MADRE-2013

Support method for decision making in assessment and appraisal of medicines

Version 4.0

Spanish Society of Hospital Pharmacy
SEFH

Group for Innovation, Assessment, Standardisation and Research in the Selection of Drugs
GENESIS

MADRE
Support method for decision making in assessment and appraisal of medicines

Procedures manual 2013
version 4.0

Based on a research project by GENESIS-SEFH group:

"MADRE Program update for drafting evaluation reports of new drugs"

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INTRODUCTION

The MADRE program is a set of tools developed to facilitate the process of drug selection.

The program's goal is to facilitate writing assessment reports in an orderly and systematic way, defining for each of the phases of the evaluation which is the recommended methodology. It consists basically of a structured assessment report and a number of application instructions and procedures, including algorithms, formulas and links to sources of information.

The MADRE program was launched in 2005 within the GENESIS group of the Spanish Society of Hospital Pharmacy (SEFH), and is currently the reference system used by a high proportion of Spanish hospitals and centers of documentation and evaluation of medicines from diverse health care systems and regions.

The update project, undertaken with the support of the SEFH, has been carried out for two years and enabled to make available to the scientific community the current version 2013.

Research group:

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CONTENTS

STRUCTURE AND LEVEL OF HELP

Base report template

There is a base form model or evaluation report with different sections and its blanks. The relevant information for the evaluation will be written in the blanks of each section.

Each of the sections and instructions are developed, with links to internet access and algorithms. The first time you use the MADRE program, you should use this version. It is designed to introduce the concepts and basis for evaluation with teacher character.

For each of the sections, there are instructions and help information available. The help text format is designed to facilitate "copy and paste" into the blanks of the base report. This uses the Word program Arial type font size 10 black for text and Arial size 8 black for the tables.

The texts of aid instructions are blue writing and should be deleted when moving blocks of text and tables to the report. Also accessible through links you can find algorithms, formulas for calculation, links to external websites, etc...

0.- Header

DRUG NAME
clinical indication
(Report to the Pharmacy and Therapeutics Committee of the xxxxxxxxxx)
Date xx / xx / xx

CONTENTS:

Glossary:

How to cite this report:

Instructions:

For writing an assessment report in a **hospital**: Replace the title by the generic name of the drug that is being evaluated and abbreviated clinical indication. Include the name of the hospital, the date of writing, and if necessary the word "draft". It is suggested that the header is customized with the logo of the hospital or anything that helps to identify the report as a center itself.

For reports prepared by **GENESIS** Reference: in the header will state that it is a report by GENESIS according to the method and shared assessment procedures established by this working group.

How to cite evaluation reports:

HOSPITAL REPORTS: Authors separated by semicolons [Last, First (Initial)]. *Drug Name (s): Indication*. Report to the Pharmacy & Therapeutics Commmittee of the Hospital xxxxx. Date of report. [Cited: date].

Available at: http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/InformesHosp_abc.htm
Also: http://gruposdetrabajo.sefh.es/genesis/

GENESIS REPORTS: Authors separated by semicolons [Last, First (Initial)]. *Drug Name (s): Indication*. Report for the GENESIS-SEFH group (reviewer). MADRID: SEFH (ed.), [year]. ISBN. [Cited: date].

Available at: http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/InformesHosp_abc.htm
Also at: http://gruposdetrabajo.sefh.es/genesis/

1.- DRUG IDENTIFICATION AND AUTHORS OF REPORT

Drug: Generic name and synonyms if any.
Clinical indication: Abbreviation for the clinical indication studied.
Authors / Reviewers: Name and clinical service authors / reviewers of the report. If it is an updated or adapted, the original report must be referenced (authors, title, hospital, date).
Type of report: Base, original, updated, adapted, public draft or final.
Conflict of Interests (Authors): The authors will make a disclosure of conflict of interest, which shall be annexed to the final report.

Instructions section 1:

Type of report:

Reports generated by hospitals:

O: ORIGINAL. Report made without using other published reports on the web of GENESIS as the main source.

U: UPDATED. Updating an old report posted on the website of GENESIS, including relevant new information.

A: ADAPTED. Made using or merging, with other minor modifications, reports published on the website of GENESIS, without adding relevant new information.

Reports written collaboratively by the group GENESIS:

PUBLIC DRAFT: Preliminary reports processed by GENESIS group proposal, drafted following the shared assessment procedure, publicly available, and with a deadline for the submission of allegations. The public draft status is maintained while the allegations are not answered.

FINAL: Report prepared by GENESIS group proposal, drafted following the shared assessment procedure which went through a public exhibition period (this is the draft with the response to allegations, evaluated and validated by the coordinating group).

"Conflicts of interest":

A conflict of interest occurs in circumstances in which professional judgment concerning a primary interest, such as patient safety or the validity of research, can be influenced heavily by other secondary interest, be it a financial benefit, promotion of prestige or any other personal / professional interest.

In professional relationships with healthcare industry can be considered six types of financial interactions:

- Receive support to attend meetings and conferences (registration, travel grants, etc..).
- Charge fees as a speaker at a meeting organized by industry.
- Receive funding for educational programs or training.
- Receive support and funding for research.
- Be employed as a consultant for a pharmaceutical company.
- A shareholder or have a financial interest in a pharmaceutical company.

In turn, potential conflicts of interest in preparing evaluation reports are considered when they exceed the amount of 2,000 euros per year.

The potential conflict of interest exists independently of the professional considers whether or not these relationships influence their scientific judgment.

Be declared conflicts of interest of the current and past three years. In the case of a hospital report or a shared report shall be entered at the end of the report as annex one of the types of conflict of interest statement.

Conflict of interest GUIASALUD

Form to disclosure of conflicts of interest

Potential conflicts of interest in preparing evaluation reports are considered when they exceed the amount of 2,000 euros per year (last three years).

- Name:

- Institution where you work:

- An institution that relates to the report. Eg: scientific societies, group work, etc... (Answer only if different from above):

Participation in the evaluation report as: 1- Author 2- Tutor 3- External Reviewer

After having read and understood the information provided on the declaration of conflicts for this report, make the following statement:

A- Personal interests (please specify) **☐YES** **☐NO**

	Activity	Institution	Date
Funding for meetings and conferences, attending courses (registration, travel bags, accommodation ...)			
Fees as a speaker (conferences, courses ...)			
Funding of educational programs or courses (staffing, facility rental ...)			
Funding for participating in an investigation			
Consulting for a pharmaceutical company			
Shareholder or business interests in a company			
Economic interest in a private company related to health (owner, employee, shareholder, private consultation ...), which can be significant in relation to the authorship of the report			
Conflicts of interest of non-economic nature that may be significant in relation to authorship in the report			

B- Non-personal interests (please specify) **☐YES** **☐NO**

	Activity	Institution	Date
Funding or financial assistance for the unit or service			
Contracting or financial aid to recruit in the unit or service			
Financial support for research funding			
Funding of educational programs or courses for the unit			

C- Other potential conflicts of interest not mentioned in previous sections (specify)

DATE **SIGNATURE**

2.- APPLICATION AND EVALUATION PROCESS

Requested by:
Service/Department:
Justification of Request:
Suggested place in therapy:
The application was received on (date):
Request as:

Instructions section 2:

If there is more than one application per drug and clinical indication, shall be entered each of the applicants, services and dates.

Justification of Request:
Main reasons to carry out the request for inclusion of the new drug; at the discretion of the applicant.

Suggested therapeutic positioning:
Indicate the protocol or therapeutic positioning suggested by the applicant who has completed the request for inclusion of the drug (see the application form).

Request as:
Report it to put on the application model GINF:
- Individually.
- It has been agreed within their service with others.
- It was agreed and also has the approval of the Head of Service.

In general this will be noted in the data section of the application for inclusion of the drug (eg GINF), especially with regard to the justification of why you are applying.

3.- DESCRIPTIVE AREA OF MEDICINE AND HEALTH PROBLEM

3.1 Medicine information

Generic name:
Trade name:
Company:
Therapeutic group. Name: ATC Code:
Route of administration:
Dispensing type: hospital, visado, ambulatory…
Licensing Information: (Note 1)

Pharmaceutical forms and price (Note 2)				
Pharmaceutical form	Units per package	Code	Cost per unit: Retail price + VAT (1) (2) (Note 3)	Cost per unit: Exfactory price + VAT (2) (Note 4)

(1) Section to be completed only for drugs with a significant impact in the area of primary care.
(2) Indicate the price financed for the NHS

Instructions section 3.1:

Note 1:

Include information on the processing status of the drug in regulatory agencies EMA (AEMPS in Spain) and FDA: approved, under review, rejected, etc. Indicate whether the new drug has been considered for fast track review or approval as an (ultra)orphan drug.

Procedures for registration of a new drug in Europe: Centralised, Mutual Recognition or National.

Centralized procedure: EMA or AEMPS website. The drugs registered by centralized procedure can be found in the EMA website http://www.ema.europa.eu/ page. If the drug is not in EMA website, this implies that the procedure is not centralized, and if so, try to figure out if it is a mutual recognition or a national procedure. Consider that the centralized registration procedure is more rigorous and transparent. At least we have the EPAR report, based on the evaluation. Link: http://www.aemps.gob.es/cima/fichasTecnicas.do

Mutual recognition: Refer to product monograph, the information provided by the laboratory and secondary sources (Example: Rev Prescrire, etc). Search in: http://mri.medagencies.org/Human/

National procedure: This type of registration is unusual for drugs of interest in the hospital. Refer to product monograph and information provided by the laboratory.

Note 2:

Data in this section (Pharmaceutical form, dose, price, therapeutic group, ...) can be obtained at:

-Product Monograph and data provided by the laboratory

-Ministry of Health: http://www.aemps.gob.es/cima. Search by active ingredient and then by trade name.

-EMA: http://www.ema.europa.eu/

Note 3:

If the drug is for hospital use and has no impact on primary care, this box can be removed.

The price is per unit: PVP (retail price) + VAT. Describes, if available, clinical packaging and standard packaging.

Note 4:

In general, the cost comparison will include PVL (ex-factory price) + VAT.

PVP (retail price) + VAT may be of interest to calculate the economic impact of drugs in primary care or to bill the medication from the hospital.

Information on the PVL (ex-factory price) + VAT (4%) of a drug is not readily available. The distribution and commercial margins depend on the type of drug and other factors, and the legislation has undergone continuous changes.

Because of these changes, consult the PVL (ex-factory price) by contacting the regional health service or the laboratory.

The PVL (ex-factory price) + VAT is often used to build up the base case scenario for economic assessment. Real prices possibly include discounts and are described below in the section on economic analysis.

3.2 Health problem

It is advised to address the bibliographic search from the start, to find information of all sections of the report, as this will give an overview of what is published on the subject.

Instructions section 3.2:

INFORMATION SEARCH FOR SECTIONS OF THE REPORT: Sections 3, 4, 5, 6, 7 y 8.

A simple way to address the search is by PICO scheme that considered from the type of patient to the study design. (See example)

Example of description with PICO scheme:

PATIENTS	Chronic C hepatitis
INTERVENTION	PR (Peg-Interferon plus ribavirine) plus protease inhibitors
COMPARATOR	PR alone
RESULTS	Variables: clinical benefit, mortality, morbidity, etc.
STUDY DESIGN	**-Disease Treatment:** Reviews, CPG (International and National Societies) or Therapeutic Guidelines **-Efficacy:** Controlled clinical trials, systematic reviews and meta-analysis, indirect comparisons. **-Effectiveness:** Observational studies. **-Secondary sources:** CPGs, HTA Agencies, etc… **-Safety:** Controlled clinical trials, systematic reviews and meta-analysis, indirect comparisons, observational studies and voluntary reports **-Economic evaluation:** Cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis.
Emerging evidence	Abstracts
Ongoing clinical trials	Interesting records for all newly marketed for drugs and off-label indications.

3.2.a Structured description of the health problem

Provide a brief description in the sections stating the following table:

Health problem	
Definition	
Signs and symptoms	
Incidence and prevalence	
Course of the disease / Prognosis	
Severity / Stages	
Burden of the disease*	

* hospitalisations, visits to the emergency department, disability, need of a carer…

3.2.b Current treatment of the disease: evidence

- Summary of current treatment in CPGs and reference texts: Conduct a structured summary and display an algorithm showing the different treatment options whenever possible. In hospital reports, consider the current treatment of the pathology locally.

- Purposes: What is the purpose of the treatment: preventive / curative / palliative?

- Effectiveness of current treatment: A brief narrative statement

3.3 Features compared to similar alternatives

Alternatives available in the hospital for the same indication.

Features compared to similar alternatives			
Name	**XXXX**	**XXXXX**	**XXXXX**
Dosage form			
Posology			
Therapeutic indication			
Adverse reactions			
Resources consumption			
Convenience			
Other			

Current standard treatment and modification expected with the new drug, according to table:

Basic data about products or processes that can compare with the new drug in this indication. State the main points on which they differ and which may be relevant a priori, such as ease of administration, use of diagnostic resources, preparation time, etc.

Include drugs and non-pharmacological therapeutic options (surgery, radiotherapy, best supportive care, etc.) as alternatives in the same indication, and its characteristics compared with the drug tested.

This section of the report provides the reader with initial positioning of the drug. The contents of the table should be reviewed and finished after writing the report and its conclusions.

4.- PHARMACOLOGICAL ACTION AREA

4.1 Mechanism of action.

Pharmacological group according to its mechanism of action. Provide a brief description, in two or three lines at maximum. In case of antibiotics, describe antimicrobial spectrum here. View technical details following links in section 4.2.

4.2 Therapeutic indications and date of approval.

Specify the indication evaluated in the report

AEMPS: [Date of approval]
EMA: [Date of approval]
FDA: [Date of approval]

Links to product information

MoH: http://www.aemps.gob.es/cima
EMA: http://www.ema.europa.eu/ema
FDA: http://www.fda.gov/

4.3 Posology, preparation and administration.

Usual dose and duration of treatment for the indication studied. View technical details following links in section 4.2.

4.4 Uses in Special Populations.

Pediatrics:
Over 65 years:
Renal impairment:
Hepatic impairment:

Indicate whether there are any limitations of use in these populations, and if so indicate attitude to follow (do not use, modify regimen, precautions ...)

4.5 Pharmacokinetics.

Provide a brief description. Extend only if it is potentially a differential element for decision-making.

5.- EVALUATION OF THE EFFICACY.

5.1.a Clinical trials available for the indication under assessment

Bibliographic search: criteria and results. The bibliographic references are abbreviated in the text: first author, journal and year.

Instructions section 5.1.a

We consider two types of strategies:

A) DRUGS RECENTLY AUTHORIZED

This type of drugs usually has few pivotal studies (maximum 2 or 3) for a specific indication. These trials are described and evaluated in the reports published by the agencies (FDA or EMA). It is common that trials have also been published in biomedical journals, but sometimes they are not at the time of writing the report.

The basis of the evaluation will be regulatory agencies reports and trial data are drawn from the them; to complement the above information, literature search is performed to locate:

- The pivotal trials that have been published.
- The post-registration published trials whose data can complement the information base.

Abstracts provide very limited quality information, lacking control that exists after publication in biomedical journals or in the reports of regulatory agencies.

As a general rule it is recommended to disregard them. However, since GENESIS evaluations are performed on many occasions at the time of drug marketing or prior to it, the number of published studies are often scarce. Abstracts may offer useful results for the evaluation process, bearing in mind that if they are included in the report we should be very cautious in assessing the results. Abstracts are sometimes a potent source of promotional material for the pharmaceutical company.

In summary, it may be justified to include abstracts on a limited basis in the following cases:

- Communications on experience of drug use in off-label indications for which there is no pivotal clinical trial, or any published trial (eg pediatric indications, special groups).
- Communications that include subgroups analysis of the pivotal clinical trials and provide relevant information to position the drug.
- Communications on new trial data or long-term results of previously known trials.

B) DRUGS LONG AUTHORIZED

These drugs usually have many published trials, plus reviews and meta-analyses. Sometimes these drugs have been approved by mutual recognition and have no agency reports from EMA or FDA.

The **basis of the evaluation will be the quality reviews and meta-analyses published**.

We can review in detail any individual clinical trial that can provide valuable data for assessment and therapeutic positioning, especially those published after the last systematic review of quality.

5.1.b Endpoints used in clinical trials

Table including definition of the endpoints used in the clinical trial.

Relationship between intermediate and final endpoints provided: discuss the robustness of the relationship.

Instructions section 5.1.b

It is recommended to include an information box with the definition and description of the variables used in the clinical trial.

List variables and their description ordered by primary and secondary variables. In case of composite variables, it is recommended to include the definition of each variable disaggregated. Usually the source of information is the section of the trial methodology.

DEFINITIONS:

- **Final endpoint**. When test results are expressed on clinical variables such as quality of life related to health, morbidity (MI or stroke) or mortality.

- **Intermediate or surrogate endpoint**: Intermediate or surrogate outcome (surrogate endpoints) have been defined as a laboratory measurement or a physical sign used as a substitute for a relevant clinical variable that directly measures how a patient feels, how it works or if it survives. Eg: taking cholesterol decrease instead of cardiovascular mortality.

When speaking of **intermediate variables**, its relationship with an important result for the patient must have been demonstrated, such that there is a strong and consistent relationship with the final clinical variable. It is desirable that there is evidence from clinical trials shwoing that an improvement in the surrogate outcome results in an improvement in the objective result (**predictive variables**). It may be that this is not so (**non-predictive variables**), it is only partially (**partially predictive variables**) or do not know the relationship (**relationship unknown**).

