verificou-se, nos últimos anos, um aumento do número de ensaios clínicos na área dos cuidados paliativos. No entanto a sua qualidade continua baixa, comprometendo a qualidade de possíveis revisões. Torna-se assim patente a necessidade de um maior esforço para promover um adequado nível de qualidade em estudos futuros e, para tal, distinguir quais as barreiras passíveis de mudança e aquelas que são baseados em percepções, podendo não ser totalmente precisas.

Atualmente, entre os obstáculos a ultrapassar encontra-se a necessidade de definir de forma mais uniforme o léxico específico da área dos cuidados paliativos e a sua população e de diversificar os estudos no que diz respeito ao domínio clínico, tipo de intervenção e ponto-chave dos cuidados paliativos abordado.

Amostras maiores e novas estratégias, como estudos *fast-track* ou a utilização mais frequente da análise segundo intenção de tratar, podem ser o caminho para a obtenção de ensaios de maior qualidade.

Palavras-chave

Cuidados paliativos, qualidade metodológica, risco de viés, ensaios clínicos

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Abbreviations

- CT - Clinical trial
- CCT – Control clinical trial
- EBM – Evidence-based medicine
- PC – Palliative care
- RCT – Randomized controlled trials
- Rob – Risk of bias

Introduction

This work was prepared as part of 2nd cycle of Masters in Palliative Care at the Faculty of Medicine, University of Lisbon.

The original idea was born from the awareness that research is necessary to improve clinical care and the perception in palliative care area of imbalance between the increasing number of publications and their report quality.

Hoping to provide the best evidence to guide health professionals in clinical practice, we make a systematic review of clinical trials in palliative care interventions with the goal of identifying the principal methodological flaws and helping to creating improvement strategies.

This paper has four main sections. In the first one, we present a brief theoretical background on the addressed issues. The second section describes the methodology used in the systematic review, followed by the presentation of the results presentation. The final section comprises of a discussion of the results, shortcomings of the study and some final conclusions.

Background

The quality of evidence

In the past few decades, the number of published clinical trials increased substantially. However, early on with this growth, some studies showed that the quality of the clinical trials may not have accompanied the growth in number.[1,2]

Methodological quality of studies is a concept that undergone several changes since first defined and comprises the evaluation of the validity of internal and external studies. By internal validity we consider the degree to which observations accurately reflect what they are intended to measure. The external validity is the extent to which internally valid research findings can be inferred back to the population of interest and other populations. The key to correctly translate the results of a research project to the population of interest rests in the ability to assure that the study was designed with proper planning, design, and analysis and that it has been conducted in a sample that accurately reflects the target sample.[3,4]

In 1970 David Sacket popularized the concept of evidence-based medicine (EBM), a tool proposed to improve quality of medical care that still provokes an enormous amount of interest and controversy across all medical fields. EBM is a methodology that integrates the best research evidence with clinical expertise and patient values into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative and preventive regiments.[5]

Nowadays, there is a wide range of therapeutic interventions available, which require health professionals to have critical appraisal skills to properly apply the evidence. Systematic reviews of randomized controlled trials (RCTs) are considered the highest standard in evidence-based healthcare available to guide clinical practice since they provide a comprehensive collection and summary of all available studies relevant to the focused research question. However some RCTs may present bias what affects their internal and external validity.[6–8]

Bias

Bias has been defined as a systematic error, or deviation from the truth that leads to predisposition towards the experimental or control group and may overestimate or underestimate the true benefits and harms of an intervention. It can be

classified in three types according to its source: the population being studied, the measurement of the outcome, and miscellaneous sources.[7,9]

Here we only describe, based on Cochrane handbook of systematic reviews of interventions, those that we mention in the course of this review[7].

- Selection bias – systematic differences in the baseline characteristics of the groups that are compared as a result of poor randomization.
- Performance bias - systematic differences between groups in the care that is provided or in exposure to factors other than the interventions of interest.
- Detection bias – systematic differences between groups in how outcomes are determined
- Attrition bias - systematic differences between groups in withdrawals from a study.
- Reporting bias - systematic differences between reported and unreported findings.

Tools to assess the quality of trials

Many tools, in different health areas, have been proposed for assessing the quality of trials. They can be divided into three groups according to the method used in quality assessment: individual factors, checklists, and scales. Scales differs from others in providing a quantitative estimation of quality that could be replicated easily and incorporated formally into the peer review process and into systematic reviews, but there is a dearth of evidence to support the inclusion or exclusion of items and to support the numerical scores attached to each of those items. There is no agreement regarding which tools are optimal to accurately determine trial quality and it has been proved that the use of more than one in a primary research may lead to different results. Most of them have not been developed using scientifically rigorous methods, lack reliability and/or have not been fully validated. Despite limitations, clinical trials used in systematic reviews or meta-analysis should be evaluated. In 1995, Moher and colleagues identified 25 scales and 9 checklists. [3,7,10]

In 1996 in order to enhance the RCT quality of reporting it was introduced the Consolidated Standards of Reporting Trials (CONSORT) statement, which consists of

a checklist that identifies 21 essential elements in the methods, results, and discussion sections necessary to evaluate the internal and external validity and with influence in studies quality. [1,11]

In 1997, a list of key methodological relevant topics for determining the methodological soundness of the trial was published in "Checklists for Critical Appraisal. The Evidence Based Medicine Workbook Checklist". A percentage score, based on descriptive variables and calculated for each study, is used as the indicator of the overall quality, which allows us to stratify trials based on their quality. There are 5 domains in the scale: results, validity: selection, measurement, statistical analysis and utility. In the first, results, estimate treatment effect and clinical importance are assess. Validity analyse eligible criteria and sample issues, measurement assess randomization, blinding, dropouts and side effects. The type of analysis and statistical method used belong to statistical analysis domain and utility examine if the result help clinicians to choose. [12]

The 33-item SPIRIT checklist applies to protocols for all clinical trials and aims to facilitate high-quality drafts. The SPIRIT documents can also serve as a practical resource for trial investigators and personnel to draft and understand the key elements of a protocol. [13]

In a review from 2013, the Jadad scale was, by far, the most cited and used tool with 5,326 citations from 1996 to July 4, 2013. This is a 5-item simple and short scale, with three domains: randomization, blinding and account of all patients. This instrument has been validated to assess the quality of reports of pain relief, but given that none of the three items included in the final version of the instrument is specific to pain reports, it has been used extensively in other clinical areas. Its main advantages are that is easy to use, contains many of the important elements that have empirically been shown to correlate with bias, and has known to be reliable and have external validity. [3,10,14]

The Cochrane Collaboration has led a shift in the approach to quality assessment, in which the concept of trial quality is linked to the internal validity of the study, namely Risk of Bias (RoB). It was developed based on a growing body of empirical evidence quantifying the association between certain design features and estimates of treatment effects. The RoB tool is a two-part instrument and includes the following areas:

- Sequence generation – Describe whether or not the study used a randomized sequence of assignments, preventing selection bias
- Allocation concealment – Refers to the techniques used to implement the allocation sequence without foreknowledge of intervention assignments. It also helps to prevent selection bias.
- Blinding – Refers to the process by which study participants and staff are kept unaware of intervention allocations after inclusion of participants in study. Blinding may reduce performance and detection bias. In this tool blinding is divided in two parts: blinding of participants and personnel (health care providers) and blinding of outcome assessors.
- Incomplete outcome data – Refers to how missing outcome data, due to attrition during the study or exclusions from the analysis, has been addressed in study. Missing outcome data increases the possibility that the observed effect estimate is biased (attrition bias).
- Selective outcome reporting – Refers to the selection of a subset of the original variables recorded, on the basis of the results for inclusion in publication with exclusion of statistically non-significant results.
- Other issues - Beyond the important potential sources previously mentioned, review authors should be alert to further issues that may raise concerns about the possibility of bias. This last domain in the 'Risk of bias' assessment tool is a 'catch-all' for other such sources of bias.

