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”

Authors and affiliations:

Roberto Marín Gil.
Virgen del Rocío University Hospital. Sevilla.

Francesc Puigventós Latorre. (PI)
Son Espases University Hospital. Palma de Mallorca.

Mª Dolores Fraga Fuentes.
La Mancha Centro Hospital. Alcázar de San Juan.

Ana Ortega Eslava.
Navarra University Clinic. Pamplona.

Eduardo López Briz.
La Fe University Hospital. Valencia.

Vicente Arocas Casañ.
Virgen de la Arrixaca University Hospital. Murcia.

Bernardo Santos Ramos.
Virgen del Rocío University Hospital. Sevilla

ISBN: 978-84-695-7629-8

DEPÓSITO LEGAL: M-12319-2013
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:
R. Marín, F. Puigventós, A. Ortega, MD Fraga, E. López-Briz, V. Arocas, B. Santos

Project undertaken with the financial support of a research grant from SEFH, call 2011.

How to cite this document:

CONTENTS

AUTHORS 2

INTRODUCTION 3

CONTENTS 4

STRUCTURE AND LEVEL OF HELP 6

BASE REPORT TEMPLATE FULL VERSION WITH INSTRUCTIONS 7-64

0. - HEADER 7

1. - DRUG IDENTIFICATION AND AUTHORS OF REPORT 8

2. - APPLICATION AND EVALUATION PROCESS 10

3. - DESCRIPTIVE AREA: MEDICINE AND HEALTH PROBLEM 11
3.1 Medicine information 11
3.2 Health problem 12
3.2.a Structured description of the health problem 12
3.2.b Current treatment of the disease: evidence 12
3.3 Features compared to similar alternatives 12

4. - PHARMACOLOGICAL ACTION AREA. 14
4.1 Mechanism of action. 14
4.2 Therapeutic indications and date of approval. 14
4.3 Posology, preparation and administration. 14
4.4 Uses in Special Populations. 14
4.5 Pharmacokinetics. 14

5. - EVALUATION OF THE EFFICACY. 15
5.1.a Clinical trials available for the indication under assessment 15
5.1.b Endpoints used in clinical trials 15
5.2.a Results of clinical trials 17
Table 1.1.a Binary variables 18
Table 1.1.b Binary variables. Analysis of non-inferiority 19
Table 1.2 Continuous variables. 19
Table 2 Variables "time to event" 20
Table 2.1 Variables "time to event". RRR and HR. 21
Table 2.2.a Variables "time to event". RAR and NNT at a given time. 21
Table 2.2.b Variables "time to event". Getting NNT / RAR from HR. 22
Table 2.3 Variables "time to event". Mean / median survival time. 24
5.2.b Evaluation of the validity and practical utility of the results 27
A. Internal validity. Limitations of design and / or comments: 27
B. Applicability of the trials to hospital practice 29
C. Clinical relevance of the results 29
  C.1 Magnitude of the treatment effect. 29
  C.2 Evidence of therapeutic equivalence. 31
  C.3 Equivalent Therapeutic Alternatives (ETAs) 32
  5.2.c Assessment screening tests used 34
  5.3 Published systematic reviews, indirect comparisons and conclusions 35
  5.3.a Published systematic reviews 35
  5.3.b Indirect comparisons (CI) 36
  5.3.b.1 Published indirect comparisons 36
  5.3.b.2 Other indirect comparisons 42
  5.4 Evaluation of secondary sources 43

6. SAFETY ASSESSMENT . 44
  6.1.a Bibliographic search description 44
  6.1.b Description of significant adverse effects 44
  6.2 Comparative clinical trials 46
  6.3 Secondary safety sources 46
  6.4 Precautions for use in special cases 47

7. ECONOMIC AREA 48
  7.1 Treatment cost. Incremental cost 48
  Example: Table with associated costs drawn from clinical trial data 49
  7.2.a Incremental cost effectiveness (ICE). Studies published 49
  7.2.b Incremental cost effectiveness (ICE). Own data 53
  7.3 Estimated number of patients eligible for treatment at the hospital 57
  7.4 Estimated budget impact on prescribing for Primary Care. 58
  7.5 Estimation of the overall regional/national budget impact 59

8. CONVENIENCE ASSESSMENT. 60
  8.1 Description of convenience 60
  8.2 Influence of convenience in treatment effectiveness 60

9. CONCLUSIONS AREA. 61
  9.1 Overview of the most significant aspects versus alternatives AND proposals 61
  9.2 Decision 62
  9.3 Conditions of use (Following the classification of GINF) 63
  9.4 Monitoring Plan 64

PARTICIPANTS AND CONTRIBUTORS 65
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 Committee of the Hospital xxxx. Date of report. [Cited: date].