- **Composite or combined variables (composite endpoint)** are those where two or more variables are considered a single measurement of results. Theya reaqre usually justified on the assumption that the effect of each component is similar. To correctly interpret the composite variables is suggested that the following questions are taken into account:

1) Are the individual variables that make up the composite endpoint are of equal importance to patients?
2) Does the frequency of events is similar in the individual variables? Estimates of risk reductions are similar and sufficiently narrow CIs?
3) Individual variables have a similar relative risk reduction? Does the clinical relevance of individual variables is similar?

The answer to these questions will determine whether it is necessary to examine the individual variables separately.

Table nº x.
Endpoints used in clinical trials

EFFICACY	**Definition (1)**	**Description (2)**	**Intermediate or final endpoint (3)**
Primary endpoint			
Secondary endpoint a			
Secondary endpoint b			
…			
…			
SAFETY	**Definition (1)**	**Description (2)**	**Intermediate or final endpoint (3)**
Primary endpoint			
Secondary endpoint a			
Secondary endpoint b			
…			

(1) Brief definition of the variable (name given in the trial)
(2) Detailed description of the variable. If expressed in numeric rating scales is important to indicate the

extension (eg. scale of 1 to 100). If expressed in categories, indicate the number of categories
(3) In case of being intermediate define whether predictive, non-predictive, partially predictive or unknown.

Make brief global review indicating if there is solid evidence of the relationship (include references whether a relationship exists between predictor published and final)

For further information:

Montori VM, Permanyer-Miralda G, Ferreira-González I, Busse JW, Pacheco-Huergo V, Bryant D et al. Validity of composite end points in clinical trials. BMJ. 2005 Mar 12;330(7491):594-6.

5.2.a Results of clinical trials

The aim of this section is to present the results of the trials in an understandable and summarized way for the reader progresses in the analysis. It displays only the essential information, with the possibility of extending this information in annexes to the final report. Two strategies are established for the presentation of the results.

A) DRUGS RECENTLY AUTHORISED

Table 1. General template for efficacy results:
Reference:

Brief description of the trial, stating the most relevant aspects:
- Number of patients:
- Design: Phase of the trial, randomization, blind or open, etc:
- Active group and control group treatment:
- Inclusion criteria:
- Exclusion criteria:
- Dropouts:
- Type of analysis:
- Calculation of sample size:

Results

Endpoint	***Active group N (n pts)***	***Control group N (n pts)***			
Primary endpoint -Variable description					
Secondary endpoints (relevant) -Variable description					
Results by subgroup - Variable description					

Presentation of results by type of variable, see instructions for assistance

-Calculators for binary: RAR and NNT and 95% CI. CASPe.; SIGN:
-Calculator for continuous variables: R.Saracho.
-Other calculators / programs GENESIS Page http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/Calculadoras.htm

INSTRUCTIONS DRUGS TYPE A) Drugs recently authorized

The description of the characteristics of the trial could be in narrative form or integrated into the table (model Table 1).

Brief description of the test, stating the most relevant aspects:

- Number of patients.
- Design: Phase of the trial, randomization, blind or open.
- Active treatment group and control group treatment.
- Criteria for inclusion and exclusion.
- Drop outs.
- Type of analysis.
- Calculation of sample size: gives target information (HR or RAR) and the delta that was being sought in the design; this will get a lot of information for later discussion.

Secondary outcomes and Subgroups are given only if they are relevant to the evaluation. The complete data can be presented in an appendix at the end of the report

Figure. Algorithm of outcomes in assessment reports. The results of each trial shall be presented following the tables specific to the type of variable: binary, continuous or survival analysis (see table model below). The algorithm shows a classification of normal patterns of presentation in clinical trial results. Below are the instructions required to extract data from each type.

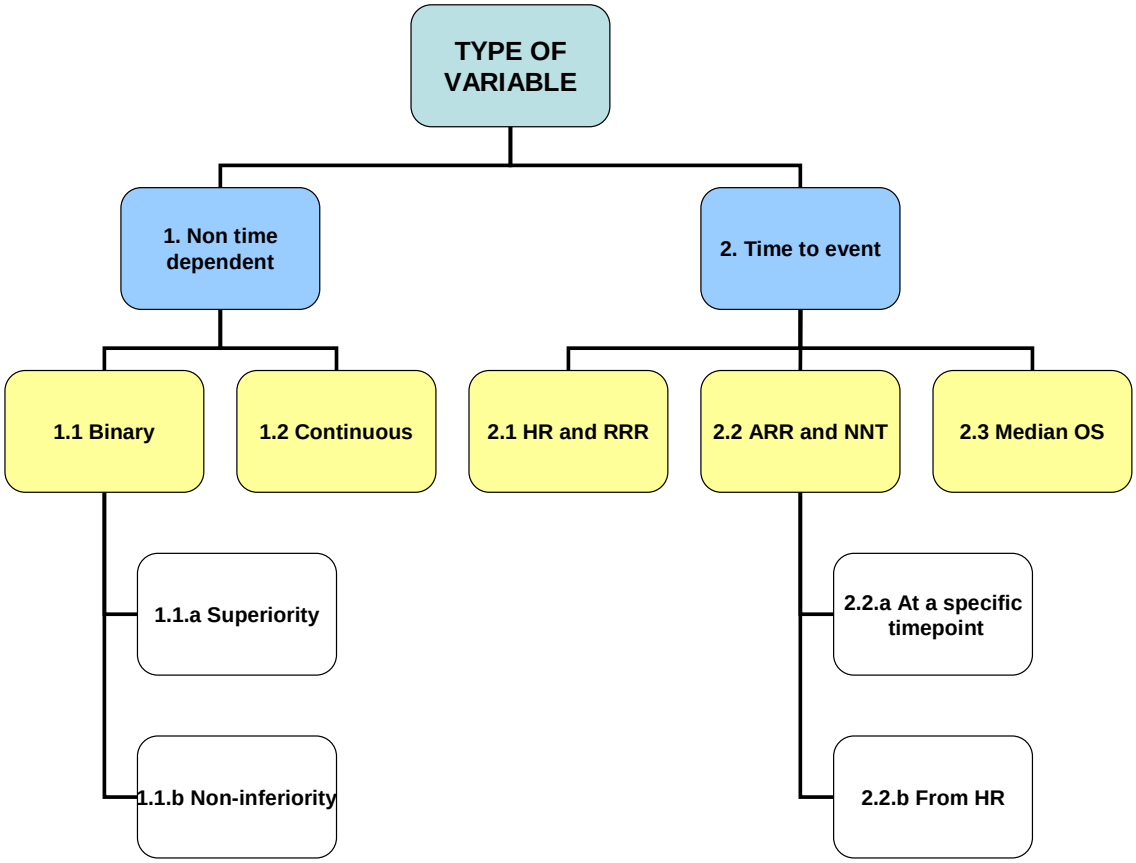


TABLE 1.1.a Binary variables. Superiority analysis

Whenever possible the results are expressed in ARR and NNT with 95% CI. Extract relevant data from the original source and if necessary recalculate the results using calculation programs described at the bottom of the table.

The model is presented as in Table 1.1.a

Table 1.1.a ***Results binary variables***					
Brief description of the trial, stating the most relevant aspects: *- Number of patients:* *- Design: Phase of the trial, randomization, blind or open, etc:* *- Active group and control group treatment:* *- Inclusion criteria:* *- Exclusion criteria:* *- Dropouts:* *- Type of analysis:* *- Calculation of sample size:*					
Results					
Endpoint	***Treatment***	***Control***	***ARR (CI 95%) *****	***p***	***NNT***

	studied N (nº pt)*	***treatment N (nº pt)****	Absolute Risk Difference		***(CI 95%)******
Primary endpoint -Variable description	*n (%)*	*n (%)*	*% (CI95 : x% to x%)*	*p*	*X (x to x)*
Secondary endpoints (relevant) -Variable description	*n (%)*	*n (%)*	*% (CI95 : x% to x%)*	*p*	*X (x to x)*
Results by subgroup - Variable description	*n (%)*	*n (%)*	*% (CI95 : x% to x%)*	*p*	*X (x to x)*
(*) If n is different for secondary endpoints or subgroup, please incluye it after the result. (**) Calculators for binary variables: ARR, NNT and CI 95%: **CASPe.; SIGN**: (***) Indicate NNT only if the result is statistically significant: p<0,05					

Binary variables (Instructions)

In the table we will present the most relevant results for primary and secondary outcomes and the magnitude of the differences between the groups:

- Absolute Risk Reduction (ARR) between the options evaluated with 95% CI.
- Statistical significance level, p.
- NNT and 95% CI: when presenting comparative trials with significant differences in efficacy results, and if the variables are binary, calculate and include the NNT (number needed to treat patients per additional efficacy unit) and CI 95%. They must be extracted from the trial data published and if necessary use the calculators.

Calculators RAR and NNT and 95% CI.

Comments for CASPe Calculator:
- Generally fits only two decimal places and rounds.
- In the case of NNT and 95% CI does not include decimals and rounds the result to the greater value.
- The NNT confidence interval when p <0.05 includes the infinite value, but in Excel is expressed that a limit of the CI is positive and the other negative.

Comments for SIGN Calculator:
- Sets the number of decimal places you wish (useful when p values are very close to 0,05). The results are more accurate

Other calculators.
Link to the website of GENESIS:
http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/Calculadoras.htm

NNT, with or without decimals:
- Clinically: It is generally expressed without decimal (rounded up). Recall that we are managing "patients", the number of patients needed to treat to get one additional unit of efficacy.
- Statistically: it is one more variable and may be suitable to express it in decimal. We recommend doing so when the NNT values obtained are very low (eg less than 5) or for economic calculations.

TABLE 1.1.b Binary variables. Non-inferiority analysis

When results are conducted using a non-inferiority analysis, shall state that the value of p corresponds to the same (eg, non-inferiority p <0.001).

When the noninferiority and superiority analyses are sequential then shall be entered both values of p (p superiority p noninferiority). The model presented as in Table 1.1.b:

Table 1.1. b ***Binary variables*** ***Results of the non-inferiority analysis***					
Study endpoint	***Treatment studied N (nºpt)***	***Control treatment N (nºpt)***	***ARR (CI 95%)*** Absolute Risk Difference *****	***p***	***NNT (CI 95%)***

Primary outcome *-Variable description*	*n (%)*	*n (%)*	*% (CI95 : x% to x%)*	p superiority p non-inferiority	*X (x to x)*

TABLE 1.2 Continuous variables.

For continuous variables the presentation of results is as follows, see Table 1.2:

Table 1.2 ***Results continuous variables***					
Study endpoint	***Treatment studied N (nº pac)****	***Control treatment N (nº pac)****	***Mean difference (CI 95%)*** **	***P***	***---***
Primary outcome *-Variable description*	*mean (sd)*	*mean (sd)*	Mean difference *(CI95% : x to x)*	*P*	---
(*) If n is different for secondary endpoints or subgroup, please incluye it after the result. (**) Calculators for continuous variables: **R.Saracho**. sd: standar deviation					

Continuous variables (Instructions)

- When the trial results are expressed as continuous variables, shall be recorded in the table the mean and standard deviation of the study group and the control group, and the mean absolute difference with 95% CI. In this case it is not possible to calculate the NNT.

Calculator **R Saracho:**

A calculator in an excel spreadsheet can be used, attached authored Ramon Saracho (Galdakao Hospital) with formulas and example taken from
http://bmj.bmjjournals.com/collections/statsbk/7.shtml

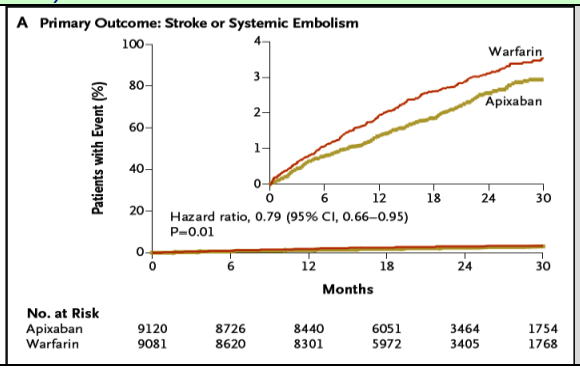
TABLE 2 Variables "time to event"

The choice of one model or another, depend on the type of trial, the area studied (cancer or cardiovascular therapy) and the results obtained. If necessary, the report may be included in more than one model. See the following Instructions.

In the report, and prior in the tables of data mining, may be of interest to match the graph of the main results, as published in the trial. See examples of graphical results in variables "time to event":

Examples.
Graphical representation of results primary endpoints for efficacy

Apixaban versus warfarin in patients with AF. (NEJM 2012)



Everolimus versus placebo (NEJM 2011)

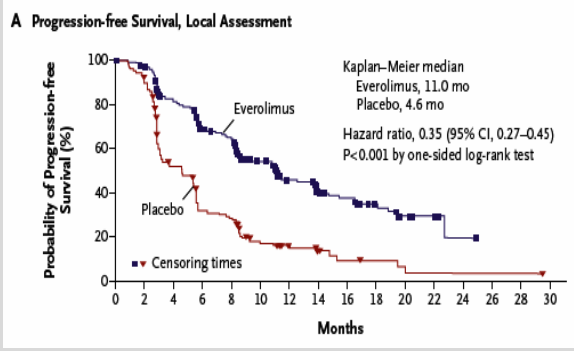


TABLE 2.1 Variables "time to event". HR y RRR.

Table 2.1 shows the template to represent HR and Relative Risk Reduction expressed in %.

Table 2.1 : Results for survival analysis: HR y RRR			
Study endpoint	***Hazard ratio HR (CI95%)***	***p***	***RRR (CI95%)***
Primary outcome -Variable description (Eg: Overall survival, Disease free survival...)	*x (CI95 : x to x)*	*p*	*X% (x% to x%)*

Variables "time to event". HR y RRR (Instructions)

In the Kaplan-Meier survival curves, the results are usually expressed as HR (Hazard Ratio), which is a relative measure. The HR event expresses the relationship between the two groups compared, not at a particular point of the study, but as a final measure that summarizes this relationship through the different follow-up intervals of the study. It is a relative measure expressing all the time tracked

The instantaneous RRR expressed in %, is calculated from the HR (1-HR) x 100. It is expressed as instantaneous "Relative risk reduction."

Example: If we consider two treatments: Treatment A versus Treatment B standard and the result is an HR = 0.65 in the variable mortality

HR = 0,65, then 1 - 0,65 = 0,35
Instantaneous RRR = 35 %

This indicates that the experimental treatment A "produces a relative risk reduction snapshot" of death of 35% compared to Drug B (at any time of the follow-up period).

Note: The HR is very similar to RR when: 1) There is low frequency of occurrence of the event and 2) Small percentage of censored data. In calculating HR at any time, we consider patients who are at risk of the event (ie, censored patients and those who have undergone the event are removed from the denominator at all times). However, to calculate the RR the denominator is the total of patients who entered the study.

TABLE 2.2.a Variables "time to event". ARR and NNT at a specific time.

Simple probability

Table 2.2.a : Results for survival analysis: RAR y NNT at a specific time (simple probability)					
Study endpoint and time	***Treatment studied N (pts in time t)***	***Control treatment N (pts in time t)***	***ARR (CI 95%)*** Absolute Risk Difference *****	***p***	***NNT (CI 95%)****
Primary outcome -Variable description (Eg: Overall survival, Disease free survival, … at year 1, at year 3 or at the end of the treatment)	*%*	*%*	*% (CI95 : x% to x%)*	*p*	*X (x to x)*
Ref: Altman DG, Andersen PK. Calculating the number needed to treat for trials whose the outcome is time to an event. BMJ 1999; 319: 1492-5					

ARR values (CI95%) and NNT (CI95%) can be calculated as **simple probability data**, using the calculator CASPe, SIGN or similarly from the results of survival analysis.

-If we take raw values obtained at the end of the trial (patients with no event over the total patients), we will have a value of ARR and NNT similar to the Table 1.1.a

-If we take the values of certain time periods: the NNT will be different for each point of the follow-up period.

Variables "time to event". RAR and NNT at a specific time (Instructions)

From the survival curves is possible to calculate the ARR and NNT for a given follow-up time, eg 1 year, 3 years or 5 years. In this case the ARR (and therefore also the NNT) will be different for each time period, but the calculation to expresses and appreciates the clinical significance of the difference in efficacy of study treatments, and incorporate them in a table as disclosed in section 5.2.

The ARR is obtained directly from the trial data in a given time: risk of each group and risk difference. If you also have the number of patients at risk ("number at risk") in a certain time we can calculate the 95% CI using the calculators above table of binary variables.

Ref: Altman DG, Andersen PK. Calculating the number needed to treat for trials whose the outcome is time to an event. BMJ 1999; 319: 1492-5

See example in the graph:

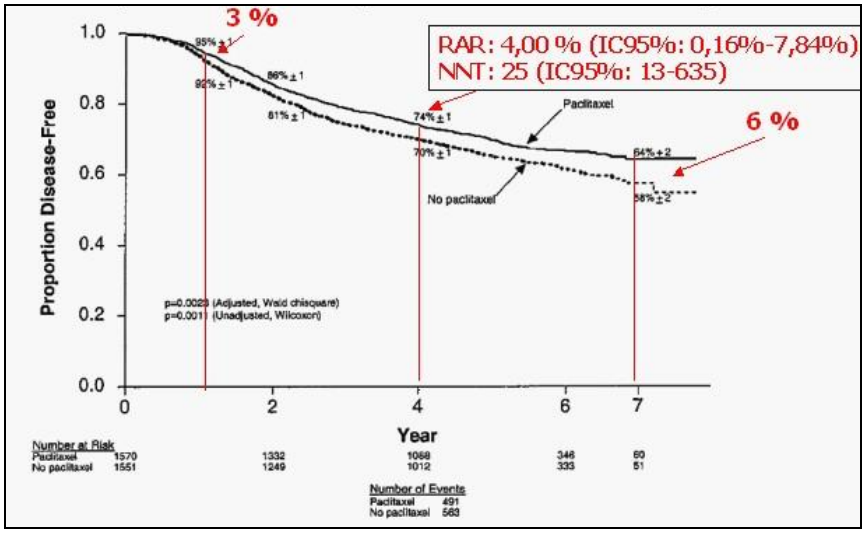


TABLE 2.2.b Variables "time to event". ARR and NNT calculated from HR.