The first part of RoB tool refers to the description of what was reported in the trial, detailed enough for the judgment to be made based on this information. The second part appraises the risk of bias for each analysed areas and classifies them in three categories: low, high or unclear risk of bias. [15]

Palliative care

Palliative care aims to provide person-centred care by controlling symptoms, integrating psychological and spiritual aspects and promoting quality of life and death, without anticipation or prolongation, through the course of the disease. [16]

Balfour Mount first used this concept in 1973 when he sought to replicate in Quebec the style of care pioneered by Cicely Saunders at St Christopher's Hospice, the first organization to practice palliative care. Since then, the term "palliative care" has suffered a series of transformations in its definition and consequently in the area of intervention and objectives. Today it is possible to identify at least thirty-seven definitions in English; all of them coincide when referring the holistic nature associated with palliative care and with main objective on quality of life and pain relief. Nonetheless there is no longer consensus around the target population and type of prognostics associated in this area. [17,18]

The World Health Organization, author of the two most common definitions, affirmed in 1990 that the target population of palliative care comprises of patients whose illness does not respond to curative treatment. Later, in 2002, the WHO defined palliative care as an approach that improves quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual[17,19].

Regrettably, most people who need palliative care have no chance whatsoever of accessing it, either due to lack of resources or through ignorance of who can benefit of this type of care. It is a widespread belief that only a person with short prognosis has the entry ticket to specific palliative care services. Although palliative care is associated with caring of people dying with cancer, specialists of the area have been gradually opening up to a range of other diseases, such as heart failure, chronic obstructive pulmonary disease, degenerative neurological stages, and the benefit of palliative care approach is increasingly recognized in the early stages of disease. [20,21]

As a result of working with patients at the end of life, Cicely Saunders soon realized that beyond addressing the more obviously physical symptoms, many underlying issues of social, emotional and spiritual all threatened patient's quality of life. Therefore, the approach to the patient in palliative care should be a patient-centered approach, considering all its dimensions (physical, psychological, social and spiritual) of equal importance. This requires not only a multi-faceted professional team but also a good communication between professionals and patient/family members. Indeed, palliative care should be seen as a partnership between experts:

health professionals, in relation to the disease process and patient and family in respect to the impact of the illness.[20,21]

Palliative care research

Although early endeavours were largely focused on the development of services, the vision of Cicely Saunders working in the United Kingdom included the rigorous and systematic collection of' evidence. During a speech in 1965, Cicely Saunders point out the crucial role of clinical investigation to demonstrate the effectiveness of what was later called palliative care. Since then a debate remains regarding the need, place, ethics and resources for palliative care research, with strong arguments both for and against. In 1993, Professor Geoffrey Hanks, the first investigator to run a randomized control trial in palliative care, stated based on the Declaration of Helsinki that research should be as natural a part of palliative care as it is in other fields of medicine. [22]

According to a search on Ovid Medline, from onset to 2005 the number of clinical trials published in this field has quadrupled[23,24]. This expansion required, since then, strategic, high-quality research and an evaluation of the state of science to inform robust research and to effectively plan the construction of a solid body of evidence to guide clinical practice and public health policy. [15,25] However nowadays palliative care research is still less developed than other areas of medicine as result of methodological, cultural, and structural barriers to research in palliative care.[17]

Standing faced with an expanding area, systematic reviews or other studies, despite the limitations that may exist, are the way forward to create an evidence-based medicine, determining what questions require further research and how to improve current practices. [23,26]

The goals of this project are to evaluate through a systematic review the methodological characteristics of control clinical trials (CCT) in palliative care area and assess their reporting quality.

Methods

Literature search

We performed a MEDLINE search through Ovid from inception to February 2015 using a pre-defined search strategy (Fig. 1.) designed by the authors based on

The Cochrane Collaboration's highly sensitive search strategy to identify RCTs in the field of palliative care.

Study selection

Clinical trials were included if there was palliative care intervention (according to the authors' definition) conducted in patients and/or family members or caregivers, with a control group, and an abstract or full-length article was available. We excluded observational studies, systematic reviews, methodological studies, study protocols, and experimental studies which did not evaluate palliative care interventions or other types of interventions in the palliative care field (cost-effectiveness analysis, evaluation of palliative care services/units, and interventions in health professionals).

Two authors (RB, MR) independently screened abstracts obtained from the database search. The full-text of potentially relevant articles was retrieved for further assessments. Disagreements were resolved by consensus or by consultation with a third reviewer (JF).

Data extraction and quality assessment

Before study selection, a checklist of 43 items was developed, based on consensus among authors about which variables to extract and how they should be recorded. Five domains were analysed:

- general information (title of the CT, name and country of the corresponding author, language of publication, year and journal of publication, journal impact factor, area and type of intervention, person dimension and key point of practice of palliative care evaluated, ethical approval and informed consent),

- methods (eligible criteria, type of study design, method of randomization, achievement of allocation concealment, type of blinding, and duration of follow-up),

- sample (intervention, total number of randomized patients and number of patients in each group, duration and timing of treatment, dropouts rate, and sample size calculation),

- data analysis (type of analysis, statistical methods used, pre-defined outcomes, assessment tools, and group comparability),
- results.

Included articles were classified by clinical domain and type of intervention. Four types of intervention were considered: pharmacological, non-pharmacological, non-pharmacological complementary therapies (such as physiotherapy, musical, and aromatherapy therapy), and home-care based (all pharmacological and non-pharmacological interventions in the patient's home).

We also had in consideration the key characteristics of palliative care more relevant in the aims of the study. They comprise of a focus on the whole-person (physical, psychological, social, and spiritual dimensions), patient-centeredness (partnership with and empowerment of the patient and family), openness and honesty in communication, an acceptance of the inevitability of death coupled with improvement in the quality of life, multi-professional teamwork integrated with community (volunteer) involvement. According to this, we made two different classifications: one based in the whole-person approach, divided trials according to the dimension of the principal person dimension's being studied (physical, psychological, social and spiritual). A second division was made in line with the other key points of palliative practice present in the study (communication, symptoms control, family support and team work). [21,27]

The methodological quality of the included studies was assessed using the Cochrane tool, Cochrane Risk of Bias.

Independently, two authors (RB, MR) extracted information on individual items of all included studies and assessed the two parts in each included study. Discrepancies were resolved through discussion or by consultation with a third reviewer (JF).

Statistical Analysis

We summarized the publication characteristics using frequencies and percentages. Pooled odd ratios (OR) and the 95% confidence interval (CI) were calculated using a random effects model for risk of dropout and mortality between intervention and

control group. For this analysis we used Review Manager 5.3.0 software, Mantel-Haenzel method to account for the heterogeneity (clinical and methodological) among studies.

Results

The electronic search identified 939 citations. After screening titles and abstracts 120 articles were deemed potentially eligible. The application of inclusion criteria excluded 13 studies. The main reasons for exclusion were: repeated in the list of references (n = 3), duplicated publications (n = 8) and non-English language (n = 2) (Fig. 2.).