See table 2.2.b

Presentation of survival analysis results with NNT (95% CI) and ARR (95% CI) from HR. (For cumulative probabilities and event-time rate). They are suitable for trials from the cardiovascular area that usually present a low event rate. Generally this can not be applied when the event rate is high, such as in most oncology trials.

There are two options, depending on the time period considered.

a) **From the HR and the cumulative probabilities obtained throughout the study period.**

b) **From HR and cumulative probabilities results based on 100 patient-years.** Estimates are obtained from events per 100 patient-years.

This enables to obtain results from HR NNT per patient exposure time which facilitates better compare the results of different studies together. It can be applied in many studies of the cardiovascular area in which the results are presented as the rate of events per 100 patient-years.

Table 2.2.b: Survival analysis results: RAR y NNT calculated from HR (Probability)					
a) Cumulative probability at the end of the trial					
Endpoint	***Treatment studied n***	***Control treatment n***	***ARR (CI95%) Calculated from HR (CI95%)***	***p***	***NNT (CI95%) Calculated from HR (CI95%)***
-Brief description of the variable	*Cumulative probability b*	*Cumulative probability a*	*X % (x% to x %)*	*p*	*HR: x (x to x)* *NNT: x (x to x)*
b) Cumulative probabilities results based on 100 patient-years					
-Brief description of the variable	Event rate per 100 patient-years b	Event rate per 100 patient-years a	*X % (x% to x %)*	*p*	*HR: x (x to x)* *NNT: x (x to x)*

Variables "time to event". RAR y NNT from HR based on cumulative probabilities (Instructions)

For the calculation of NNT (95% CI) from HR (95% CI) based on cumulative probabilities (obtained from final results or outcome annualized), we can use the spreadsheet designed by Eduardo Lopez Briz (2010) and modified by Iziar Martínez-López (2012). It is based on the equation 1 of the article:

> *Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ 1999; 319:1492-5*

Calculator López-Briz-Iz:

http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/CalculadoraNNTdesdeHR(LopezBriz-iz)_2012.xls

NNT RATE OF EVENTS-TIME

- It is very common in cardiovascular trials presenting results in cumulative incidence rates per 100 patient-years, from which one can calculate the NNT (CI95%) based on the HR (CI95%). The NNT obtained refers not to all patients but "patient-years". For example, if the NNT is 300, it means that for every 300 patient-years treated with the drug, we were able to avoid an event in one patient.

The NNT is obtained from the data of annual incidence rate (hazards) of the event per 100 patients where:

- Number of events / sum of units of time that the subjects of the population have been at risk.
- The inverse of the difference between the incidence rate represent the incidence rate of events prevented per patient - time

The **"Annualization" NNT** is applicable provided that we have:

- Few losses
- Risk constant over time
- NNT is not time dependent
- Benefit constant treatment over time
    - Is it the same treat 12 patients for 1 year to 6 for 2?
    - Long-term follow-ups and / or chronic treatment
    - The longer the follow up, the greater the absolute event rate

Advantages: Standardization → better interpretation and comparability

- Suissa D, Brassard P , Smiechowski B, Suissa S. Number needed to treat is incorrect without proper time-related considerations. J Clin Epidemiol. 2012 Jan,65(1):42-6.Epub 2011 Aug 4.

-Mayne TJ, Whalen E, Vu A. Annualized was found better than absolute risk reduction in the calculation of number needed to treat in chronic conditions. J Clin Epidemiol.2006 Mar,59(3):217-23

Presenting results together

Sometimes it may be of interest to include in the same table the results of survival analysis with RAR (CI95%) and NNT (CI95%) at a given time according to simple probabilities (Table 2.2.a) and the results of analysis survival with NNT (95%CI) and RAR (95%CI) from HR based on cumulative probabilities, or more frequently - time event rate annualized (Table 2.2.b).

An example of extraction from the Aristotle trial results including both sets of results:

Example. *Efficacy results from the Aristotle triale*:
Reference: Granger CB et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92.

Endpoint	*Apixaban N (9.120)*	*Warfarina N (9.081)*	*ARR (CI95%) at 1,8 year (*)*	*NNT (CI95%) at 1,8 year (*)*	*NNT (CI95%) Per patients-year (**) from HR*
	Total patients with event (events per 100 patients-year)				
Stroke and syst. embolism.	*212 (1,27%)*	*265 (1.60%)*	*0,6% (0,13% a 1,06%)*	*168 (95 a 773)*	*HR:0,79 (0,66-0,95) NNT:300 (185-1260)*
Stroke	*199 (1,19%)*	*250 (1,51%)*	*0,6% (0,12% a 1,02%)*	*175 (98 a 832)*	*HR:0,79 (0,65-0,95) NNT:317 (190 - 1334)*
Haemorraghic stroke	*40 (0,24%)*	*78 (0,47%)*	*0,4% (0,2% a 0,7%)*	*238 (153 a 535)*	*HR:0,51 (0,35-0,75) NNT:435 (328 – 853)*
Systemic embolism	*15 (0,09%)*	*17 (0,10%)*	*NS*	*NA*	*NA*
Death for any causae	*603 (3,52%)*	*669 (3,94%)*	*1,1% (0,8% a 1,8%)*	*132 (67-6951)*	*HR: 0,89 (0,80-0,998) NNT:235 (129-12948)*
Myocardial infarction	*90 (0,53%)*	*102 (0,61%)*	*NS*	*NA*	*NA*

(*) NNT (95% CI) and ARR (CI95%) probability calculated according to simple calculator using CASPe or similar. Estimates are obtained at 1.8 years.
(**) NNT (95% CI) calculated from the HR and cumulative probabilities (annual incidence rates per 100 patient event) drawn from the results of the study, using the calculator Lopez Briz (from equation 1 Altman article BMJ 1999). Estimates are obtained by patient-years.
NS: Not significant (p> 0,05). NA: Not suitable

TABLE 2.3 Variables "time to event". Mean (median) survival time.

See Table 2.3

In survival analysis with a high rate events, for example in oncology results are presented of the median survival time and the median difference.

Table 2.3 : for results of the survival analysis
Median survival time

Endpoint	*Treatment studied N (nº pts)*	*Control treatment N (nº pts)*	*Difference in median survival*	*p*	*---*
Primary endpoint -Variable description (Eg: Mean (median) survival time)	*Mean or median b*	*Mean or median a*	*Mean or median difference b - a*	*p*	*---*

Calculation of median times of survival. Difference in median survival (Instructions)

In oncology is frequent to present results in **median overall survival time (OS)** or the **median time of progression free survival (PFS)**. It is the time when the cumulative probability of survival or having the event (OS or PFS) is 50 %. We take the point where the survival probability is 0.5 on the Kaplan-Meier curve and check what time it corresponds to.

From a clinical perspective, the **median time of SG or SLP** is considered the preferred summary measure of the distribution of survival times. The **difference in median survival** has the

advantage of avoiding assumptions about long-term survival patterns beyond the follow-up period of the trial. However there may be variability in the difference in median survival at the point chosen and not reflect the actual survival difference between treatments.

In principle the survival benefit between two curves can come better expressed with the **mean difference in survival**. This can be estimated by calculating the area under curve of empirical survival. However, the survival curves are often incomplete (right censored) and duration of clinical trials is rarely sufficient to monitor all patients until death. The final part of the survival curve can be extrapolated using mathematical models; however, a degree of error between the fitted curve and thumb is inevitable.

It can not be recommended "a priori" preference for mean or median. In most cases the median survival time of the control and intervention group and their difference will be the only available published data. If means data are also available, both must be considered, and if there is much difference between the values obtained we must analyze the factors that have caused this difference: inadequate monitoring, proportion of patients censored, subgroups with prolonged survival…

MEDIAN: not affected by extreme values, so it is recommended in the case of non-normal variables if we eliminate the influence of these extremes. Just pick up the information from the first half of the survival curve, given that this part of the curve is the least affected by confounding factors, eg chemotherapy treatments on subsequent lines. You would give a biased estimate if the shape of the curve changes in the 2nd half.

MEAN: Collect all the trial information so it is not affected by the shape of the curve but by extreme values. In case of a large number of censored patients may also be affected.

In addition, when using OS or PFS data, **the right thing is its joint assessment along with the HR**, the global statistical interpretation of the curve as a relative measure of the relationship of events.

References:

EMA/CHMP. Appendix 1 to guideline on the evaluation of anticancer medicinal products in man. Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials. EMA/CHMP/27994/2008. Rev 1. 5 Dec 2011
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/12/WC500119965.pdf

Tappenden P, Chilcott J, Ward S, Eggington S, Hind D, Hummel S. Methodological issues in the economic analysis of cancer treatments. European Journal of Cancer. 42 (2006) 2867–2875

Ocana A, Tannock IF. When Are "Positive" Clinical Trials in Oncology Truly Positive? J Natl Cancer Inst 2010;103:1–5

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Confidence levels calculation (CL) (Instructions)

The CL provides additional information about the values of p and the CI. CL values are of interest to interpret the trial results and their clinical relevance.

If the p-value is 0.05, indicates that the probability of success in denying the null hypothesis is 95% and therefore embrace the alternative hypothesis. But, how should we interpret a p-value close to 0.05? Eg 0.06. In this case the probability of success in denying the null hypothesis is less than 95%, but with a value very close to it.

If the variable under consideration is of great clinical weight (eg mortality), it is possible and desirable to determine what exactly this probability value. It is what is called "confidence level"

Calculation only recommended in very specific cases in which p values are presented borderline and the variable is of clinical relevance. You should be very cautious in their interpretation. If we have a delta value for therapeutic equivalence, we can also apply it in these cases to determine the exact probability that the results are in that range. (See additional information recommended)

It also has a calculator Confidence Levels (CL) (Free statistical software: Dr. Shakespeare's Confidence Calculator. Publish a page that can be downloaded excel. Link to Shakespeare calculator. Link *http://www.theshakespeares.com/Free_statistical_software.html*

Fur further information:

Shakespeare TP, Gebski VJ, Veness MJ, Simes J. Improving interpretation o clinical studies by use of confidence levels, clinical significance curves, and risk-benefit contours. Lancet. 2001 Apr 28;357(9265):1349-53. Review. PubMed PMID: 11343760
http://www.pitt.edu/~super1/lecture/lec10421/index.htm

Escrig Sos J, Miralles Tena JM, Martínez Ramos D, Rivadulla Serrano I. Intervalos de confianza: por qué usarlos. Cir Esp 2007; 81: 121 – 125. s
http://www.elsevier.es/revistas/ctl_servlet?_f=7064&articuloid=13099760

INSTRUCTIONS DRUGS TYPE B). Long authorized

These drugs usually have many published trials, plus reviews and meta-analyses and have been approved by mutual recognition, so that there are no agency reports from EMA or FDA. **The basis of the evaluation will be the quality reviews and meta-analyses published**

It is generally presented following the same data formats and tables but if there are many clinical trials is recommended to summarize trial results in a single table. Overall same scheme as Tables 1 and 2, see table 3.1.

Table 3.1

Variable description

Results binary variables

References	***Treatment studied N (nº pts)*****	***Control treatment N (n pts)*****	***ARR (IC 95%)*** * Absolute Risk Difference*	***p***	***NNT (CI 95%)******
Trial 1 (ref) year	*%*	*%*	*% (CI95 : x% to x%)*	*p*	*X (x to x)*
Trial 2 (ref) year	*%*	*%*	*% (CI95 : x% to x%)*	*p*	*X (x to x)*
Trial 3 (ref) year	*%*	*%*	*% (CI95 : x% to x%)*	*p*	*X (x to x)*
Trial 4 (ref) year	*%*	*%*	*% (CI95 : x% to x%)*	*p*	*X (x to x)*

(*) Calculators for binary variables: ARR, NNT and CI 95%.**CASPe.; SIGN**
(**) If n is different for secondary endpoints or subgroup, please incluye it after the result.
(***) Indicate CI 95% and NNT only if the result is statistically significant: p<0,05

Table 3.2

Variable description

Results continuous variables

References	***Treatment studied N (nº pts)*****	***Control treatment N (n pts)*****	***Mean difference (CI 95%)*** *	***p***	***---***
Trial 1 (ref) year	*mean*	*mean*	*Mean difference (CI95% : x to x)*	*p*	*---*

Trial 2 (ref) year	*mean*	*mean*	*Mean difference (CI95% : x to x)*	*p*	---
Trial 3 (ref) year	*mean*	*mean*	*Mean difference (CI95% : x to x)*	*p*	---
Trial 4 (ref) year	*mean*	*mean*	*Mean difference (CI95% : x to x)*	*p*	---
(*) Calculator for continuous variables: **R.Saracho** (**) If n is different for secondary endpoints or subgroup, please incluye it after the result.					

In the meta-analysis, results are often presented in the form of RR or OR. Follow the form of results as set forth in table 3.3. It has some formulas for calculating the NNT from RR or OR in a meta-analysis.

Access NNT calculators from RR or OR: link to calculators in the GENESIS web

If there are several meta-analyses or any subsequent clinical trial, summarize them in a single Table.

Table 3.3
Meta-analysis reference:

Brief description of the meta-analysis
N. of trials N. of patients.
Inclusion and exclusion criteria of trials:
Active treatment group and control group:

Resultados

Meta-analysis endpoint	***Treatment studied N (nº pts)***	***Control treatment N (nº pts)***	***ARR, RR u OR (CI 95%)***	***P***	***NNT (CI 95%)****
Primary endpoint *-Variable description*	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
Secondary endpoint of interest *-Variable description*	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
Subgroup results *- Brief variable description*	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*

* Access NNT calculators from RR or OR: link to calculators in the GENESIS web

Clinical and statistical heterogeneity: Meta-analysis are conducted usually retrospectively so that combining the results of studies conducted with different protocols on different patients with different doses of drugs also on occasions. The studies present therefore heterogeneity.

There is some evidence to assess statistical heterogeneity between studies (Cochran's Q, I2) but it is also important to ensure that there is no such clinical heterogeneity that prevents the combination of results.

To this we must assess whether the effect of the various studies is always produced in the same direction and if the effect size is consistent.

Fur further information:

Instructions section 5.3.a *"Systematic reviews"*

5.2.b Evaluation of the validity and practical utility of the results

A. Internal validity. Limitations of design and / or comments**:**

Instructions:

A-Exposing critically the key study areas in terms of internal validity. We consider three basic aspects to ensure that a clinical trial has a good level of validity:
- Randomization and concealment of the randomization sequence
- Comprehensive monitoring of all subjects

- Analysis by intention to treat.

In addition to the above three points, a number of secondary features which provide guidance on the quality of clinical trial: Masking, baseline comparability of the groups, comparability of groups throughout the follow-up and variables used

It is recommended to give narrative form to the main critical points.

B-Complete the unified table for bias from the Cochrane Collaboration

To complement the previous point is recommended to review the aspects of validity that can further influence the interpretation of results. For this we use the Cochrane Collaboration tool for assessing the "risk of bias" of a study.

The same includes a) a description of the trial design, b) observations that support the evaluation and c) a final assessment of the "risk of bias" (assigned a rating of 'Low risk' of bias, 'High risk' of bias or 'unclear risk').

Apply the attached questionnaire (see Table), which is completed at the beginning of the evaluation of the trial. This questionnaire is qualitative and replaces JADAD scale included in the previous version. It is included as an annex to the final report.

Table 5.2.b.1
Unified table for bias from the Cochrane Collaboration
Risk of bias assessment

Item	**Description**	**Support for assessment**, evaluation based observations.	**Assessment of risk of bias** (High Risk, Low Risk, Risk unclear)
Selection bias			
Allocation sequence generation			
Allocation concealment			
Realization bias			
Staff and patients blinding			
Detection bias			
Clinical evaluator blinding			
Result evaluator blinding			
Attrition bias			
Incomplete outcome data managment			
Notification bias			
Selective outcome reporting			
Other sources of bias			

Evaluations should consider the risk of bias of sufficient magnitude to have a significant impact on the results or conclusions of the trial. If not described in sufficient detail about what happened in the study, usually risk of bias will be assessed as 'Unclear'. It should also be assessed as 'Unclear' if you know what happened in the studio but the risk of bias is unknown, or if the item available is not relevant to the study (especially for assessing blinding and incomplete outcome data, in which the result evaluated by the item was not measured in the study).

To complete the table, the Cochrane Collaboration gives a guideline and description of the tool for assessing risk of bias.

- Cochrane Handbook for Systematic Reviews of Interventions:
http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm

- CONSORT

For a critical review of a clinical trial can be employed-CONSORT list, but is focused mainly to meet quality criteria for publication and in practice is very complex in its application in the context of an evaluation report. List-CONSORT, for further information: http://www.consort-statement.org/consort-statement/overview0/

B. Applicability of the trials to hospital practice

Instructions:

Expose the external validity or applicability of the trials to hospital practice. Reply and expose the highlights in relation to the following questions:

Is the comparator the appropriate standard?
Is the treatment time adequate?
Is the regimen of the comparator treatment the usual?
Is the treatment regimen of the drug the one finally approved?

Is the measured outcome variable evaluated routinely in the clinic?
Do you might consider the difference obtained as clinically relevant improvement?
Are there similar patients who receive the drug in the hospital?

Are the clinical monitoring and patient care similar to the hospital?
Is the follow up time adequate?

The following survey facilitates the analysis of the external validity of the trial. Be worded in the annex to the final report

5.2.b.2 Table 3
APPLICABILITY OF THE TRIALS TO HOSPITAL PRACTICE

	YES/NO	JUSTIFY
Is the comparator the appropriate standard?		Drug, dose, posology, duration of the treatment
Do you consider the results clinically relevant?		Do you might consider the difference obtained as clinically relevant improvement?
Is the measured outcome appropriate?		Is the measured outcome evaluated routinely in the clinic?
Do you consider the inclusion and exclusion criteria adequate?		Are there similar patients who receive the drug in the hospital?
Are the results directly applicable to routine clinical practice?		Feasibility in our enviroment
Other limitations to external validity		Comments

C. Clinical relevance of the results

C.1 Magnitude of the treatment effect.

Instructions:

We will present a narrative an assessment of the magnitude of the effect, depending on the outcome variable and the history of other drugs available for the same indication. Consider the following:

Defining a value as clinically relevant, must be considered from the standpoint of clinically and statistically.

From the **clinical point of view** some criteria should be considered:

- It should be noted the inherent variability of the results of the therapeutic application in a particular clinical environment.

- As already stated, in equivalence and non-inferiority studies the margin to outline clinical irrelevance is the so-called "delta", which can be defined as the maximum difference between the treatments that we consider clinically irrelevant. In studies of equivalence is defined by a range that is defined between a lower and an upper limit, while in the non-inferiority studies is defined by only the lower limit.

- In the studies we estimate superiority based on the minimum efficacy differences used to calculate the sample size.

- In any case, it is important to review the report and our own judgment and assess what is relevant in the context of variable type (intemediate, final) and the particular disease process.

After defining what is considered relevant minimum value from the clinical point of view, we can raise it from the **statistical point of view**.

In studies of superiority we observe the following:

- If the value of the ARR found in the trial is statistically significant, and CI95% is above the value adopted for clinical relevance (delta value), we conclude that the study treatment is clinically superior. (Case B in Figure 1).

- If the value of the ARR found in the trial is statistically significant, and CI95% confidence is below the value adopted for clinical relevance (delta value), we conclude that the study treatment is clinically equivalent (Case C in Figure 1).

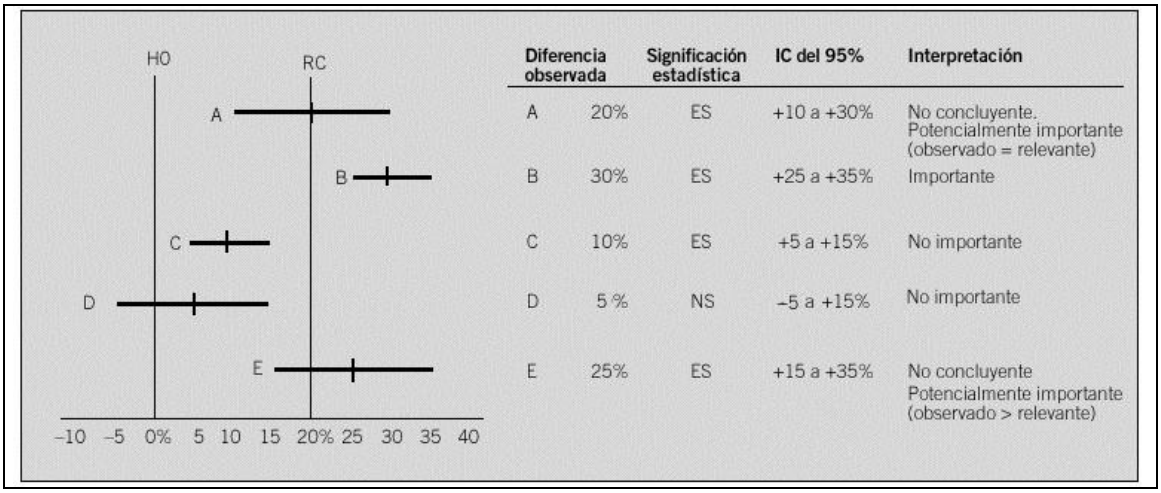
- If the value of the ARR found in the trial is not statistically significant, and CI95% confidence is below the value adopted for clinical relevance (delta value), we conclude that the study treatment is clinically equivalent; we also consider that the drug could be somewhat higher or somewhat lower but clinically unimportant (Case D figure 1).

Cases A and E indicate superiority and potential clinical importance, although not conclusive, must be taken into account as indicative of superiority.

The advantage of non-inferiority and equivalence studies, is that in the same study we define the delta value considered clinically relevant. In superiority we must estimate it based on the above points.

Figure 1. Hypothetical results of a study comparing active treatment vs placebo. It is considered that the minimum clinically relevant ARR is 20%.

ES: statistically significant difference. NS: not statistically significant. Adapted from Argimon JM. Med Clin (Barc) 2002, 118:382-4.



	Diferencia observada	Significación estadística	IC del 95%	Interpretación
A	20%	ES	+10 a +30%	No concluyente. Potencialmente importante (observado = relevante)
B	30%	ES	+25 a +35%	Importante
C	10%	ES	+5 a +15%	No importante
D	5 %	NS	−5 a +15%	No importante
E	25%	ES	+15 a +35%	No concluyente Potencialmente importante (observado > relevante)

C.2 Evidence of therapeutic equivalence.

Instructions:

The process begins with the identification of clinical trials and studies available that provide information to determine whether the drug is therapeutically equivalent to another reference drug. After the selection, relevant studies are classified according to their level and degree of evidence. Sort according to criteria of the table.

Levels and degrees of evidence of therapeutic equivalence.

Type of study		Level of evidence	Degree of evidence
"Evidence"	Equivalence and non-inferiority RCTs	**1**	High
"Estimation"	Equivalence RCTs without clinical relevance	**2**	High
	Superiority RCTs without statistical significacance	**3**	Moderate
	RCTs vs a common comparator	**4**	Moderate
	RCTs vs a different comparator	**5**	Low
	Observational studies		
"Support"	Reviews, CPGs, recomendations, expert opinions, clinical judgement	"Support to levels above"	

RCTs: Randomized Clinical Trials.

From a practical approach, the studies to determine therapeutic equivalence can be grouped into two broad groups: those that reveal equivalence and those that estimate equivalence. The evaluation of the quality and validity of studies modulates the level of evidence to determine the degree of evidence: high, moderate, low or very low.

According to the studies identified, we will evaluate the need to apply the criteria and methodology defined in ETA guideline (see next section). For more information:

Pinteño M, Martínez-López I, Delgado O. Equivalentes terapéuticos: Concepto y niveles de evidencia. El Comprimido.com 2006; nº 6: 14-18.
http://www.elcomprimido.com/articulos%20PDF/El%20Comprimido_n_6.pdf

Delgado O, Puigventós F, Pinteño M, Ventayol P. Equivalencia terapéutica: concepto y niveles de evidencia. Med Clin (Barc) 2007; 129 (19): 736-45.

C.3 Equivalent Therapeutic Alternatives (ETAs)

Instructions:

Determine if two or more drugs are Equivalent Therapeutic Alternatives (ETAs). According to the studies identified in the previous section, we apply the criteria and methodology defined in ETA guideline

Ref: Emilio Jesús Alegre Del Rey; Silvia Fénix Caballero, Rocío Castaño Lara, Francisco Sierra García, Esther Márquez Saavedra. Grupo GHEMA (Grupo hospitalario de evaluación de Fármacos de Andalucía). Guía ATE. Evaluación y posicionamiento de fármacos como alternativas terapéuticas. 2012

Relevant aspects of ETA Guideline (ETAG):

We can consider Equivalent Therapeutic Alternatives (ETAs) those drugs that can be used interchangeably to treat most patients with a certain clinical condition, without a priori, once considered the best available evidence, a greater or clinically relevant benefit can be expected for selecting one or the other.

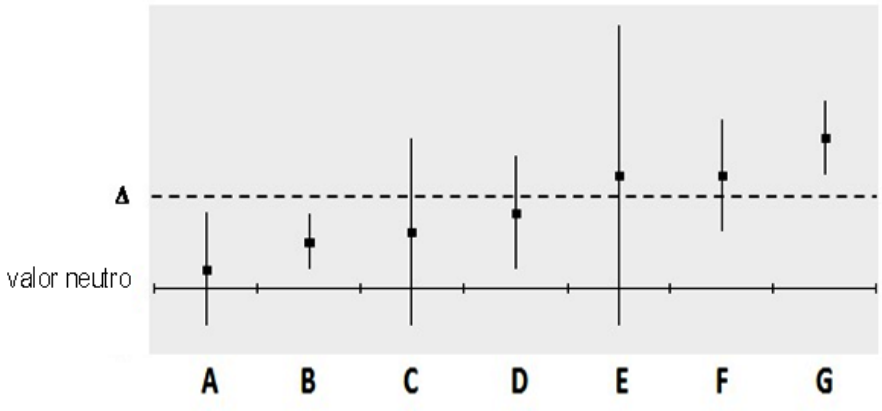
The statement as ETA does not always imply therapeutic equivalence demonstration in a clinical trial with a direct comparison specifically designed for this purpose. It may happen that, in most patients, once considered the best available evidence, there are no results that make you opt for a drug or other in the therapeutic decision making process. In this case, between two treatments with similar expected benefit, it is reasonable to use the one with the lowest cost for a proper utilization of resources, without prejudice to any justified exceptions in patients or specific patient groups.

The basic concepts underlying the methodology developed in the ETAG are those of the three following tables.

NOTE: The classification of Table 1 has been made considering three questions:

1) If there is significant difference.
2) If the measure of risk (ARR, RR, HR, OR, difference in mean or median) is located inside or outside the range of equivalence.
3) If the 95% CI of the risk measure falls within the margin of equivalence, it is exceeds partially or completely out of it

Table 1.
RANGE OF CASES WE CAN FIND OF VALUES AND CI95% REGARDING DELTA VALUE



In the various cases, considerations for positioning as ATE / no ATE would be:

A. EQUIVALENT (statistically and clinically).
B. CLINICAL EQUIVALENCE (minor difference).
C. PROBABLE CLINICAL EQUIVALENCE.
D. PROBABLY DIFFERENCE IRRELEVANT.
E. POSSIBLE SIGNIFICANT DIFFERENCE.
F. PROBABLY SIGNIFICANT DIFFERENCE.
G. SIGNIFICANT DIFFERENCE. Exists and is clinically relevant difference. Not ATEs

TABLE 2,
INTERPRETATION OF THE DIFFERENCE

ITEMS TO DEFINE THE DIFFERENCE			INTERPRETATION	
1. Statistically significant difference?	2. ARR, OR, RR or HR exceed delta value?	3. CI95% outside the range of equivalence?	Clinically relevant difference	Grade of equivalence
NO	**NO**	**NO**	NO	**A. EQUIVALENT (statistically and clinically).**
YES	**NO**	**NO**	NO	**B. CLINICAL EQUIVALENCE (minor difference).**
NO	**NO**	**YES partially**	Doubtful. Probably not (<50% probability)	**C. PROBABLE CLINICAL EQUIVALENCE.**
YES	**NO**	**YES partially**	Doubtful. Probably not (<50% probability)	**D. PROBABLY DIFFERENCE IRRELEVANT.**
NO	**YES**	**YES partially**	Doubtful. Probably yes (>50% probability)	**E. POSSIBLE SIGNIFICANT DIFFERENCE.**
YES	**YES**	**YES partially**	Doubtful. Probably yes (>50% probability)	**F. PROBABLY SIGNIFICANT DIFFERENCE.**
YES	**YES**	**YES totally**	YES	**G. SIGNIFICANT DIFFERENCE.**

Table 3
RECOMMENDED POSITIONING

Interpretation *(Statistically significant difference + clinical relevance)*	**Recommended Positioning Scenario 1** *When a worse outcome in the studied variable DO NOT imply serious / irreversible damage*	**Recommended Positioning Scenario 2** *When a worse outcome in the studied variable DO imply serious / irreversible damage*
A. EQUIVALENT (statistically and clinically).	**ETA**	**ETA**
B. CLINICAL EQUIVALENCE (minor difference).	**ETA**	**ETA**
C. PROBABLE CLINICAL EQUIVALENCE.	**ETA**	**no ETA***
D. PROBABLY DIFFERENCE IRRELEVANT.	**ETA**	**no ETA**
E. POSSIBLE SIGNIFICANT DIFFERENCE.	**ETA***	**no ETA**
F. PROBABLY SIGNIFICANT DIFFERENCE.	**no ETA**	**no ETA**
G. SIGNIFICANT DIFFERENCE.	**no ETA**	**no ETA**

* These cases are more Doubtfuls and admit some exceptions (see previous justification).

5.2.c Assessment screening tests used

In this section of the report will include a summary of the critical aspects to be taken into account in assessing the usefulness of a screening test (pharmacogenetic tests , biomarkers ...) .

- Analytical validity of the test (diagnostic accuracy)
- Clinical validity of the test
- Clinical utility in routine practice

Instructions :

We present concisely the most important aspects of each of the three points:

- Analytical validity (diagnostic accuracy): The accuracy with which a particular feature can be identified by a test.
- Clinical validity: strength of association between the variant and clinical outcome. Eg: Efficacy, adverse reactions...
- Clinical utility: effectiveness and safety of clinical intervention implemented as a result of the screening test. Here we take into account practical aspects like the availability of testing and severity of adverse reactions in the safety profile of the drug.

There are several sources of information available to specific content on pharmacogenetics.

For more information see:

- PharmGKB (http://www.pharmgkb.org/) is a source of knowledge about pharmacogenomics, covering clinical information, including dosing guidelines and technical information related to genetic testing, drug-gene associations clinically relevant and genotype-phenotype relationships.

- The Working Group EGAPP (http://www.egappreviews.org/) was established in 2005 to support the development of a systematic process to evaluate the available evidence on the validity and utility of genetic testing in clinical practice. This independent and multidisciplinary group prioritizes and selects the tests, shows critical information gaps and provides guidance on the appropriate use of genetic tests in specific clinical situations.

We must make a critical reading of the information in these sources because many of the genetic tests have no clinical utility, are not cost-effective or have not been tested in the general population.

5.3 Published systematic reviews, indirect comparisons and conclusions

For drugs long authorised, systematic reviews and meta-analysis will be the basis of evaluation.

5.3.a Published systematic reviews

In the meta-analysis results are often presented in the form of RR or OR. Presentation will follow the form of results as set forth in Table 3.3. There are formulas for calculating the NNT from RR or OR in a meta-analysis.

Access NNT calculators from RR or OR in the GENESIS website

If there are several metaanalysis or any subsequent clinical trial, summarize them in a single table.

Reference:					
Results					
Brief description of the meta-analysis N. of trials N. of patients. Inclusion and exclusion criteria of trials: Active treatment group and control group:					
Meta-analysis endpoint	***Treatment studied N (nº pts)***	***Control treatment N (nº pts)***	***ARR, RR u OR (CI 95%)***	***P***	***NNT (CI 95%)****
Primary endpoint *-Variable description*	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
Secondary endpoint of interest *-Variable description*	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
Subgroup results *- Brief variable description*	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
(*) Indicate CI 95% and NNT only if the result is statiscally significant: p<0,05 (**).Calculator for ARR, NNT and CI 95% from CASPe. Access NNT calculators from RR or OR: link to calculators in the GENESIS web					

Instructions:

For the interpretation of the results of the meta-analysis, its validity and practical application will follow the same criteria for evaluation of a clinical trial:

Internal validity. Limitations of design and / or comments.
Applicability of the results to the hospital practice.
Clinical relevance of the results.

Regarding the validity, meta-analysis are performed by combining the results of studies with different protocols on different patients with different doses of drugs also on occasions. The studies present therefore heterogeneity. It is therefore important to assess this issue and expose it.

Degree and type of heterogeneity, consistency of results.
Statistical I2

The variability in participants, interventions and outcomes studied can be described as clinical diversity (sometimes called clinical heterogeneity), and variability in study design and bias risk can be described as methodological diversity (sometimes called methodological heterogeneity).

The variability in the effects of the intervention being evaluated in different studies is known as statistical heterogeneity and results from clinical or methodological diversity, or both, between studies. Statistical heterogeneity is evident when the observed intervention effects are more different than would be expected if they were due only to random error (chance).

Test to measure statistical heterogeneity

You must first consider to what extent the results of the studies are consistent. To this we must assess whether the effect of the various studies is always produced in the same direction and if the effect size is consistent. It is important to ensure initially that there is no clinical heterogeneity that prevents the combination of results.

Statistical heterogeneity between studies was determined by considering the similarity of the point estimates, the extent of overlap of confidence intervals and statistical criteria, such as the test for heterogeneity and the I2 statistic.

The chi - squared ($\chi 2$, or Chi2).
Evaluate whether the observed differences in the results are compatible with chance. A low p-value (or larger chi-squared statistic relative to its degrees of freedom) provides evidence of heterogeneity of intervention effects (variation in estimates beyond chance). $p<0.10$ indicates that there is heterogeneity and that no statistical significance.

- The I2 statistic describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance)

A rough guide for interpretation is:

- 0 % to 40%: it may not be important;
- 30 % to 60 %: may represent moderate heterogeneity *;
- 50 % to 90 %: may represent substantial heterogeneity *;
- 75 % to 100 %: considerable heterogeneity *.