General features

Of the 107 clinical trials included, 12.15% (n = 13) were published between 1989 and 1999, 45.79% (n = 49) between 2000 and 2009, and 41.12% (n = 44) between 2010 and 2015. (Fig. 3.) Studies were published in fifty-seven different journals, with the most reported being: Journal of Pain and Symptom Management (14.9%, n=16, impact factor [IF]: 2.47), Palliative Medicine (13.1%, n=14, IF: 2.85), Journal of Palliative Medicine (9,3%, n=10, IF: 2.06) and Journal of Clinical Oncology (5.6%, n=6, IF: 17.9). The country of origin of the first author varied. Most studies were conducted in the United States (USA) (26.2%, n=28), the United Kingdom (UK) (21.5%, n=23), Australia (11.2%, n=12), and Canada (6.5%, n=7). Of all studies, 15% (n=16) lacked mention of approval by an ethics committee.

Types of design

Of all the studies, 82.3% (n=88) had a parallel design and 17.7% (n=19) had a crossover design.

The most used comparator was non-intervention/best supportive care (46.7%, n=50) followed by placebo (27.1%, n=29) and other interventions (25.2%, n=27). Analysing type of intervention and type of comparator demonstrated that non-intervention/best supportive care was essentially used in non-pharmacological interventions (80%, n=40), while other interventions and placebo were more used in pharmacological interventions (88.9%, n=24 and 62.1%, n=18). Another intervention was chosen more often than placebo in pharmacological interventions.

Duration of follow-up varied between studies, the most common periods were 1 month (14%, n=15), 2 months and 2 weeks (9.3%, n=10 each). The shortest follow-

up was 30 minutes (at the end of an intervention) and 54 months was the longest period reported.

Eligibility

Eligibility criteria varied significantly throughout studies. All patients were at least 18 years old and no studies indicated the sex or ethnicity of participants. According to what has been previously reported, oncological disease is often an inclusion criterion. In three studies (2.8%), dementia was also an inclusion criterion, while it was an exclusion criterion in 29 studies (27.1%). The expected remaining lifespan of participants varied between "less than a week of life" and 24 months, with 6 months of life being the most commonly considered period. In 66.4% (n=71) of articles this data was unknown.

Medical fields

The three medical fields with the most trials in palliative care were: oncology (56.1%, n=60), mental health (15.9%, n=17) and general practice (9.3%, n=10) (Fig. 4).

Types of interventions

Regarding the type of intervention, 44.9% (n=48) of studies reviewed were non-pharmacological interventions, 43.9% (n=47) pharmacological interventions, 7.5% (n=8) non-pharmacological complementary therapies interventions and 3.7% (n=4) home-care based interventions (Fig. 5).

Palliative care classifications

With respect to the dimension of the person being studied, 63,6% (n=68) analyzed the physical dimension, 13,1% (n=14) the psychological dimension, 14% (n=15) the social dimension and 9,3% (n=10) the spiritual dimension. Classifying the studies according to the other key points of palliative care practice we found that 70,1% (n=75) of the studies were based on symptoms control evaluation, teamwork and communication have the same representation of 12,1% (n=13), and 5,6% (n=6) studies highlighted family support.

Outcomes and assessment tools

There was a significant diversity of outcomes and in 40.2% (n = 43) no primary outcome was explicit. Whenever mentioned, the most cited primary outcomes were: pain intensity (20.3%, n=13), improvement in quality of life (12.5%, n=8), improvement in dyspnea (9.4%, n=6), and survival rate (7.8%, n=5). The most common secondary outcomes were: improvement in quality of life (29.9%, n=32), improvement in depression and anxiety (19.6%, n=21), use of rescue doses or palliative care services (15.9%, n=17), or presence of side effects (15%, n=16).

In the absence of a pre-specified main outcome, we considered all outcomes as secondary.

For outcome assessment 137 different scales and questionnaires were used, only eleven (8.03%) were used in more than five studies. Twenty (14.6%) of the 137 are recommended by the National Palliative Care Research Center, 5 (3.7%) belong to the group of most used scales. (Fig. 6.)

Statistic Analysis

Four studies (3.7%) failed to describe statistical planning, one (0.93%) only used descriptive analysis. In the majority of studies the analysis per protocol was deduced from the presence of dropouts and the absence of intention-to-treat analysis reporting. Half the studies (50.5%, n=54) used intention-to-treat analysis, 47.7% (n=51) analysed per protocol and in two articles (1.9%) it was not possible to conclude which statistical analysis had been used. Sample size calculation was not indicated in 38.3% (n= 41) of studies, and 8.4 (n=9) used a convenience sample.

Dropouts

The mean sample size was 113.1 ±139.1 [9 – 820] participants. The mean percentage of dropout frequency (n = 99 studies) was 22%, 40.2% of studies had a dropout rate > 20% (cut-off used to assess risk of bias). The main causes of attrition were symptom burden and clinical deterioration.

Pooled results from studies that reported one or more dropouts (n=90) showed higher dropout rates among the control groups (OR = 1.38; 95% CI = [1.11, 1.72]). The results were statistically significant, however, a moderate heterogeneity (I2= 68%) was present. To overcome this limitation a model of random effect was used. (Fig. 7)

Mortality

The average number of deaths in mortality analysis was 17.8 +/- 62,5 patients. Forest plot analysis of mortality showed a small level of heterogeneity (I^2=26%), with a statistically significant higher risk of mortality in the control groups (OR = 1.32; 95% CI = [1.04, 1.67]). (Fig 8.)

Quality of reporting analysis

Only in two papers (1.9%) were all domains considered as having low risk of bias while in 22 (20.52%) there was a low risk of bias in half of the domains (4/7). In eight studies (7.5%) there was a high risk of bias in half the categories and in 25 (23.4%) studies the risk of bias was unclear. (Fig. 9)

Only one study was not randomised. Computer generator randomisation was the most used mechanism, present in 37.38% of studies (n=40). Regarding the type of randomisation: 23.4% (n=25) used randomisation in blocks, 12.2% (n=13) stratified, 4.7% (n=5) simple, stratified in blocks and 0.9% (n=1) used a minimisation method. Most studies used a person, unconnected with the study, (e.g., an independent statistical colleague or the pharmacist) to guarantee allocation concealment.

Regarding blinding, 19.6% (n=21) of studies were double-blind, 14% (n=15) single-blind, in 6.54% (n=7) all elements were blinded and 19.6% (n=21) were open-label studies. In 40.2% (n=43) this information were not reported.

According to the instructions of Cochrane tool, when the primary outcome was not explicit risk of bias was considered to be high, in one study it was not clear if the variables were chosen or not based on the results.

Discussion

This review identified 107 CCTs assessing palliative care intervention in patients and/or families/ or caregivers. Although a minority in this clinical area, the number of these types of studies increases every year, and are, for the most part, performed in the USA and the UK. The amount of missing data is very high in almost all methodological features evaluated.