* The importance of the observed value of I2 depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (eg p value from the chi-square test, or an confidence interval for I2).

For further information:

-*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Disponible en www.cochrane-handbook.org.*

-Centro Cochrane Iberoamericano, traductores. Manual Cochrane de Revisiones Sistemáticas de Intervenciones, version 5.1.0 [actualizada en marzo de 2011] [Internet]. Barcelona: Centro Cochrane Iberoamericano; 2012. Disponible en http://www.cochrane.es/?q=es/node/269

-Nordmann AJ, Kasenda B, Briel M. Meta-analyses: what they can and cannot do. Swiss Med Wkly. 2012 Mar 9;142:w13518. doi: 10.4414/smw.2012.13518. PubMed PMID: 22407741. Disponible en: http://www.smw.ch/content/smw-2012-13518/

5.3.b Indirect comparisons (IC)

5.3.b.1 Published indirect comparisons

Table 5.3.b.1 **RESULTS OF PUBLISHED INDIRECT COMPARISONS**				
Primary endpoint	Intervention A / control	Intervention B/ control	RR/OR/HR/MD/ARR (CI 95%)	P (weight if meta-analysis)
RESULTS OF DIRECT COMPARISONS (in case we have a direct comparison)				
Primary endpoint	Intervention A/ control	Intervention B/ control	RR/OR/HR/MD/RD (CI 95%)	p
INTERPRETATIÓN OF THE RESULTS OF THE INDIRECT COMPARISON **Correctly interpreted?** **YES** ☐ **NO** ☐ **Doubtful** ☐				
How we interpret the results: Heterogeneity was discussed? **YES** ☐ **NO** ☐ **Doubtful** ☐ Sensitivity analysis carried out? **YES** ☐ **NO** ☐				
Comments:				
Is the IC justified: **YES** ☐ **NO** ☐ **Doubtful** ☐				
AUTHOR: Manufacturer ☐ Sponsored by manufacturer ☐ Independent body ☐ Name:				

The purpose of Table 5.3.b.1.1 is to facilitate the extraction of the information needed to assess the similarity of the characteristics of the clinical trials being compared, basic aspect of an IC assessment published.

Table 5.3.b.1.1. RESULTS OF PUBLISHED INDIRECT COMPARISONS: ***Reference:***				
RCTs comparison				
NON-ADJUSTED IC ☐ NETWORK METANALYSIS ☐ ADJUSTED IC ☐				
Drug A:				
Type of study, design…	Intervention A (N) **(dose, treatment duration)**	Control(N) **(dose, treatment duration)**	Patients characteristics **(age, genre…)**	Study duration **(follow up)**
Phase III RCT……				
Drug B:				
Type of study, design…	Intervention B (N) **(dose, treatment duration)**	Control(N) **(dose, treatment duration)**	Patients characteristics **(age, genre…)**	Study duration **(follow up)**
Drugs	Drug A	Drug B	Drug C	
N of trials				
N of comparators				
DIRECT COMPARISON: YES ☐ NO ☐				
Type of study, design…	Intervention A (N) **(dose, treatment duration)**	Control(N) **(dose, treatment duration)**	Patients characteristics **(age, genre…)**	Study duration **(follow up)**
MÉTHODS USED FOR THE INDIRECT COMPARISON				
Bucher ☐ Bayesian ☐ Frequentist ☐ Non SPECIFIED ☐ Otro ☐ _____ Bias adjusment specified? ☐Yes ☐ Unknown ☐ NO				

Instructions:

Direct comparative clinical trials are the gold standard for the comparative evidence, provided they have good methodological quality; but direct comparisons are not always available, so that indirect comparisons are being given a growing role in decision making. Although it is necessary to

evaluate and interpret them critically, so we must ask whether the data are appropriate, if the methodology used is correct and assess the adequacy of the data reported.

SUMMARY OF RESULTS PUBLISHED CI. We can find different types of CI: adjusted simple, narrative (invalid), mixed treatment comparisons, meta-analysis of treatment networks (Network meta-analysis, meta-analysis of multiple treatments or mixed treatment meta-analysis).

Generally, follow the model of data in table 5.3.b.1, which is included in the text of the report.

INTERNAL VALIDITY AND APPLICABILITY OF THE PUBLISHED CI. To assess the validity and applicability of the CI, there are complete checklists and summary lists. Tables fill is recommended 5.3.b.1.2 and 5.3.b.1.3 (see below). There are different types of indirect comparisons:

• Unadjusted indirect comparison or naïve
• Indirect comparison "informal" or narrative (informally indirect comparison)
• Adjusted indirect comparisons
• Treatment networks and multiple treatments meta-analysis. Mixed treatment comparison (MTC) or meta-analysis network or network meta-analysis.

The validity of indirect comparisons is influenced by the consistency of the relative efficacy of therapeutic interventions in various clinical trials. The loss of power leads to wider confidence interval than direct comparisons. Ideals adjusted indirect comparisons must:

• include a comparative treatment effect calculated properly with its CI
• be based on good quality trials
• based on similar RCTs

Basic assumptions of indirect comparisons:

A) Assumption of **Homogeneity**: similar to that applied in meta-analysis of clinical trials in determining the heterogeneity (Q test statistical significance of Cochrane or I2). At the moment there are no statistical tests similar for the CI

B) Assumption of **Similarity** from two perspectives: clinical similarity in the basic characteristics of the patients participating in various trials and similarity in the methodology used (study characteristics, data analysis…). Similarity is more likely when the patient characteristics (age, sex, severity of disease, co-morbidities, concomitant therapy) and methods of the study (timing, duration or dose of treatment outcomes, monitoring, loss to follow up) are similar (with similar baseline risk of common comparator arms).

> Other autors prefer use the more descriptive term **transitivity** for three main reasons:
> 1.- Transitivity describes better aim of the assumption (to compare two treatments via a third one).
> 2.- Similarity reduces to homogeneity for a single head-to-head comparison, whereas transitivity clearly refers to more than comparisons.
> 3.-Similarity may wrongly suggest that similarity is required for all characteristics of trials and patients across the evidence base, when in reality, valid indirect comparison can be obtained even when studies are differences in characteristics that are not modifiers (Salanti G. Res Syn Meth 2012;3:80-97)

C) Assumption of **Consistency**: applies when there is both direct and indirect evidence. By having direct evidence / indirect discrepant results may occur, consistency or substitutability refers to the results of direct and indirect comparisons are compatible, ie both results have the same direction of their effects. Inconsistency therefore is conflict between direct and indirect evidence

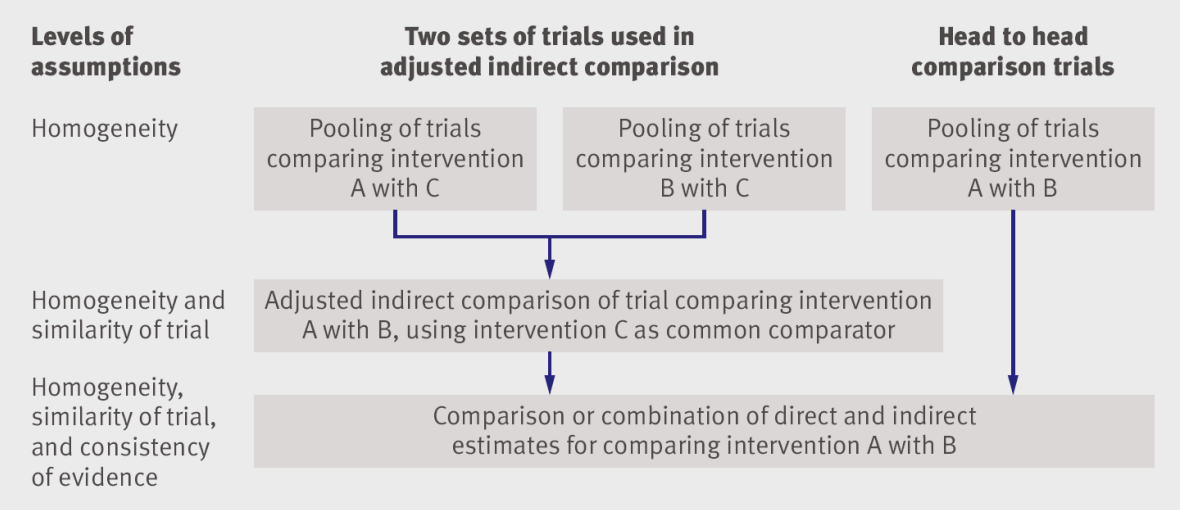


Figure from: Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ. 2003;326:472

Consistency is a system of relationships between sources of evidence. The heterogeneity represents the variation in the same treatment effect between studies and the inconsistency in the evidence is the discrepancy between the different types of comparisons

.

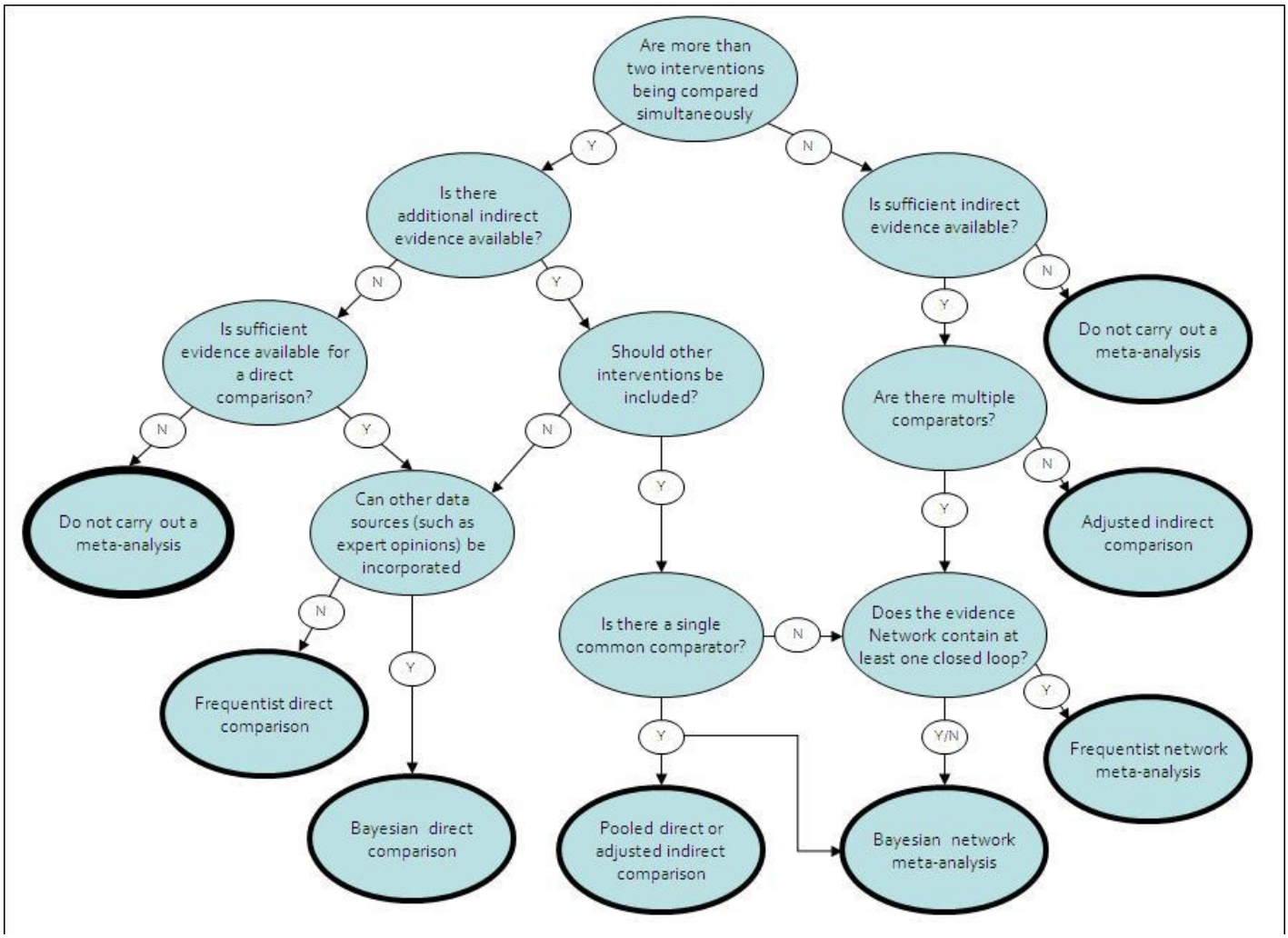


Figure from: Use of Network Meta-analysis in Systematic Reviews. Agency for Healthcare Research and Quality. August 2012. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/354/1238/Use-of-Mixed-Treatment_FinalReport_20121004.pdf

Internal validity analysis for IC

Reference of the assessed IC:

Table 5.3.b.1.2 Internal validity analysis for IC		
	YES/NO	**JUSTIFY**
- Is it appropriate to the method used for indirect comparison? **Reject comparisons "naïve" made with point estimates derived from different controlled trials or different active arms of controlled trials**		
- Is clearly stated how they conducted the search and selection of trials for inclusion?		
- A full description of the methods of analysis / synthesis of the evidence is made? **Bias Management**		
- We analyze the homogeneity of the trials and stability of the effects? **All trials respond to the same clinical question regarding the type of patients studied and the treatments compared**		
- Is there results concordance? **The result is the same regardless of the chain of comparisons used to obtain it**		
-If there is a direct comparison, it shows consistency in the results?		
-Interpretation of results. Do they allow drawing clear conclusions? **Analyze significant differences in baseline risks and responses in the placebo group**		
-Other biases or limitations found in the study		

Applicability analysis for IC

Table 5.3.b.1.3 APPLICABILITY ANALISYS FOR IC		
	YES/NO	**JUSTIFY**
Do you consider the / comparators appropriate? Is common comparator the ususal treatment in our enviroment?		
Are the results clinically significant?		
Is the variable used adequate?		
Are the inclusion criteria and / or exclusion of patients appropriate?		
Generalization of the findings (Population of patients in the trials and between trials)		
Do you think that the results can be directly applied to clinical practice?		
Other biases or limitations found in the study		

E.g. Table for IC:

Ford JA, et al. The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison in a systematic review. BMJ. 2012 Aug 13;345:e5182. doi:10.1136/bmj.e5182.				
Comparison BvITV versus RvITV				
Primary endpoint	BvITV / Láser	RnITV /Láser	OR (CI 95%)	P
% Patients improved more than 2 lines (10 letters) on the ETDRS BCVA	Bevacizumab: 21/77(27%) Laser: 6/73(8%)	Ranibizumab: 60/152 (39%) Laser: 19/148 (12,8%)	0,95 (0,23-4,34)	

INTERPRETATIÓN OF THE RESULTS OF THE INDIRECT COMPARISON
Correctly interpreted? **YES** [X] **NO** [ ] **Doubtful** [ ]
How we interpret the results: Heterogeneity was discussed? **YES** [X] **NO** [ ] **Doubtful** [ ] Sensitivity analysis carried out? **YES** [ ] **NO** [ ]
Other comments: We included five RCTs with a follow up 6-12 months to a common comparator (multiple laser treatment). Similar enough to make the CI. Because they were small studies the confidence interval was very wide. If the confidence interval to 95% crossed the line of no effect the result was interpreted as not significant (according to authors). Generally higher heterogeneity was found in ranibizumab studies
Is the IC justified: YES [X] **NO** [ ] **Doubtful** [ ]
AUTHOR: Manufacturer [ ] **Sponsored by manufacturer** [ ] **Independent body** [X] **Name:** *Health Services Research Unit, University of Aberdeen; Warwick Evidence, Division of Health Sciences, Warwick Medical School, Coventry. UK*

***Table 12. R*esults ot the studies included in the IC by *Ford et al*:**

COMPARISONS OF RCTs

NON-ADJUSTED IC [ ] NETWORK METANALYSIS [X]

ADJUSTED IC [ ]

Drug A: Bevacizumab (BvITV)

Reference,Type of study, design, eyes (patients), country…	Intervention A (N) (dose, treatment duration)	Control(N) (dose, treatment duration)	Patients characteristics (age, genre…)	Study duration (follow up)	Type of study, design…
BOLT study Michaelides *et al* 2010 RCT, SB; R; unicentric, n=80 (80) (2 publicactions) UK	1,25 mg BvITV (n=42) weekly for 6 weeks (n of injections, range 3-9)	Laser (n=38) Monthly treatment (range 1-4)	Difference in mean BCVA at 12 months	CSME with at least 1 previous laser tt. 64,2±8,8 years F/M: 31/69 % 90% DM 2 BCVA mean basal= 55,2 letters CRT mean basal= 494,65 µm	12 months Follow up 2 years
Sohelian *et al* 2009 RCT, DE; one center, n= 150 (129) (2 publications) Irán	Group 1: 1,25 mg BvITV (n=50) (retreatment every 12 weeks if indicated) + simulated laser. Group 2: 1,25 mg BvITV + 2 mg TIV (n=50) (retreatment every 12 weeks if indicated) + simulated laser. Retreatment in 14 eyes y 3rd tt in 3 eyes	Laser + simulated injection (retreatment every 12 weeks if indicated) (n=50) Retreatment in 3 eyes y 3rd tt in 1 eye	Difference in mean BCVA (logMAR) at 6 months	CSME without previous treatment 61,26±6 years F/M: 47%/53% (eyes) BCVA mean basal= 0,66 log MAR CRT mean basal= 333,33 µm	6 months

Drug B: Ranibizumab (RnITV)