Rate of publications and research domains

A systematic review of study quality in the palliative cancer literature from 2011, made in two six-month periods in 2006 and 2009, supports our conclusions

about the number of published trials noting that RCT comprised only 5,6% (n=47) of the studies. Furthermore, a systematic review of methodological and structural challenges in palliative care from 2006 also draws attention to the fact that only a small fraction (4,3%) of publications in palliative care were randomised studies or studies performing prospective evaluations of interventions of medical or non-medical origin. A review of evidence-based practice in palliative care reports that between 1970 and 2005 the number of clinical trials in palliative care increased from 0,2% to 0,8%. According to the authors the most common study designs were retrospective case series (31,2%, n=262), prospective case series (19,5%, n=164) and cross-sectional studies (17,7%, n=149). [22,28,29]

The therapeutic data in palliative care is still dominated by oncology and interventions related to symptoms control. Other aspects such as communication, education, spirituality and family support remain "orphaned" topics, representing 5% or less of the total RCT in palliative care. Albers et al. (2011) and Hui et al. (2011), point out in two systematic reviews the imbalance between pharmacological interventions in oncology studies and interventions not related with control of symptoms or in other clinical domains. The National Institute of Health (NIH) in the USA report on palliative care research trends and funding finds that while the number of publications tripled in the last decades, gaps in important topic areas were evident, noting that two out of every three publications concerned cancer and few reflected the growing needs of patients.[30] Since the palliative care approach is characterized by a holistic approach to patient and has widened its scope of intervention in recent years, our study highlights this important gap in the literature and wants to draw attention to the need of further research. [28,31,32]

Defining "palliative care"

In recent years, with increased awareness that non-oncology patients could benefit from a palliative approach, palliative care has significantly extended its area of intervention. In 2007, a survey of the European Association for Palliative Care showed a large degree of diversity in study populations, not only with respect to the diagnostics but also the demographic characteristics, location where medical care is provided, type of analgesic, and treatment methods.[17] This represents a major challenge for research where there is a lack of a common lexicon and where such as a

large discrepancy in terms like "palliative care", "end-of-life" and “caregiver" makes it difficult not only to ensure that all readers facing the same study reach similar conclusions, but also in defining the population and specific interventions of palliative care. [22,25,32]

In a 2005 study of methodological approaches used in systematic reviews of end-of-life care, it has been reported that an important obstacle to a systematic review is the lack of a coherent, widely accepted definition of key word.[33] In our review, in order to circumvent this obstacle, we have chosen to interpret as palliative intervention whatever the author considered as such.

In this review the prognosis of patient ranges between “less than one week” and 24 months. Actually, the majority of specialized palliative care services are provided in the hospital when patients are near death and families are under stress.[34]

One reason for the inadequate use of palliative care may be misperceptions about the meaning and/or scope of palliative care services. The definition of palliative care points towards a population with life-limiting disease, when cure is not possible which, in a narrow perspective, may be understood as “end of life care”. However some diseases, especially chronic diseases, severely affect the quality of life of patients and family members for many years and new models suggest an integrated approach in which life-prolonging therapies are balanced with measures aimed at maximizing quality of life, promoted by strategies of symptoms relief and good communication about the prognosis and goals of care.[22,34,35]

In 29 studies (27,1%) dementia was an exclusion criterion, while it was an inclusion criterion in only 3 studies (2,8%). Globally, the number of people who die with dementia is increasing and it’s widely know that one of the typical trajectories of progressive chronic disease are characterized by the gradual decline over a long period of time, with motor function decline often accompanied by cognitive impairment/dementia. Dementia is a life limiting condition, currently without cure. The importance of a palliative approach to these patients is recognised, with a growing recognition of how much specialist palliative care can offer in these cases. Therefore, dementia should be considered as part of the palliative care population as their exclusion threatens the external validity of the studies. [36,37]

The use of placebo-control trials

The most used comparator was non-intervention/best supportive care (46.7%, n=50). This was used especially in studies of non-pharmacological interventions. Placebo and another intervention (active drug that is in current use) were used essentially in studies testing pharmacological interventions, and was another intervention used more often than placebo (88.9% versus 62.1%).

Best supportive care (BSC) interventions, defined by Jassem et al. (2008) as "treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen"[38] are often used as a comparator in palliative care trials. However, this control method has been criticized for poor reporting and for giving the impression of being largely determined by convenience and status quo practice, and originating lack of BSC standardization among trial participants. According to a 2015 review of inconsistencies in control arm design, BSC studies failed to standardise BSC delivery across trial sites, lacked evidence-based symptom management, and failed to provide access to palliative or supportive care services. To overcome these threats, the authors suggest that researchers integrate the published BSC standards into their BSC RCTs, and improve their subsequent documentation of the components of their BSC control arm.[39,40]

The placebo effect has been shown to be relatively consistent over many studies and has been approximated to account for up to 35% of the treatment effect.[9]

In 1997 two articles[41,42] with arguments for and against placebo-control trials in palliative care were published. The two agree that many of the interventions in palliative care have never been proven to be effective and their use is based on anecdotal reports and/or physician preferences. Hardy et al. (1997), in line with the tenets of evidence-based medicine[9], uses this as one of the reasons to encourage the use of placebo-control trials and states that when there is no evidence that a drug is better than placebo, and knowing the powerful effect of placebo, there can be no argument against the use of it.[41] Kirkham et al. (1997) highlight that placebo is not included as a criterion that determines strength of evidence in evidence-based medicine, and that there are difficulties intrinsic to the use of placebo-control trials. These are related to funding research of available drugs, obtaining of ethical approval and consent of patients, and with the difficulty in publishing a paper showing that a licensed and well-established drug is more effective than placebo. [42]

Assessment tools

The choice of assessment tools is very important in study protocol. In this review only 3,65% of scales used were recommended by The National Palliative Care Research Center.[43] Although several instruments can be used to assess outcomes, not all were developed and validated for palliative care population and therefore are not the most appropriate.[44] These are important issues and are highlighted in a review of evidence-based practice in palliative care as one of the challenges to reach high quality of research. This author refers that to consider a study valid, there should be a clear link between interventions and outcomes, what can be achieved by selecting a homogenous population, using a single well-defined intervention and analyzing outcomes with objective and clinically relevant end-points.[29]

Sample and dropouts

The mean sample size was 113.1 ±139.1 [9 – 820] participants. There was a dropout rate > 20% in 40.2% of studies. Small sample sizes, high attrition rates and lack of statistical power were findings of our results which are frequently reported as being the majors challenges in palliative care research.[30,45–47]

The perception that it is unethical to involve people with palliative care needs in research is not uncommon, given that the patient and family are more vulnerable.[22] In a review conduced by Aoun and Nekolaichuck[28], the authors showed precisely the opposite, based on several studies in which the participation in an experimental protocol is not perceived as an additional stress, but rather as a personal gain in a selfless perspective related to a moderate to high benefit. To caregivers, this collaboration is seen as an added value for patients, for themselves, and for future families that need palliative care assistance. Recently, another study named MORECare[30] provided unanimous support that it is ethically desirable for patients and family with palliative care needs to be offered the opportunity to be involved in research and stated that internationally relevant recommendations were produced to overcome some of ethical challenges. In a review of recruitment strategies[47], the author addresses this issue and concludes saying that recruitment to clinical trials is always challenging and suggests that palliative care researchers learn from colleagues in different disciplines about how to overcome challenges of gatekeeping and consent in vulnerable populations. An article of 2010[48] reports the strategy successfully used

to recruit patients with opioid-induced bowel dysfunction to a large-scale randomised clinical trial. Key changes included the adoption of a more flexible rescue laxative regimen; reduction in the treatment period from 6 weeks to 3 weeks; study assessments completed in the home, hospital, or clinic setting (as appropriate); reduction in the number of blood samples required; and elimination of a number of patient-completed questionnaires.

In this review a cut-off of ≤ 20% of losses to follow-up was used, as recommended by Evidence-Based Medicine (EBM) ''Levels of Evidence'', which use this value to separate ''high''- and ''low''-quality randomized trials because of the serious threats to validity involved.[49] In comparison with a systematic review on dropouts in sublingual allergen immunotherapy trials[50] of 81 studies (9998 participants) which reported a dropout rate > 20% in 18.8% and considered this to be an overall low dropout rate, our review identified a significantly higher percentage of studies above this cut-off (40.2% of studies).

Missing data are a potential source of bias and interpretation of results is always problematic when missing data are substantial. According to European Medicine Agent (EMA) guidelines on missing data in confirmatory clinical trials[51] it is unavoidable for some data to be missing, but ignoring it is not acceptable.

As a strategy to minimize dropouts and maintain the equivalence between groups, some authors recommend the use of delayed intervention for the control group, through randomised fast-track studies and/or intention-to-treat analysis. Despite the fragility of results arising from the present level of heterogeneity, forest plot analysis shows that dropout rate were higher in control groups. Unpowered studies can result in false-negative findings, and these suggestions should therefore be considered. [28,31]

Quality of reporting analysis

A key finding of this systematic review was the low overall reporting quality of CTs in palliative care and the amount of missing data in trial reporting. Although the number of published studies has increased significantly in the last years, we found no significant improvement in the overall methodological quality of these studies nor did reporting of important methodological safeguards against bias improve. Only 2/107 papers (1.9%) were evaluated as having a low risk of bias in all domains, and

20.5% (n=22) in half of domains. Twenty-five studies (23.4%) were assessed as having an uncertain risk of bias in half of domains (Fig. 8). A review of evidence-based practice in palliative care from 2015[29] supports our findings, reporting that despite the growth in published literature, palliative care could not be considered an evidence-based discipline as there is a lack of high quality evidence which would require it to labeled as such. The author attributes this to the difficulties in recruitment, in reaching samples with a significant power, and to the attrition rate and difficulties in defining outcomes. In another study from 2014 the authors state that recent reviews in the field continue to report a lack of strong evidence for important topics, either as a result of insufficient research attention or methodological weaknesses in existing studies.[45]

The aspects of quality which were poorly reported were allocation concealment and blinding. In a systematic review of primary treatment in brain tumors[52], the authors suggest that allocation concealment, blinding, type of analyses and details of randomization were poorly reported and relate this with the impression that it is easier for an author to describe clinical features of studies than to report methodological characteristics, and that there is a lack of awareness on behalf of authors on the importance of these features. With regards to blinding this could be partly explained by the fact that in many interventions these methods are difficult to apply, however, it is important to minimise bias especially when outcome of interest is subjective. The following example can illustrate why whenever possible these methods should be apply and reported.[53] A review of acupuncture studies for low back pain from 1998 illustrates the importance of these methods. The non-blinded studies found acupuncture to be relatively useful for the short-term treatment of low back pain with a very low number needed to treat with benefit. However, in analysis of blinded studies, no such effect was found and results were not statistically significant.[9,54] The “other bias” domain has the highest percentage of “uncertain risk of bias”. The assessment of this item was based on comparability of groups and sample size calculations, but most of all with a global perspective of each trial. Studies with major gaps in other key methodological characteristics have a higher probability of having other bias.

The domains where there is a higher percentage of low risk of bias are “incomplete outcome data”, “sequence generation”, and “selected outcome reported”;

nevertheless scores are not very high, with only one item > 60% (incomplete outcome data – 64.5%). In appraisal of selective outcome reported the rate of dropouts and type of analysis was used. It is commonly known that a high rate of dropouts increases the risk of selection and attrition bias, threatening the internal and external validity of studies. [9,49]

In 2014 Sleeman and Murtagh[30] highlighted the importance for research reporting to be transparent, complete, and provided in a way that can be readily used by clinicians. Our results demonstrate the absence, in a significant percentage of studies, of an explicit primary outcome, which increases the risk of reporting bias if it is not sure that variables were not chosen based on study results. We hypothesize that the difficulty of defining a common lexicon and knowing who comprises the population of palliative care research is the basis of this and other methodological flaws.

Quality of primary studies

As was reported above, the overall quality of reporting of studies is low. Sample size calculation is missing in 46,7% of included studies and attrition rate is higher than 20% in 40,2% of studies, which leads to lead to a high percentage of unpowered studies. These (unpowered studies) are often viewed as a major problem in clinical research, once they can be misleading, either by missing realistic moderate treatment effects that would be clinically important or by overestimating the size of the treatment effect and finding them to be statistically significant purely due to chance.[55] The junction of these two limitations (low overall quality of reporting and lack of power in samples) in primary literature threatens the possibility of more rigorous methods of information gathering. Systematic reviews are designed to minimize bias because they typically outline the research strategies and follow a rigid methodology during the evaluation process. Nevertheless Visser et al. in 2015[29] report that most of primary studies used in palliative care reviews were methodologically flawed and those considered to be of higher quality, inadequately powered. Wee et al. reports in 2008[26]: “Cochrane reviews in palliative care are well performed, but fail to provide good evidence to guide clinical practice, because primary studies are few in number, small, clinically heterogeneous, and of poor quality and external validity”. [26,29,56]

In line with our results, in a 2015 review to identify key priorities for future palliative care research, the author points out, among others items, the rigor in studies through representative samples (enhancing recruitment and retention of study participants), the used of validated and standardize instruments and an adequate reporting of study aims and data collection methods.[46] Chen et al., 2014, in a survey to palliative care researchers about the barriers to improve research in palliative care, highlights as one of the five major identified barriers the serious shortage of skilled researchers able to lead research and train other. Participants refer the lack of training programs and formal training opportunities, such as research fellowships as limiting factors to equip a researcher workforce.[45] Nowadays, to help investigator in this field tools, such as CONSORT statement, were created to help investigators in the report of studies and raise studies quality. [53,57]

Shortcomings

Our electronic search used only MEDLINE. Research strategy used filters highly sensitive and there is a large discrepancy defining palliative care, the number of retrieved citations was excessively high for a feasible search and with a high percentage of results that did not meet our inclusion criteria. This and the comparison between our number of included studies and the same number in others reviews, were the reasons that supported our chosen process. A study of methodological approaches for systematic reviews of end-of-life care of 2005 mentions the same difficulty.[33] In their study the search identified 24,423 titles of which 134 were intervention studies.

Conclusion and recommendations

With a greater number of people living longer and suffering from chronic diseases, palliative care research becomes increasingly necessary. It is not enough to simply publish more, it is also necessary that the quality of evidence also improves. To this end, it is important to distinguish the barriers that are amenable to change and those that are based on perceptions that may not be entirely accurate.

The way a study population is defined depends on the aim of the study. It is likely that some studies in which study population was not specified or not described take into account that palliative care is more than end-of-life care would not have been retrieved by our research strategy. The opposite also happens with many

publications that are misleadingly associated to palliative care. [58] In order to develop and improve research, the palliative care field needs to develop more uniformity and define palliative care lexicon and population. It is also necessary to widen areas and types of intervention and palliative care domains.

Observational studies are very useful to identify, for example, relations between patient characteristics and symptoms. However, experimental and high quality trials as RCT increase the level of evidence and avoid selection bias and confounders. Larger samples and new strategies, such as fast-track studies or intention-to-treat analysis, could help to perform the high quality trials and intervention studies needed to verify hypotheses defined by observational studies.

To our knowledge, this is the most comprehensive attempt to review clinical trials in palliative care literature. We provide an overview of this expanding area and highlight the need to further improve the quality of reporting and scope of palliative care research. Specifically, greater efforts should be made to reach a common lexicon and reduce the frequency of methodological flaws such as primary outcome statements, comparability of groups at baseline and handling of losses to follow-up.