Reference,Type of study, design, eyes (patients), country…	Intervention A (N) (dose, treatment duration)	Control(N) (dose, treatment duration)	Patients characteristics (age, genre…)	Study duration (follow up)	Type of study, design…
RESTORE study 2011 RCT phase III, DB; R; international, n= 345 Patients EU, Turkey, Canada and Australia	Group 1: RnITV 0,5 mg (monthly for 3 months, retreatment if needed) + simulated laser (n=115). Group 2: RnITV 0,5 mg (monthly for 3 months, retreatment if needed) + laser (monthly if needed) (n=118).	Laser (monthly if needed) + simulated injection (n=110)	Mean change in BCVA (month 1 to 12 vs basal)	63,5 ±8,75 years F/M:41,84/58,16% BCVA mean basal = 63,5 letters CRT mean basal = 418,5 µm	12 months
READ-2 study Nguyen *et al* 2009 RCT phase III, DB; R; multicentric international, n= 126 US 2 publications	Group 1: 0,5 mg RnITV months 0, 1, 3 y 5 (n=42). Group 2: 0,5 mg RnITV months 0, 3 + Laser months 0 y 3. 1 week after Rn (if needed) (n=42). Retreatment at 6 months if criteria fulfilled: Rn 1 every 2 months and Laser every 3 months	Laser months 0 y 3, if needed (n=42).	Mean change in BCVA (month 6 vs basal). Until 24 months in the extensión study	62 years F/M: 59/41 % BCVA mean basal = 26,0 letters (20/80) CRT mean basal = 229,65 µm	6 months 2nd publication 2 years

DRCR.net 2010 RCT phase III, DB; R; multicentric, n= 854 (691) US 2 publications	Group 1: 0,5 mg RnITV retreatment if needed + Early laser. (n=187). Group 2: 0,5 mg RnITV con retreatment if needed + Delayed laser. (n=188). Group 3: 4 mg TIV con retreatment if needed + Early laser. (n=186).	Early laser+ simulated injection (n=293).	Mean change in BCVA (1 year vs basal)	63±10 years F/M: 44/56% BCVA mean basal = 65,7 letters CRT mean basal = 386,5 µm	12 months

Drugs	**Drug A: BvITV**	**Drug B: RnITV**
N of trials	2	3
N of comparators	1 (Laser)	1 (Laser)

DIRECT COMPARISON: YES ☐ NO ☒ *

Awaiting results of comparative trials in DME

METHOD USED FOR THE INDIRECT COMPARISON

Bucher ☐ **Bayesian** ☒ **Frequentist** ☐

Non specified ☐ **Other** ☒ **Dias**

Bias adjusment specified? ☐Yes ☐ Unknown × NO

5.3.b.2 Other indirect comparisons

We recommend using the Bucher method for adjusted IC, generally follow the pattern of results of the table below:

Table 5.3.b.4
INDIRECT COMPARISONS (Bucher methods, Wells calculator 2009)

	Events treatment / Nº of patients (n1/N)	Events control / Nº of patients (n2/N)	RR/OR/HR/MD/RD (IC 95%)	p
REFERENCE 1. Endpoint Med 1 vs Comp				
REFERENCE 2. Endpoint Med 2 vs Comp				

ADJUSTED INDIRECT COMPARISON

	RR/OR/MD/RD/HR (IC 95%)	p
Endpoint Med 1 vs Med 2		

-Software ITC Wells GA, Sultan SA, Chen L, Khan M, Coyle D.Indirect treatment comparison [computer program]. Version 1.0. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
-Calculator Joaquín Primo

Instructions:

As support for the IC, we can use the following table which describes the results and characteristics of the trials or meta-analysis of which we set for IC. (Table 5.3.b.2.2). This Table is optionally included in the text of the report or appended to the end.

Table 5.3.b.2.2
Indirect comparison (Characteristics of selected studies)

	Study design	Efficacy outcomes	Duration	Patients characteristics	Results control group	Doses
Ref 1 Med1 vs comp						
Ref 2 Med 2 vs Comp						

In column 1 include RCTs or metaanalysis of common comparators drugs we will consider. At a minimum there should be comparability of populations and methodological similarities

INTERNAL VALIDITY AND APPLICABILITY OF OWN PROCESSING CI

See checklists previous section

For further information

Wells GA, Sultan SA, Chen L, Khan M, Coyle D. Indirect evidence: indirect treatment comparisons in meta-analysis. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
Disponible en: http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/884

5.4 Evaluation of secondary sources

5.4.1 Clinical Practice Guidelines

5.4.2 Previous evaluations by independent bodies

National
International

5.4.3 Expert opinions

5.4.4 Other sources.

Instructions:

Overall describe them briefly and summarized only the most relevant points that may be useful for therapeutic positioning.

5.4.1 Clinical Practice Guidelines: The description of the health problem and its treatment have been addressed in section 3, including the published CPG of reference. Only include in this section CPGs that have incorporated the drug under evaluation and propose therapeutic positioning for it.

5.4.2 Previous evaluations by independent bodies

National
Performed by regional documentation centers, hospitals and HTA Agencies.

Other countries
Of special interest, reports from NICE (England and Wales), CADTH (Canada), SMC (Scotland), NPS-RADAR (Australia), NHS (London New Drugs Group), MTRAC (Midlands Therapeutics Review and Advisory Committee), Germany (IQWIG)...

5.4.3 Expert opinions
Editorials published in magazines, often in the same issue that has been published in the pivotal clinical trial, are also of great interest. Letters to the editor help us in critical appraisal.

5.4.4 Other sources. Example: Micromedex.

6. SAFETY ASSESSMENT.

6.1.a Bibliographic search description

Bibliographic search description: strategy and results of the search.

Instructions:

Depending on the novelty of the drug evaluated (or comparator) may need to seek additional information on adverse effects (meta-analysis, cohort studies, case series, etc.), So that, as in the analysis of efficacy, you need to review the search strategy and the databases that have been searched.

6.1.b Description of significant adverse effects

Reference:					
Brief description of the trial and design					
Safety results					
Safety endpoint evaluated in the study	***Treatment studied N (pt)***	***Control treatment N (pt)***	***ARR (CI 95%)*** Absolute Risk Difference*	***P***	***NNH (CI 95%)***
-Variable description	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
-Variable description	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
-Variable description	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
-Variable description	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
-Variable description	*%*	*%*	*% (CI95 : x% to x%)*		*X (x to x)*
(*) CI 95% included in the Table only if p<0,05 Calculator ARR and NNH and CI 95 % from CASPe. **Click here.** **-Calculators/programs in GENESIS web:** http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/Calculadoras.htm					

Instructions:

Expose in section 6.1.b the general safety profile

Recomendation 1:

Report about safety data can be obtained from EMA / FDA information or from the published trial. Another option is to rely on the label, which usually presents a summary of the safety profile.

Basis: Product label contains a list of adverse effects of the new drug detected in premarketing clinical trials. Keep in mind that the design and calculation of sample size from a clinical trial are carried out according to their main objective, which in most cases is to demonstrate a greater efficacy. The sample size is not typically defined to determine differences in adverse effects.

When possible be exhibited ARR and or NNH with CI95%, provided that the differences are significant (p <0,05). To calculate this use the same system used for the efficacy calculation. See calculators.

Recomendation 2:

Adverse effects were reported (most recent Summary of Product Characteristics, SPC) by systems and only with the characterization of the frequency required, and are not the actual percentages of the clinical trial, which appear only in the scientific discussion.

Interpretation:
Very common> 1/10 patients
Common> 1/100 patients and <1/10 patients
Uncommon> 1/1000 patients and <1/100 patients

Rare> 1:10,000 patients and <1/1000 patients
Very rare <1:10,000 patients

In addition, adverse reactions identified (frequency greater than placebo) should appear in the text: the more frequent, more severe and where they exist, or at least have been declared, the irreversible. The complete list of adverse reactions should be annexed.

The severity of adverse reactions is done according to the classification of the National Institute of Health (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Recomendation 3

In the safety table include the comparison versus control, including frequency, severity and reversibility (if applicable) as follows:

1. Organize adverse reactions identified by systems / disease (MedRa) or symptom
2. Adverse effects on laboratory
3. Abuse or dependence if applicable
4. Use of rescue medication if appropriate
5. Withdrawals due to adverse events

Recomendation 4:

May be useful information about the LHH (Likelihood to be Helped versus Harmed = likely to be helped against being damaged) calculated from the primary outcome NNT and NNH of the most serious adverse reaction or relevant: LHH = (1/NNT) / (1/NNH).

The meaning of LHH is the number of patients who will benefit for every patient harmed in some adverse effect. Eg, a drug used to prevent cardiovascular mortality has an NNT 20 but has for gastrointestinal bleeding NNH 100, the two values compared to drug B. His will LHH (1/20) / (1/100) = 5, which means that for every 5 cardiovascular deaths avoided will produce one additinal gastrointestinal bleeding.

This information may be useful for therapeutic positioning section and conclusions.

Sierra F. Evidence-Based Medicine (EBM) in practice: Applying Number Needed to Treat and Number Needed to Harm. Am J Gastroenterol 2005; 100 (8):1661-3.
http://www.nature.com/ajg/journal/v100/n8/pdf/ajg2005299a.pdf

Recomendation 5

Include if applicable comment on potential adverse reactions (class effects) and lack of data

6.2 Comparative clinical trials.

Same scheme as 5.2.

The safety objective xxxxx is a defined goal in trial methodology. Subgroups and overall results are shown in Table, where we can highlight xxxx

Reference:					
Brief description of the trial and design					
Safety results					
Safety endpoint evaluated in the study	***Treatment studied N (nº pt)***	***Control treatment N (nº pt)***	***ARR (CI 95%)*** Absolute Risk Difference*	***P***	***NNH (CI 95%)***
Main safety endpoint *-Variable description*	*% (N)*	*% (N)*	*% (CI95 : x% to x%)*		*X (x to x)*
Safety results by subgroups *-Subgroup 1* *-Subgorup 2* *-Subgroup 3* *etc*	 *%(n1)* *%(n2)* *%(n3)*	 *% (n1)* *% (n2)* *% (n3*	 *% (CI95 : x% to %)* *% (CI95 : x% to x%)* *% (CI95 : x% to x%)*		 *X (x to x)* *X (x to x)* *X (x to x)*

(*) CI 95% included in the Table only if p<0,05 (**).n1, n2,n3 sample size for each subgroup
Calculator ARR and NNH and CI 95 % from CASPe

Instructions:

The section 6.2 will run only if the trial objectives (either primary or secondary), include any safety feature. Example: bleeding risk in case of antithrombotics. Results will be presented similarly to the section of efficacy.

6.3 Secondary safety sources

-Previous evaluations by independent bodies
  National
  International
-Expert opinions
-Other sources: Pharmacovigilance

Instructions:

Review pharmacovigilance alerts:

- AEMPS: http://www.aemps.gob.es/vigilancia/DrugsUsoHumano/home.htm

- EMA *European database of suspected adverse drug reaction reports.. http://www.adrreports.eu/*

- FDA MedWatch FDA information program about safety and reporting of adverse effects: http://www.fda.gov/Safety/MedWatch/default.htm

6.4 Precautions for use in special cases

Precautions in pediatrics, pregnancy, elderly, kidney failure, etc..

Contraindications

Interactions

Monitoring of adverse effects: tests to be performed, frequency of checkups, etc…

Instructions:

Describe whether may be significant in relation to other drugs for the same indication.

Refer to product label:

MoH Spain: http://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=detalleForm (search for active and then by trade name).

EMA:
http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 (Section European Public Assessement Reports)

Notes

In many occasions there are new drugs approved in adults, but not in children (eg Azithromycin injection), so with the inclusion of the drug in formulary, you can not completely replace the oldest. Must remain available both in the local formulary.

On other occasions the interactions (eg voriconazole) may be an important point for the decision on drug use conditions. Practical limitations to ensure the correct use of a drug that has significant potential risks if their use is widespread, can help you decide on the appropriateness of including it in the formulary.

It is interesting to know the aspects related to monitoring of adverse effects, especially if they involve differences with standard treatments or comparators, and must be taken into account in the economic evaluation (eg oral anticoagulants).

7. ECONOMIC AREA

7.1 Treatment cost. Incremental cost

The incremental cost per patient is the difference between the cost of treatment per patient for an alternative treatment and cost of treatment per patient for the reference

Comparison of treatment costs evaluated against other/s alternative/s			
	Drug A Dosage form	**Drug B** Dosage form	**Drug C** Dosage form
Unit price (+VAT) *			
Posology			
Daily Cost			
Full treatment cost or annual cost			
Direct costs associated ****			
Global cost *** or annual global cost			
Incremental cost *** versus reference treatment**			

* Refers to the cost of the dosage form (vial, syringe, tablet ...). For reports from a hospital, assess drug price according to offers, tender agreement, centralized competition, etc..
**Direct costs associated: These are costs that can be considered in addition to the cost of the drug studied. Such as other drugs required, additional testing, monitoring and laboratory, screening tests (pharmacogenetics, biomarkers ...), infusion devices or complications. Be taken into account where relevant.
*** Full treatment cost + direct costs. In oncology, the overall cost is calculated as the average number of cycles received (median if average not available) until progression with each drug.
**** Overall cost difference compared to the drug tested

As alternatives, non-pharmacological interventions may be included in additional columns when relevant. If necessary you can add more rows, for example, add a row of the cost per time unit, ex. the cost / cycle in cancer chemotherapy. It is recommended to add this line of cost to the cost per day and the cost of full treatment.

Instructions

Drug and associated direct costs:

- Comparison with reference therapy at usual doses. If the usual doses do not match those used in the clinical trial from which we will take efficacy data for the incremental cost efficacy, should be indicated in the table and we should calculate the cost of trial doses to use this information in analyzing incremental cost efficacy.

- If the use of the drug involves a significant associated resource use will be considered as direct associated pharmacological costs (eg AEs management as antiemetic therapy in the comparison of two cytostatics), monitoring costs of treatment (eg INR of anticoagulants), laboratory costs, hospitalization costs, staff time, systematic screening costs or pharmacogenetic testing. Sometimes you can extract the associated resource consumption data from clinical trials or clinical practice, but we have to include the cost of the different alternatives we are considering in order not to penalize one of the alternatives and not others (Eg: see table Palifermin). Regarding unit costs, you have the database Oblikue eHealth (subscription required), http://www.oblikue.com/inicio.htm

- The perspective of the analysis will be the hospital or health system. So in principle does not include indirect costs (eg lost productivity of the patient). Only in the case that the impact on indirect costs is very relevant to the choice of treatment we will also repeat the analysis including

indirect costs as long as we can calculate, at least in an approximate way, and we must be aware that the results are difficult to compare with later studies which can not consider indirect costs.

PVL (ex-factory price) + VAT, local discounts or tendering agreements?

- It is generally used PVL (ex-factory price) + VAT prices for hospital reports as a basis for comparisons. In drug reports for use in ambulatory prescription mainly, use the Retail price + VAT

'But since the decision is at the level of a specific hospital, in this section may include data with offered or negotiated price at the time of writing the report, and that the economic study will be more real and valid for making decisions in our center. In this case, please indicate both prices, since the price offered may not be maintained over time.

EXAMPLE: Associated costs from a clinical trial

Spielberger R, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers.			
Other efficacy and safety results			
	Palifermin (N =106)	Placebo (N =106)	p
Use of Total Parenteral Nutrition (% patients) **Total Days Total parenteral nutrition** **NPT required for mucositis** **Total days with TPN in patients who required PN for mucositis**	31% 459 11% 158	55% 761 43% 569	< 0,001
Use of opioids in mg of morphine (median (range))	212 (0-9418)	535 (0-9418)	< 0,001
Patients with febrile neutropenia	75%	92%	< 0,001 (CI 95% of the difference 7-27)
Infections hematologic	15%	25%	

	Palifermin	**No treatment of mucositis**
Unit price (ex-factory price plus VAT) *	781,5 € / vial of 6,25 mg	0
Posology	60 mcg/kg/day x 6 doses	0
Full treatment cost	4689 €	0
Costs associated approximate **parenteral Nutrition** **Febrile neutropenia (cost antibiotics) to** **Hematologic infection (cost antibiotics) to** **morphine** **TOTAL costs associated**	 4,33 days x 60 €/day = 259,8 € 75% (0,75 x 350 €) = 262,5€ 15% (0,15 x 350 €) = 52,5 € 212 mg X 1€ = 212€ 787€	 7,18 days x 60€/day = 430,8€ 92% (0,92 x 350€) = 322 € 25 % (0,25 x 350 €) = 87,5 € 535 mg X 1 € = 535 € 1375 €
Overall cost	5476€	1375€
Incremental cost	4100€	

[a] Costs per patient calculated by multiplying the probability of the patient to suffer the effect of the cost of antibiotics

7.2.a Incremental cost effectiveness. Studies published

There are published pharmacoeconomic studies which compare the drug xx with placebo and/or drug yy. Of these, xx are cost-utility studies (ref ...) and xx other studies, specify (ref ...)
One table per study

Reference			
-Type of study: **- Source of data: clinical trial, observational study Markov model ...** **- Perspective:** **- Population of the base case:** **- Main outcome:** **- Time horizon:** **- Costs included in the study:** **- Costing (DRGs, e-Health, ...):** **- Discount rate applied to costs and health outcomes.:** **- Utility values considered:** **- Sensitivity analysis:** **-Conflict of Interest:**			
COSTS (1)	**Drug A**	**Drug B**	**Incremental costs (2)**
Treatment cost (3)	xx €	xx €	Incremental cost of treatment xx€
Patient cost (4)	xx €	xx €	Incremental cost by patient xx €

EFFECTS (1)	Drug A	Drug B	Incremental effects (2)
LYGs gained	xx LYGs	xx LYGs	Incremental LYGs by patient xx LYGs
QALYs gained	xx QALYs	xx QALYs	Incremental QALYs by patient xx QALYs
Calculated utility (5)	xx	xx	--
INCREMENTAL COST EFFECTIVENESS RATIO (1)			**ICER**
Base case			€ / LYG ó € / QALY
Other scenarios of interest			€ / LYG ó € / QALY

(1) Present the data from the publication. If publications are available other results or evaluations, the table will suit them.
(2) Difference between drug A and drug B
(3) Cost of treatment with the study drug and the drug presented in the reference study
(4) Overall resource cost of each option presented in the study
(5) Relationship QALYs / LYGs

Other published studies: critical review and applicability of published pharmacoeconomic studies.