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Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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3 controlled clinical trial.pt. (88618)

4 randomized.ab. (309487)

5 placebo.ab. (158176)

6 clinical trials as topic.sh. (170815)

7 randomly.ab. (224178)

8 trial.ti. (133051)

9 non?randomized.ab,ti. (8500)

10 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (941361)

11 exp animals/ not humans.sh. (3986356)

12 10 not 11 (868454)

13 1 and 12 (939)

Figure 1 – Research strategy description

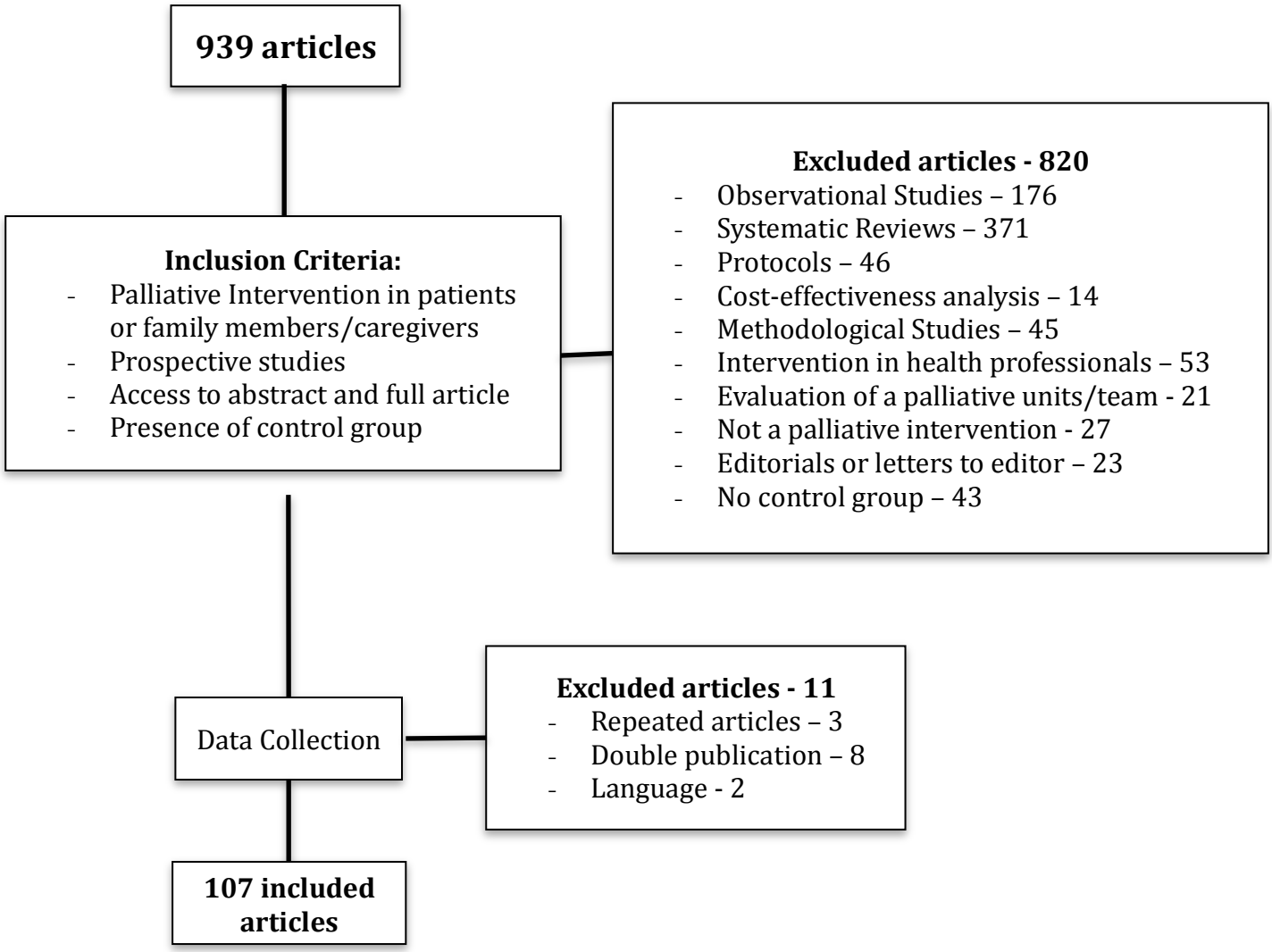

Figure 2 – Flow diagram of study selection process

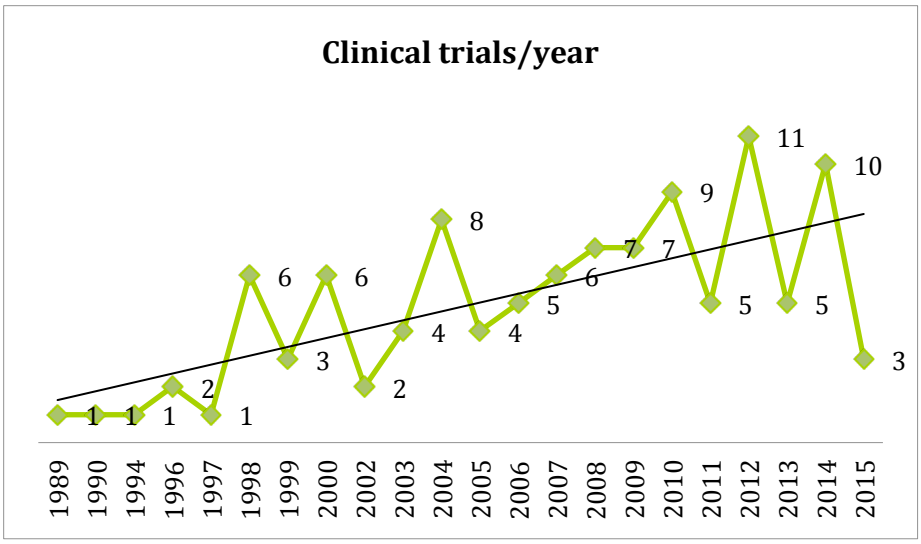

Figure 3 - Number of clinical trials published over time

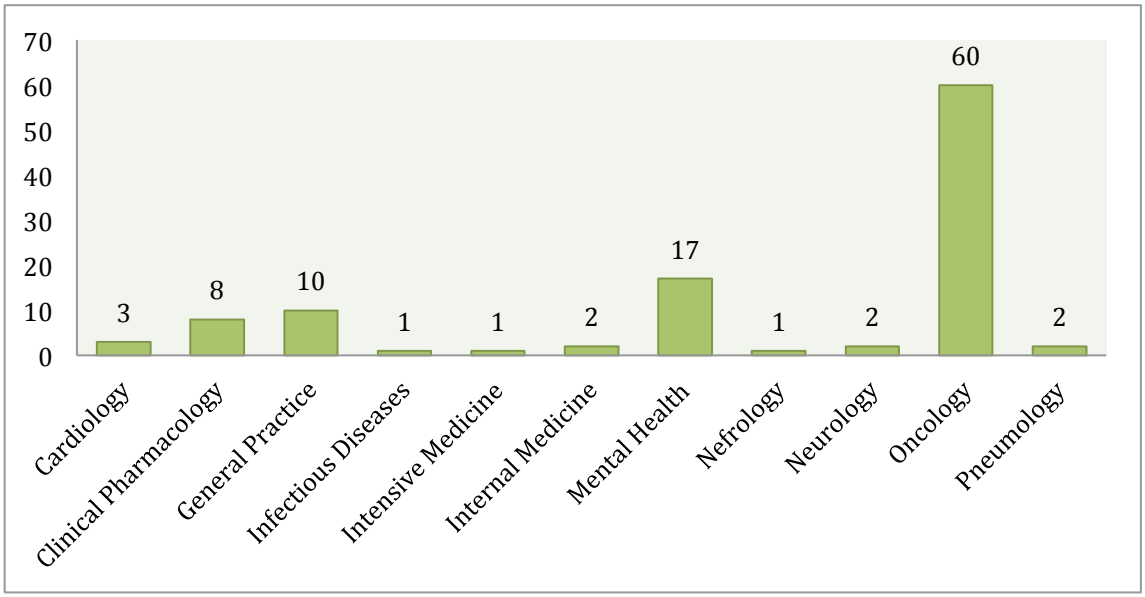

Figure 4 – Distribution of included CT among medical fields

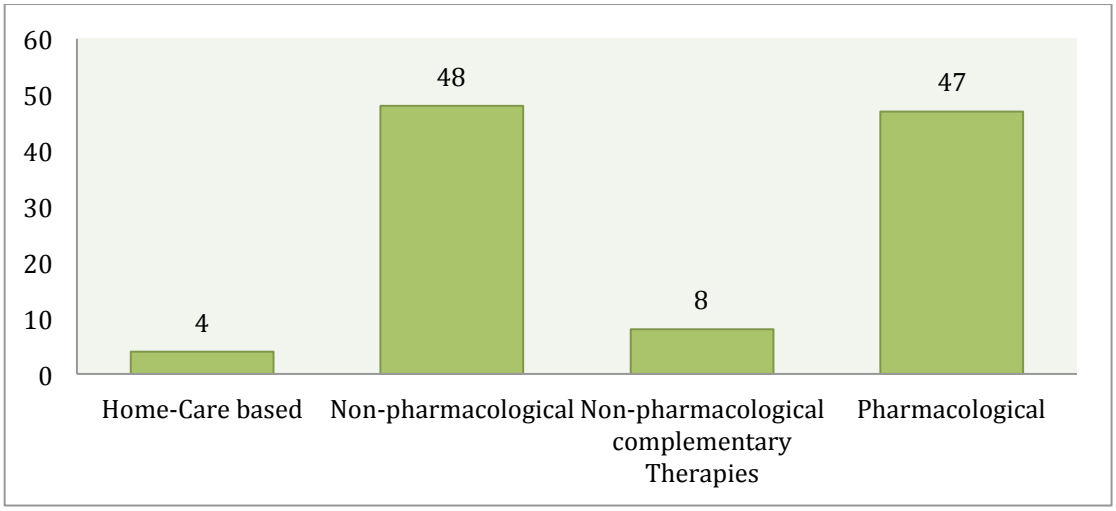

Figure 5 - Distribution of included CT among types of intervention

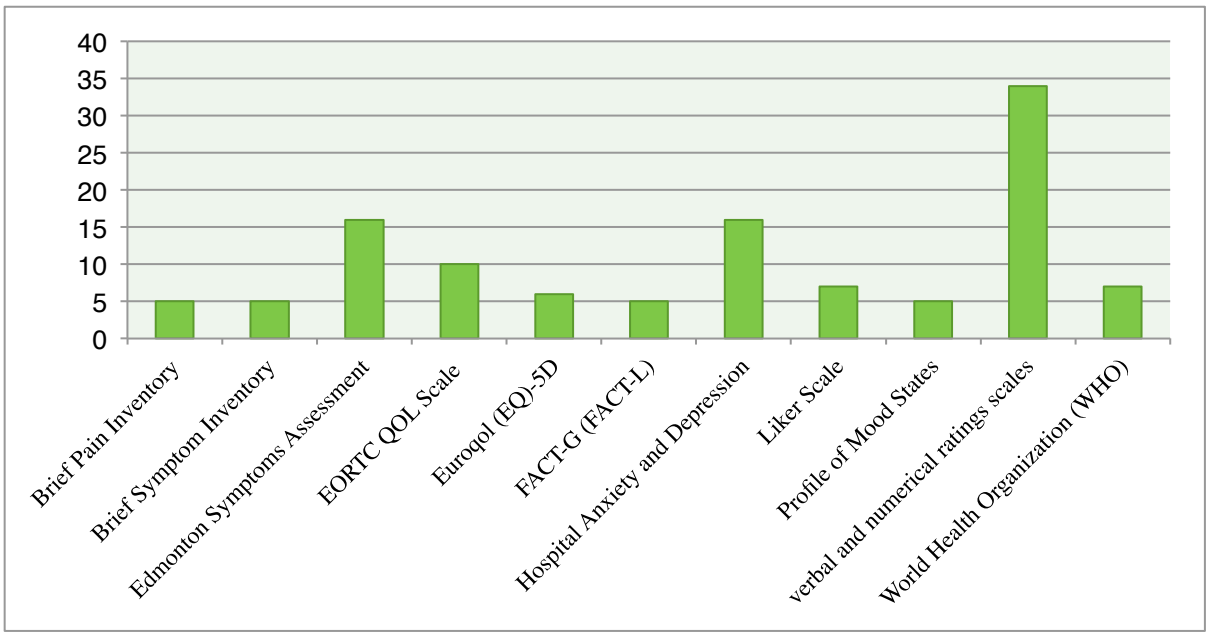

Figure 6 – Distribution of the most used evaluation scales in included studies

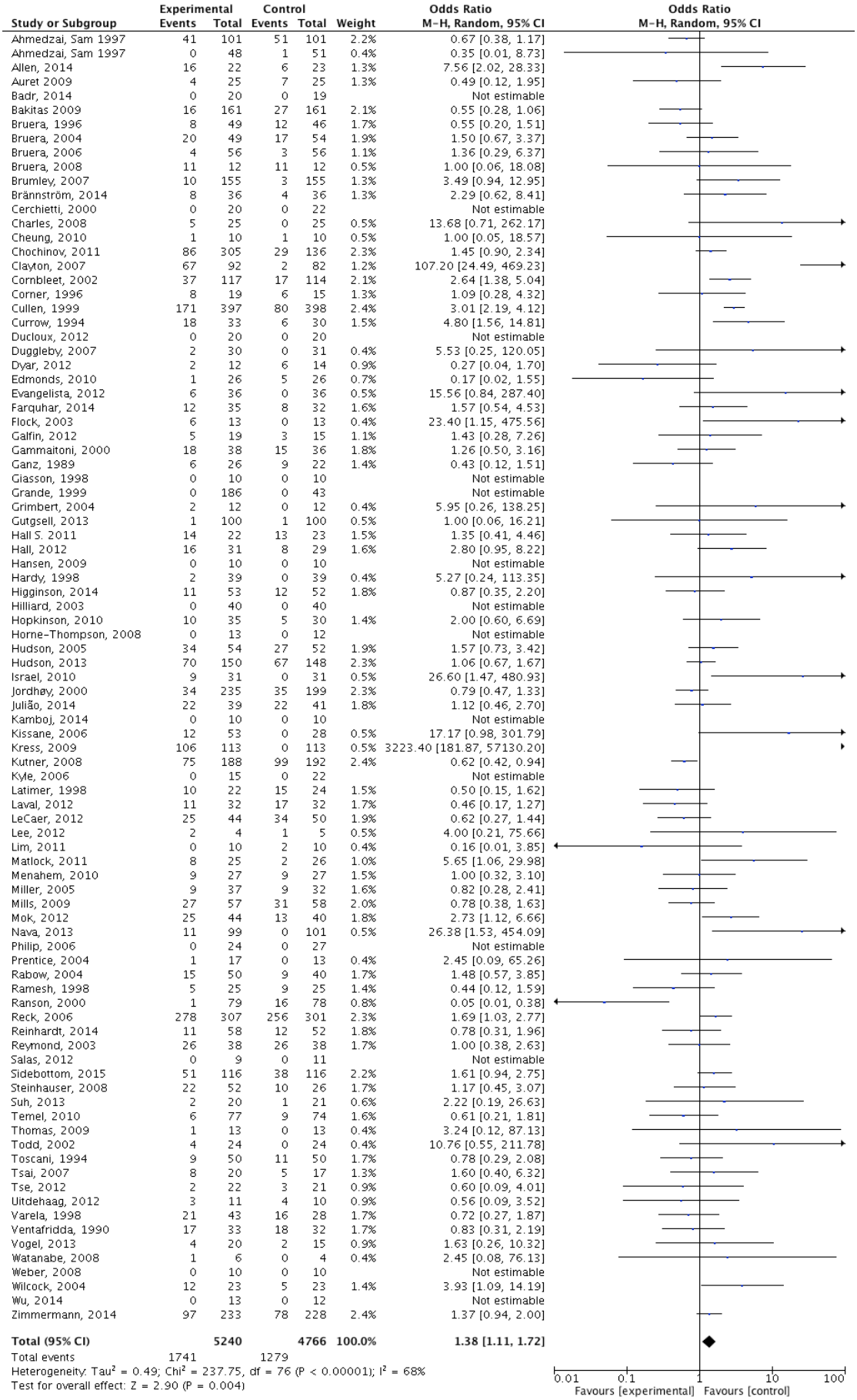

Figure 7 - Forest plot comparing dropouts between intervention and control group

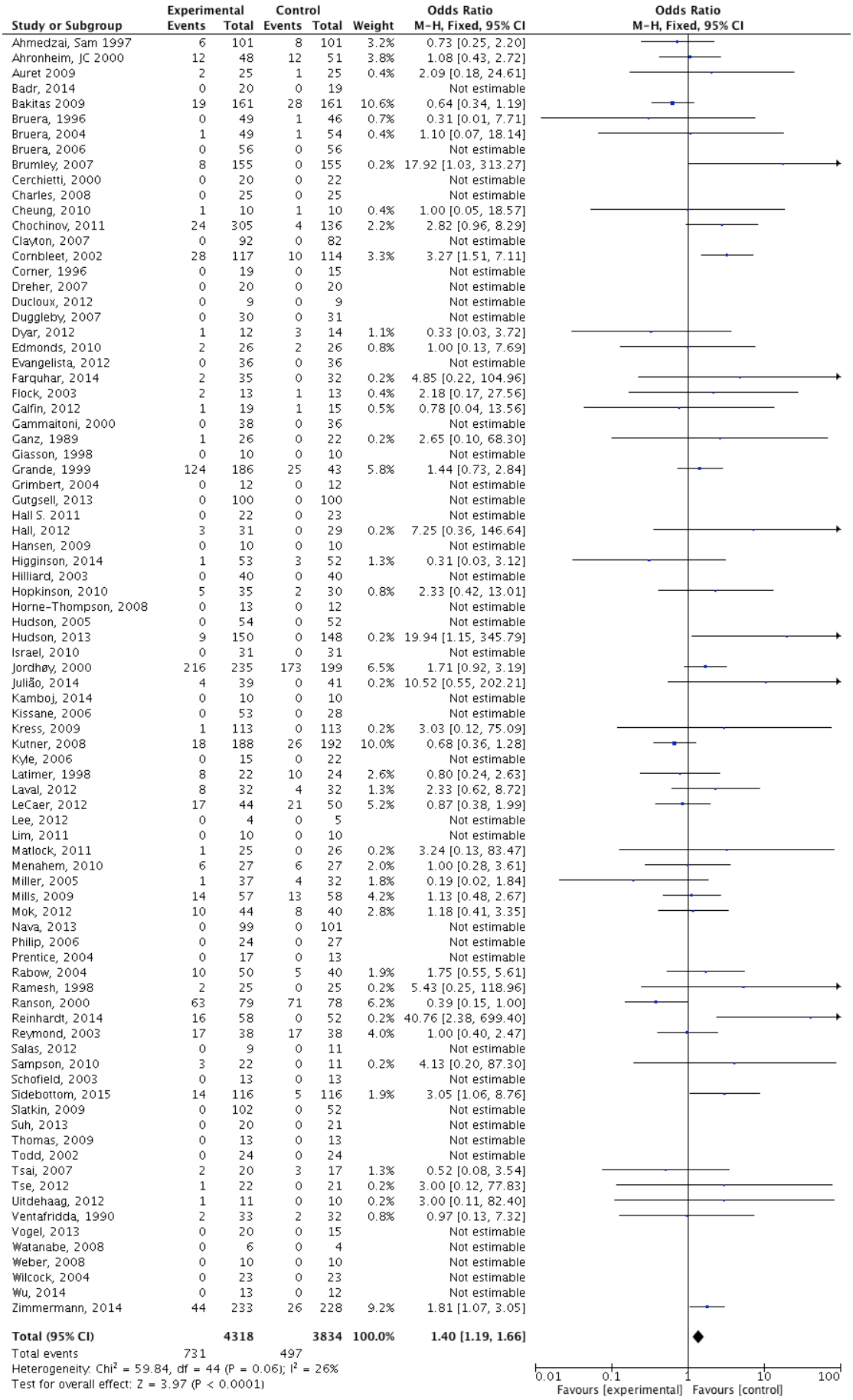

Figure 8 – Forest plot comparing mortality between intervention and control group

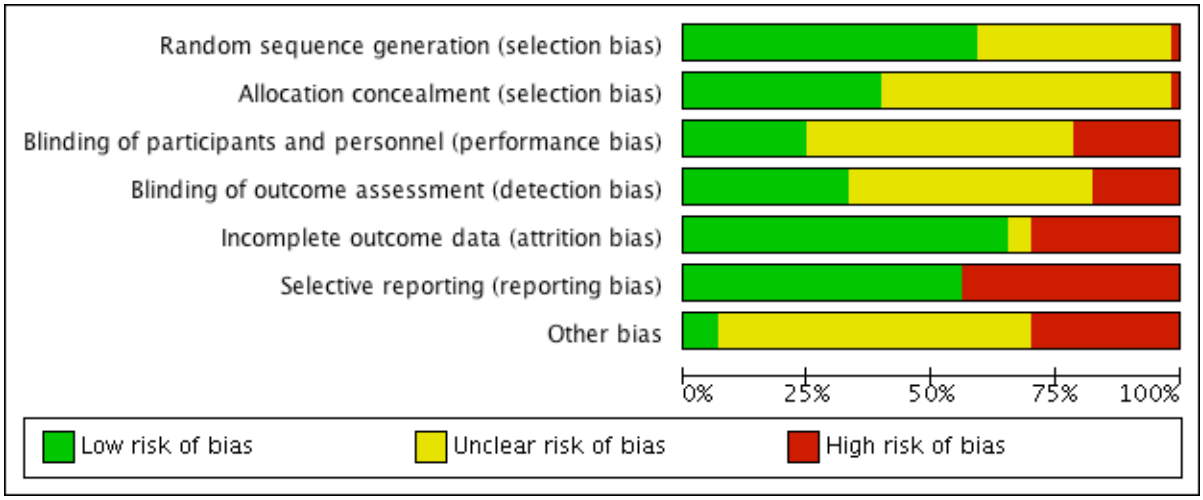

Figure 9 – Risk of bias in included studies assessed using the Cochrane tool

Attachment

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