Make brief narrative summary of the base case results and present the main results of the sensitivity analysis.

Instructions:

Observation 1

How to express the results

Data extraction and how to tabulate facilitates its subsequent interpretation and adaptation for new estimates based on changes in costs. Of special interest is to determine the possible impact on the ICER of using different costs for the drug.

To compare the incremental cost effectiveness derived from the application of different therapeutic interventions whose efficacy data are measured with different variables, you have to use a variable in health outcomes that simultaneously collect all health outcomes and is common to all healthcare areas, and this is the QALY (quality adjusted life years). When there is no information to measure QALYs we can use other variables like life years gained (LYGs), but this unit has the disadvantage of not incorporating a crucial health outcome for patients such as the quality of life.

The end result of utility cost studies that compare two options, is usually presented in the form of QALY gains, increased costs and resulting value of the ICER euros / QALY. See example in following table:

Results of cost-effectiveness analysis of the revised base case, incorporating corrections and amendments identified by the ERG (Evidence Review Group) *

	Best supportive care		**Ipilimumab**		**Increments**		**Incremental cost-effectiveness ratio****
	Cost per patient	QALYs per patient	Cost per patient	QALYs per patient	Cost per patient	QALYs per patient	Cost per QALY gained
NICE €**	13.563,2	0,7043	109.000,1	1,5066	95.436,9	0,8022	**118.961,9**

**Ref: Dickson R, Boland A, Bagust A, Blundell M, Massey G, Dundar Y, Davis H and Marshall E. Ipilimumab for previously treated unresectable malignant melanoma: A Single Technology Appraisal. LRiG, The University of Liverpool, 2011. http://www.nice.org.uk/nicemedia/live/12092/56688/56688.pdf*
** 1 £ = 1,23 €

When economic evaluation source is a reference (eg NICE, SIGN) and meets quality requirements, consider reproducing this table in the evaluation report (previous table example assessment from the report of ipilimumab in melanoma GENESIS)

Observation 2

Critical review and applicability of published pharmacoeconomic studies

Published pharmacoeconomic studies will be reviewed to assess both the quality of the study itself (internal validity) and the degree of applicability of their results to our hospital (external validity) and to guide the implementation of our own studies. An important aspect is also to assess the robustness of the results, ie, to study the sensitivity analysis of the study.

Basic aspects to consider in order to assume the extent to which the study results are applicable in our environment:

- Costs applied: types and values.
- Suitable comparator.
- Perspective from which the study is done.
- Time horizon (generally the longer the time horizon of the study will gain in QALYs and more likely that the ICER does not cross the threshold).
- Discount rates applied to both costs and the health outcomes.
- Utility values applied in different health states.
- Plausibility of model decision trees, Markov models.
- Probability applied to decision models.
- Monetary threshold values to consider cost-effective treatment.
- Sensitivity analysis performed.

These points should be evaluated to determine the validity and applicability of pharmacoeconomic study to our area.

Internal Validity

There are numerous checklists to make this assessment, for example are recommended:

Recomendations and checklists	Reference
Reference	
Spain	*Lopez Bastida J, Oliva J, Antoñanzas F, Carcía-Altés A, Gisbert R, Mar J, Puig-Junoy J Propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias. Informes de evaluación de tecnologías sanitarias SESCS 2006/22 (Gac Sanit.2010;24(2):154–170)* http://scielo.isciii.es/pdf/gs/v24n2/especial1.pdf
Drummond	*Drummond et al. Methods for the economic evaluation of health care programmes. Oxford medical publications. 3rd edition. 2005*

For further information

Other checklists of interest:

CHEC. *Evers S et al. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. Int J Heath Technol Assess in Heatlh Care 2005; 21:240-245*

BMJ:

Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996 Aug 3;313(7052):275-83.

Check-lists for a model:

Soto J. Heath economic evaluations using decision analytic modeling. Principles and practices- Utilization of a checklist to their development and appraisal. Int J Heath Technol Assess in Heatlh Care 2002; 18:94-111

Philips Z. Et al. Review guidelines for good practice in decision-analytic modelling in health technology assessment. Heatlh Technol Assess 2004; 8(36):iii-iv, 1-158.;

Sculpher M et al. Assessing quality in decision analytic cost-effectivenes models. A suggested framework and example of application. Pharmacoeconomics 2000; 17:461-477

Cleemput I, Neyt M, Van de Sande S, Thiry N. Belgian guidelines for economic evaluations and budget impact analyses: second edition. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre(KCE). 2012. KCE Report 183C. D/2012/10.273/54
https://kce.fgov.be/sites/default/files/page_documents/KCE_183C_economic_evaluations_second_edition_0.pdf

On the University of York website (http://www.york.ac.uk/inst/crd/index.htm) a large number of published evaluations have been reviewed critically.

Drummond is the most widespread checklist, the comparison between different guides demonstrate that the assessor influences the result of the evaluation far more than the list used.

External validity:

The validity and applicability especially to our environment are often limited due to the existence of differences between countries or between different parts of the same country in terms of therapeutic strategies, health organization, resource utilization or unit costs. The promotional purpose of an economic evaluation and other biases may also be important.

When we try to apply the study data to our environment is important that we find disaggregated data. It might help us to separate a part that we want to include in our local evaluation, which parameters, identified in the sensitivity analysis, are more important on our analysis and therefore can make a difference in our decision. Then we can assess whether these parameters are similar to our study population and therefore we expect similar conclusions or not.

In this section we have to justify if we believe that the data can be extrapolated to our environment and why and whether we can only extrapolate some data.

For furthehr information:

Ortega A: Posibilidad de generalizar los resultados de una evaluación económica. Farm Hosp. 2003; 27(4): 205-9
http://apps.elsevier.es/watermark/ctl_servlet?_f=10&pident_articulo=13118806&pident_usuario=0&pcontactid=&pident_revista=121&ty=28&accion=L&origen=elsevier&web=www.elsevier.es&lan=es&fichero=121v31n6a13118806pdf001.pdf

Thresholds for ICER

In Spain: The judgment to recommend the adoption or rejection of a health intervention based on the incremental cost effectiveness is not defined. In most studies published in our country the authors recommend the adoption of the intervention when that figure is below **30,000 euros / QALY**

Ref: Sacristán, Oliva et al ¿Qué es una tecnología sanitaria eficiente en Españ? Gac Sanit 2002;16:334-43

Puig-Junoy J, Peiró S. De la utilidad de los fármacos al valor terapéutico añadido y a la relación coste-efectividad incremental. Rev Esp Salud Pública 2009; 83: 59-70
http://www.msc.es/biblioPublic/publicaciones/recursos_propios/resp/revista_cdrom/vol83/vol83_1/RS831C_59.pdf

NICE: Reference threshold of 20,000-30,000 pounds / QALY. Situations:

- <20.000 £/QALY: Technology accepted, is an efficient use of NHS resources.
- 20.000-30.000 £/QALY: pay special attention to the level of uncertainty associated with the estimate, if defined properly to changes in quality of life provided by new technology and innovative nature
- > 30.000 £/QALY: inefficient use of NHS resources, lower probablidad technology recommendation.

"End-of-life" (EoL) criteria for ICER

NICE established in 2009 recommendations on the acceptable thresholds for drugs indicated for treatment at the end of life (EoL). The ICER NICE accepts for treatments that meet EoL criteria is superior to that of other technologies: between £ 40,000 to £ 50,000 per QALY gained (in EUR : € 50,200 to € 62,800) approximately. If the EoL criteria are not met, we should take the normal threshold of 20,000-30,000 pounds / QALY

EoL criteria (must satisfy all):

- Life expectancy of patients treated <24 months.
- Increased survival > 3 months (compared to current NHS treatment) .
- Lack of alternative treatments with comparable benefits available on the NHS.
- The treatment is indicated for small patient populations (< 7,000 patients / year) *

* For the number of patients will take into account all the indications of the drug.

If EoL criteria are met:

Additional weight should be given to QALYs gained, so that the threshold considered cost effective for NICE increases. The Committee decides on the magnitude of the additional weight.

You can also consider the impact of giving greater weight to QALYs achieved in the later stages of terminal illness, with the assumption that the period of prolongation of survival is experienced in full quality of life similar to that of a healthy individual of the same age

In addition, the evaluation committees will have to be convinced that the estimates of life extension are robust and can be shown or reasonably inferred from progression-free survival and overall survival (taking into account the comparative tests and reviewing the efficacy), and that the assumptions used in the modeling of economic reference cases are objective, plausible and robust

For further information:

EoL Criteria:

NICE. Update report on the application of the 'end-of-life' supplementary advice in health technology appraisals. Carole Longson, Director, Centre for Health Technology Evaluation Peter Littlejohns, Clinical and Public Health Director. Ref 09/55. July 2009
http://www.nice.org.uk/media/835/8E/ITEM7EndOfLifeTreatments.pdf

Corbacho Martín B, Pinto Prades J. L. (2012). Impacto de los criterios para situaciones terminales en la evaluación de fármacos oncológicos. Documento de trabajo 2012/2. Cátedra de economía de la salud: Dr. D. José Luis Pinto Prades. Universidad Pablo de Olavide, Sevilla.
http://www.upo.es/cades/export/sites/catedra-economia-salud/galerias/Publicaciones/Criterios_para_situaciones_terminales_en_la_evaluacion_farmacos_oncologicos.pdf

International:

Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2008. KCE reports 100C (D/2008/10.273/96) https://kce.fgov.be/sites/default/files/page_documents/d20081027396.pdf

7.2.b Incremental Cost Efficacy Ratio (ICER). Own data

Incremental Cost Effectiveness Ratio
Continuous variables

		Endpoint	Efficacy A	Efficacy B	Difference (CI95%)	Incremental cost	ICER (CI95%)
Reference x	Main population		Ef A units	Ef B units	Ef A – Ef B = D (D inf-D sup)	A-B	(A-B) / D (A-B) / D inf (A-B) / D sup

	Subgroup 1						
	Subgroup 2						
Reference y	Main population						
	Subgroup 1						
	Subgroup 2						
Efficacy data are taken from section 4.1 and the incremental or differential cost of section 7.1							

Interpretation: According to the study data and the cost of treatment(etc.), the additional cost per each year of life gained estimated is € xx, but also supports a ICE between xx and xx € € ...

Incremental Cost Effectiveness Ratio (ICER) Binary variables						
Reference	Study type	**Endpoint**	**Comparator**	**NNT (CI 95%)**	**Incremental Cost (A-B)**	**ICER (CI95%)**
Reference x	Main population	xxxx	xxxx	N (Ninf-Nsup)	(A-B)	(A-B) x N (A-B) x N inf (A-B) x N sup
	Subgroup 1					
	Subgroup 2					
Reference y	Main population					
	Subgroup 1					
	Subgroup 2					
It presents the results of the base ICER according to the NNT calculated in section 5.2 and the incremental or differential cost of section 7.1						

Interpretation: According to the study data and the treatment cost, the additional cost estimated per each additional patient to heal/live is € xx, but also supports an ICER between xx and xx €€.

Sensitivity analysis which tests the impact on the ICER of the variables for which there is uncertainty in the initial estimate

Incremental Cost Effectiveness Ratio (ICER) Sensitivity analysis			
Variable	**Range**	**Maximum ICER**	**Minimum ICER**
CI95% of the result			
Treatment cost			
Treatment duration			
Average (or median) number of cycles (Onco)			
Monitoring costs			

You can delete rows from the table if not relevant and introduce as many factors as it deems appropriate, especially those in which there is greater uncertainty (see instructions).

Instructions

Regarding the tables, we can estimate the ICER based on data from section 5.2 (Efficacy) and section 7.1 (Incremental or differential cost).

We will generally present the result of the ICER for the main outcome of the pivotal trial. Final variables are preferable as survival or quality-adjusted survival of life, if they are not available, analyze the most relevant variable or analyze several. Depending on the interest, further data evaluation can be calculated.

The present scheme allows different lines:

- ICER Subgroups
- ICER Efficacy data from more than one test.

Sensitivity analysis for example with regard to:

- Based on the 95% CI of the NNT of section 7.1 for binary variables or 95% CI of the outcome variable of continuous variables
- Incremental costs based on PVL (ex-factory price) + VAT or discounts offered
- Incremental costs calculated with different dose ranges. When there are different possible regimens for patients, for calculating baseline we use the doses used in the clinical trial from which we will draw efficacy data, because with this pattern we have obtained the results of the doses that we are using. If we change the doses the results may change.
- Calculations with different ranges of resources consumed different drug or unit costs of these resources consumed.

Observation 1: Type of variables in the ICER analysis

The best way to express the results would be like measuring incremental cost-effectiveness and health outcomes **adjusted life years (QALYs).** However, this health outcome is very difficult to be calculated when evaluating drugs and therefore we are forced to use other outcome variables.

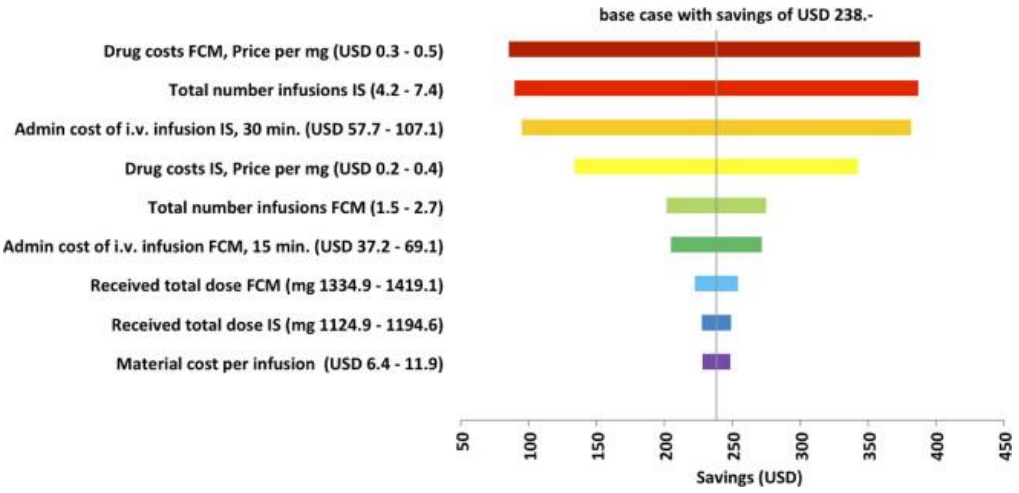
We prefer **final outcome variables**, such as years of life gained, than the intermediate variables as percentage of responding patients, BP control, etc. But nevertheless, often only have the latter. They only make sense if you can relate to the final variables. Usually this occurs for drug registration, otherwise it would be hard for them to be used as a result of a clinical trial. What may be more difficult is to find a numerical (eg an equation or a set of them) that relates the intermediate result with the end result. But if there is, it is useful because it would allow us to transform the intermediate result in the final result, eg cost per life year gained or cost per QALY and be able to use uniform criteria for assessing the efficiency, regardless of the healthcare area we are dealing with. In many cases they are hard to get or model in the short time that we have, and we are forced to use intermediate results to the important limitation that this has to make decisions. You cannot compare different healthcare areas and we end considering if it seems "reasonable" or not a particular incremental cost per additional unit of effectiveness.

Observation 2: Sensitivity analysis

It would be appropriate to make a **probabilistic sensitivity analysis** by varying all possible variables that can change at once in all its possible range of values and estimate the acceptability curve to say how likely it is that the ICER is below a value threshold. This analysis could be done with the program DATA by TreeAge or Excel, but would require creating the model previously and entering the data of the variables in the model.

This can be tricky to do with all drugs, so we should at least make the **univariate sensitivity analysis** by varying each variable separately between their possible values and thus have an idea of what possible values could take the ICER. In univariate sensitivity analysis can be useful to perform the analysis of the worst and best scenario and the threshold value.

The results can also be presented as a diagram to visualize easily what are the key factors and variability of the ICER. Example:



Observation 3: Binary variables. Formulas for calculating the ICER

The ICER is the cost of getting a unit of additional health effects, changing to the next alternative.

Incremental Cost Efficacy Ratio calculation (binary variables)
ICER = (Cost per patient of option A - Cost per patient of option B) / (Efficacy of A - Efficacy of B).

In the case of **binary variables**, usually we calculate from NNT and 95% CI. Efficacy is expressed as the probability and not a percentage.

The formula is equivalent to:
ICER = NNT x (cost per patient of option A - Cost per patient of option B)

Observation 4: Continuous variables

For **continuous variables** (eg median survival time) can not be calculated NNT and ICER will refer to efficacy variable studied. Efficacy data will be transformed into units that we are useful for evaluation, eg for calculation of ICER based on the variable of additional months of survival put in years of life gained survival (AVG).

When data used are overall survival (OS) or progression-free survival (PFS), the most widely **recommendation in the literature is to use the mean and the mean difference between the groups** being compared, if available, as it gives us a better idea of the difference in area under the curves and therefore the overall benefit to the population. In the NICE estimates are generally used to mean survival parameters in economic evaluations (such as the costs and quality of life related to health).

In cost-effectiveness analysis we seek to maximize social welfare as the sum of the welfare of each individual and therefore we seek to maximize the sum of QALYs in the whole population (hence the mean is recommended).

Published oncology trials do not include many times the means and their differences and present the differences with median survival; therefore we use median OS as the basis for calculating our estimates. Means are likely to be higher than the medians, but as we use differences between them, the mean difference can be higher, lower or equal to the median difference. We must be aware that it is an extrapolation.

See also section "Variables" time to event. "Median survival time"

Tappenden P, Chilcott J, Ward S, Eggington S, Hind D, Hummel S. Methodological issues in the economic analysis of cancer treatments. European Journal of Cancer. 42 (2006) 2867–2875

Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available from http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis_finalv2.pdf

Observation 5: Base for the calculation of ICER with own data.

- **In a first approximation,** we only calculate an incremental cost efficacy ratio estimate based on the acquisition cost of the drug and efficacy data from the pivotal clinical trial. The sensitivity analysis should be noted and we need to estimate between what limits the calculations are valid or expected. In this approach we do not take into account other costs associated with pharmacological or non-pharmacological interventions.

- A **second approach** is to add direct costs associated. Associated costs can be pharmacological (eg antiemetic therapy in cancer drugs) or non- pharmacological costs.

One option is to build on the hospital stays generated by each option. The incremental efficacy cost in this second approach can contemplate the **drug acquisition cost plus the cost of hospital stay**. In many pivotal clinical trials or publications, parallel results are disclosed for both drugs compared in the trial: length of stay in inpatient units. Within direct healthcare costs, the cost per stay for conventional unit and cost per ICU stay are known and account for hospital cost time medical, health staff and other resources used in patient care. This data is generally known and available in the information systems of hospitals. If you own real data have cost per stay, we can use the data base Oblikue eHealth healthcare costs, which defines a standard limit values for most healthcare processes (this data base is used as reference in Spain). It has the disadvantage that the data is private and not open access.

- **Full pharmacoeconomic analysis**. It would be desirable to have complete pharmacoeconomic studies, conducted from the perspective of our health care system, applying our costs and our profits. And cost-effectiveness thresholds per QALY that were of reference for our area.

While this is not feasible with the resources and perspective arising GENESIS reports, it is possible to make approximations using our model based on data developed by independent reference groups, such as NICE. To the extent that equity and collaboration with experts allow, is a feasible way that decisions are made based on economic analysis and outlook suitable quality. See section below on published economic evaluations.

- **Analysis by Subgroups**. Despite the limitations, the analysis of the results of the subgroups, we can calculate the incremental cost per subgroup efficacy. Results of clinical trials providing sufficient data allow recommending the drug in patients who have shown a significant benefit with acceptable incremental cost efficacy ratio. This stratification is the first step to incorporate these concepts in the guidelines and treatment protocols.

- **Other approaches**. It may also be of interest to apply different drug costs (negotiated prices, cost monitoring, etc.) and other health care costs associated with treatment. Also, if we have our own data to estimate an expected result closest to the effectiveness, we apply and compare efficacy data from the clinical trial of reference.

7.3 Estimated number of patients eligible for treatment at the hospital

In case of continuous variables:

Estimated number of patients considered for treatment in the hospital every year, annual estimated cost and annual efficacy units				
Annual number of patients	Incremental cost per patient	Efficacy difference between drugs studied	Annual budget impact	Efficacy units per year
A	B	D units	A x B	A x D

Note: more rows can be added to express the results by subgroups of patients or restrict the terms of use. In this case the annual number of patients, the difference in efficacy and therefore the annual budget impact and the efficacy units gained annually will be different.

In case of binary variables:

Estimated number of patients considered for treatment in the hospital every year, annual estimated cost and annual efficacy units				
Annual number of patients	Incremental cost per patient	NNT	Annual budget impact	Efficacy units per year
A	B	C	A x B	A/C
Note: more rows can be added to express the results by subgroups of patients or restrict the terms of use. In this case the annual number of patients, NNT and therefore the annual budget impact and the efficacy units gained annually will be different.				

Interpretation: It is estimated that, over a year, there will be a total of xx treated patients with the new drug. The additional annual cost to the hospital will be xxxx euros. The estimated number of patients who will benefit during the period of one year shall be xx (define variable evaluated in the pivotal trial)

Additional annual cost to the hospital: Estimated impact on the budget of the services.
Service xxxx: Global Impact and budget%: xxxx

Calculate the budgetary impact with different scenarios for different positionings.

Instructions

We estimate the number of patients eligible for hospital treatment for a period, for example one year. This information could be found in hospital records also we have an estimate in the application for inclusion, along with recommendations and conditions of use proposed for the new drug. Thus we get the additional expense in the hospital expected from the introduction of the new drug as well as the expected benefits for the health of the patients during the same time period, say one year.

Estimating the economic impact and health outcomes dimension helps us to predict what will be the expected costs and health benefits in a particular area (eg our hospital) and at the specified time (eg one year), therefore helps us to size what the new drug really offers.

Occasionally the estimated impact per medical service must be made, mostly of interest to estimate whether it can significantly affect the budget for the service and have it planned in the budget level.

7.4 Estimated budget impact on prescribing for Primary Care.

BUDGET IMPACT IN THE AREA				
Drug	Retail Price per package	DDD	DDD Cost	DDD Cost difference
A				
B				
BUDGET IMPACT OF THE SUBSTITUTION				
Total DDD of drug B per year: N . DDD Cost difference: d				
Budget impact of a 100% substitution per year: N x d				
Budget impact of a 5 % substitution per yea:r (Nxd) x 5 %				

Instructions:

To discharge prescription treatments in which the most relevant area of cost is the outpatient setting, you will estimate the annual impact of the possible induction.

This will calculate the difference in the average cost per DDD of the drug substituted, calculate the cost per DDD of the new drug and find the difference in cost per DDD. Multiplying the difference in cost by the total number of doses consumed per year (estimated impact of the total replacement) and by a small percentage, says 5%, of the total DDD (estimation of a small induction).

To make this estimate requires two conditions:
- Know the reference drug consumption in DDD in the area for the particular indication being evaluated
- Check that the DDD established for drug reference drug is the usual dose for the particular indication being evaluated

7.5 Estimation of the overall budget impact at regional / state

Just fill in for GENESIS reports

Similar to Section 7.3 and the method described therein, and subject to the availability of data at large areas, regional or national, can be an overall estimate of the economic impact of interest to managers and to the prioritization of resources.

Use prevalence and incidence data to estimate potential candidates to receive the new treatment, see section 3 of this report. Describe different scenarios depending on different conditions.

Some key points in the budget impact analysis (BIA):

A) Clear analysis objective: Describe clearly the target population analysis, and whether it is justified to define subgroups of analysis. Clearly describe whether treatment totally or partially replaces the options currently available or it is added to the standard treatment routine.

B) Selected impact variables: They must come from sources with a higher level of evidence and allow evolution of the economic impact of the new treatment. Eg pharmaceutical costs, hospitalizations, use of epoetin…

C) Relevant costs: In addition to what was stated in section 7.1 of costing for the BIA is very important that these variables within the competence of the decision maker of the budget concerned. In reality there is a budget isolation (silo effect) that makes the introduction of a new drug not taking into account savings in another area. Eg welfare, ambulance or productivity...

D) Population dynamics and estimated implementation of the new drug: Clearly describe the volume and the expected evolution of the target population. To do this, indicate the proportion of target population who use the drug initially expected and/or in the first 2-3 years of its introduction.

E) Considerations: Trying to make a simple, transparent and clearly reproducible to allow us to estimate the economic impact of the new drug in different situations and under different assumptions of decision (eg different purchase prices, selection of subgroups with a high benefit) to show the influence of uncertainty in the analysis.

Ref: Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, Orlewska E, Watkins J, Trueman P. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. Value Health. 2007 Sep-Oct;10(5):336-47.

8. CONVENIENCE ASSESSMENT.

Instructions:

Develop especially this section if the efficacy, safety and / or efficiency are comparable, if there is evidence of differences between efficacy and effectiveness, and convenience aspects are clearly differential between assessed drugs and alternatives.

8.1 Description of convenience

- Administration, dosage, availability, acceptability by the patient that influence compliance.

- Features pharmacy circuit (storage, preparation...) or physician workload (visits, monitoring…).

8.2 Influence of convenience in treatment effectiveness

Include in this section ONLY survey data reflect a direct impact of convenience in the effectiveness and / or efficiency of treatment. Eg pattern/route of administration that facilitates adherence to treatment and improves clinical outcomes.

You must demonstrate if you have a study that measures the convenience and impact. Expose its results

9. CONCLUSIONS

9.1 Overview of the most significant aspects versus alternatives AND proposals

A) Clinical and therapeutic aspects

- Compared clinical benefit: Efficacy / effectiveness, safety / tolerability, drawbacks of current treatment and unmet needs.
- Subgroups of patients with differential risk/benefit compared to the average.
- If benefits and risks are quantifiable, calculate the LHH = (1/NNT) / (1/NNH).
- Another possibility is to calculate benefits and risks per 1000 patients treated.

B) Cost, Cost Effectiveness and budget impact

Instructions:

Summary of the information contained in the previous sections of the report:

A) Clinical and therapeutic aspects

If quantifiable benefits and risks calculate the LHH = (1/NNT) / (1/NNH) or benefits and risks per 1000 patients treated

Examples (Ticagrelor GENESIS Report 2012):

Estimation of the benefit / risk of ticagrelor for every 1000 patients treated.

a) According to the overall PLATO trial data, for every 1000 patients treated with ticagrelor instead of clopidogrel we will prevent 10 deaths from vascular causes and 11 nonfatal MI but produce 15 hemorrhages of which 7 are non-serious bleeding CABG, 61 patients will experience dyspnea and 5 should be discontinued for this reason.
b) In patients with ACS and planned intervention, per 1000 patients treated with ticagrelor instead of clopidogrel we will prevent 8 deaths from vascular causes, 13 MI and 10 stent thrombosis, but there will be 18 major or minor bleeding not related to CABG.

Another way to evaluate the benefit / risk is by LHH (versus Helped likelihood to be harmed) that defines the number of patients who will benefit from treatment for each patient harmed, and is calculated as LHH = (1/NNT) / (1/NNH), in our case ,this would be:

a) Global Data: (1/56) / (1/142) = 2.5, ie, for every 2.5 patients who obtained efficacy primary outcome (cardiovascular death + MI + stroke) we would have 1 patient suffering major bleeding not related to CABG.
b) In patients with ACS and planned intervention : (1/61) / (1/57) = 0.9 is, for every 0.9 patients who obtain efficacy primary outcome (death from any source + IM + stroke) one patient will suffer a major or minor bleeding not related to CABG

B) Cost, incremental cost efficacy and budget impact.

Summary of the economic evaluation section. Where appropriate specific proposals drug acquisition price (based on threshold values of cost per QALY utility, EoL or other criteria) and efficient use.

Examples (Report of Ipilimumab GENESIS 2012)

Even recognizing the role that ipilimumab can play in the treatment of metastatic melanoma, an unfavorable incremental cost effectiveness ratio (ICER) forced to seek alternative funding formulas. From this viewpoint, various approaches can be made:

a) Increase (relative) effectiveness
When we speak of relative increase in effectiveness we can use the treatment in subgroups of patients in which the clinical benefit is maximized. This will keep the costs (numerator) but we can reduce the ICER by increasiong effectiveness units (denominator).

b) Decrease the cost of acquisition
If one accepts the parameters described previously by NICE for cancer drugs used in terminal situations (see table above) and respect the original QALY, it is possible to calculate the selling price so that the cost per QALY is between € 49,200 and € 61,500 (values threshold as EoL): The price per vial of 200 mg of ipilimumab (VAT included) must be between € xxxx and xxxx € (*confidential data*).

c) Risk-sharing Programs
The implementation of risk-sharing programs, where the cost is proportional to the "successes" of treatment to get a discount on non-responders.

9.2 Decisión

-The proposal of the authors of the report is to be classified as: View GUIDE GINF
Identify whether the proposal includes the removal of other drugs of the Formulary

Instructions:

Classification of applications GINF Guide Version 3.0

Applications will be ranked according to the procedure described on this page and issuing a decision according to the chart on the next page.

1. A total absence of data or insufficient data in major sections (1,2,3,17 questions and / or Table section B) can be considered exclusive, as it implies the absence of a fundamental requirement and practically forces to reject the request and include it in the **Category A-1**. If the application is deemed relevant, the committee may require additional information or modifications necessary to ensure compliance with the basic requirements and be reassessed.

2. If the indication for the drug requested is treated on an outpatient basis, the drug is not Hospital use (question 5) and is not required during hospital administration, will be classified as **Category A-2**.

3. If in questions concerning the efficacy, effectiveness and safety (Section B) is detected absence of clinical trials , or trials with major methodological problems , or tests without clinically relevant outcomes , is classified in **Category B -1**.

4. If in questions concerning the efficacy , effectiveness and safety (Section B) are detected quality clinical trials in which there are clinically relevant outcomes reporting a worse profile efficacy / safety of the new drug against the alternative currently on the hospital is classified in **Category B -2.**

5. If in questions concerning the efficacy, effectiveness and safety (Section B) there are no criteria for choosing between the new drug or alternative and there is no difference in the profile of cost-effectiveness, the new drug may be considered therapeutically equivalent to therapies existing and classified in **Category C**. This decision can be motivated by two situations:

Comparative clinical trials exist to the alternative in which demonstrate therapeutic equivalence OR clinically relevant outcomes exist in parallel assays of each alternative against a third comparator whose methodology, study population, outcome variable and other relevant characteristics are similar.

Market conditions and the implications it may have whether or not the new alternative equivalent in the hospital management will lead, as appropriate, to **Category C -1 or C -2 category**.

6. If the results of clinical trials on efficacy, effectiveness and safety have significant clinical advantages compared to currently available therapeutic alternative in the hospital, OR the profile is clearly favorable cost-effectiveness will be included in the directory , removing or not alternative drug.

7. The classification in **Category D or Category E** will depend on the need to prevent adverse effects, ensuring that the management shall be conducted by more experienced clinicians, bring only patient subpopulations for which the drug is tested are treated or any other circumstance that advises a specific restriction.

Given the above criteria, the Pharmacy and Therapeutics Committee drug classified in one of the following categories, appearing explicitly in the minutes of the relevant meeting.

A. THE DRUG IS NOT INCLUDED IN THE GFT for lack of some basic requirements.

A-1. NOT INCLUDED IN THE FORMULARY: it is not possible an adequate assessment of the application information.

A-2. NOT INCLUDED IN THE FORMULARY: it is indicated in a condition that does not require hospitalization or served from Units Day

B-1. NOT INCLUDED IN THE FORMULARY: insufficient evidence that there is a better relationship efficacy/safety compared with current treatment is performed in the hospital.

B-2. NOT INCLUDED IN THE FORMULARY: the evidence indicates a worse profile efficacy/safety compared to current treatment performed in the hospital.

_____

C-1. The Drug is comparable regarding efficacy and safety to the existing alternatives within the proposed indications. Furthermore, it presents no improvement in the cost-effectiveness profile, or in the organization or management of services. So NOT INCLUDED IN THE FORMULARY.

C-2. The Drug is comparable regarding efficacy and safety to the existing alternatives within the proposed indications, and with no improvement in cost-effectiveness. However, it is estimated that joining purchasing procedures might be advantages in management. Therefore IS IN THE FORMULARY AS AN EQUIVALENT THERAPEUTIC ALTERNATIVE to existing options, so that the particular drug that will exist at all times will be the result of the public procurement procedure.

_____

D-1. INCLUDED IN THE GFT with specific recommendations.

D-2. INCLUDED IN THE GFT with specific recommendations and a commitment to reassessment of the same after the PTC period appropriate.

_____

E. INCLUDED IN THE GFT no specific recommendations.

9.3 Conditions of use (Following the classification of GINF)

Instructions:

The therapeutic positioning decision is based on scientific criteria and efficiency about the place that should take a drug in the therapeutic scheme of a specific health problem.

Specific indication of the approval decision:

- Subgroups or types of patients based on clinical features, severity or stage, presence of markers or other
- Methods clinical, laboratory or others to classify these patients and to determine the indication of the drug

Positioning with respect to alternative treatments

- Previous treatment should have received or should be contraindicated, indicating clear contraindication causes

Particular treatment scheme

- Dose, guidelines and initial duration of treatment
- Criteria for evaluating the effectiveness or therapeutic failure
- Stopping rules (if applicable)

Other criteria restricting

- Restriction on certain clinical services, sections or units or even individual physicians .
- Restriction by individualized procedure: case by case approval by a Permanent Commission within the PTC or equivalent.

9.4 Monitoritng plan

Instructions:

Identify systems to define restricted use through prescription systems, validation and dispensing. To be considered:

- Procedure: a) Through the electronic prescription system b) Through manual dispensing systems c) Other
- Impact: a) Validation prior to dispensing b) Subsequent validation

Identify if approved subsequent evaluation or audit. It should include:

- Person or persons responsible for implementation
- Date to be held
- Primary Objectives

Identify needs to amend the Therapeutic Interchange Program
Identify need for re-evaluation and probable dates of the same

PARTICIPANTS AND CONTRIBUTORS MADRE V4.0

The MADRE update project has been carried out by RAND-UCLA method that combines the best available evidence with expert opinion.

The participation of experts and professionals involved in drug review process in different areas, but especially in the hospital pharmacy, has been key.

We want to record their extraordinary professional and selfless contribution at various stages of project development.

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