Available at: [http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/InformesHosp_abcd.htm](http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/InformesHosp_abcd.htm)
Also: [http://gruposdetrabajo.sefh.es/genesis/genesis/](http://gruposdetrabajo.sefh.es/genesis/genesis/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_abcd.htm](http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/InformesHosp_abcd.htm)
Also at: [http://gruposdetrabajo.sefh.es/genesis/genesis/](http://gruposdetrabajo.sefh.es/genesis/genesis/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)**

<table>
<thead>
<tr>
<th>Activity</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding for meetings and conferences, attending courses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(registration, travel bags, accommodation ...)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fees as a speaker (conferences, courses ...)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding of educational programs or courses (staffing, facility rental ...)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding for participating in an investigation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consulting for a pharmaceutical company</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shareholder or business interests in a company</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conflicts of interest of non-economic nature that may be significant in relation to authorship in the report</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B- Non-personal interests (please specify)**

<table>
<thead>
<tr>
<th>Activity</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding or financial assistance for the unit or service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contracting or financial aid to recruit in the unit or service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial support for research funding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding of educational programs or courses for the unit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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)

<table>
<thead>
<tr>
<th>Pharmaceutical forms and price (Note 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical form</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

(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.


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:**

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>Chronic C hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERVENTION</td>
<td>PR (Peg-Interferon plus ribavirine) plus protease inhibitors</td>
</tr>
<tr>
<td>COMPARATOR</td>
<td>PR alone</td>
</tr>
<tr>
<td>RESULTS</td>
<td>Variables: clinical benefit, mortality, morbidity, etc.</td>
</tr>
</tbody>
</table>

**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:

<table>
<thead>
<tr>
<th>Health problem</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td></td>
</tr>
<tr>
<td>Incidence and prevalence</td>
<td></td>
</tr>
<tr>
<td>Course of the disease / Prognosis</td>
<td></td>
</tr>
<tr>
<td>Severity / Stages</td>
<td></td>
</tr>
<tr>
<td>Burden of the disease*</td>
<td></td>
</tr>
</tbody>
</table>

* 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.

<table>
<thead>
<tr>
<th>Features compared to similar alternatives</th>
<th>XXXX</th>
<th>XXXX</th>
<th>XXXX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
</tr>
<tr>
<td>Dosage form</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resources consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convenience</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
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. E.g: 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 showing 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. They are 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>
<thead>
<tr>
<th>Table n° x. Endpoints used in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
</tr>
<tr>
<td>Primary endpoint</td>
</tr>
<tr>
<td>Secondary endpoint a</td>
</tr>
<tr>
<td>Secondary endpoint b</td>
</tr>
<tr>
<td>...</td>
</tr>
<tr>
<td><strong>SAFETY</strong></td>
</tr>
<tr>
<td>Primary endpoint</td>
</tr>
<tr>
<td>Secondary endpoint a</td>
</tr>
<tr>
<td>Secondary endpoint b</td>
</tr>
<tr>
<td>...</td>
</tr>
</tbody>
</table>

(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:


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:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Active group N (n pts)</th>
<th>Control group N (n pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Variable description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary endpoints (relevant)</td>
<td>Variable description</td>
<td></td>
</tr>
<tr>
<td>Results by subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Variable description</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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.

![Algorithm of outcomes](image)

**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
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:
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

<table>
<thead>
<tr>
<th>Study endpoint</th>
<th>Treatment studied</th>
<th>Control treatment</th>
<th>Mean difference (CI 95%)</th>
<th>P</th>
<th>---</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>Variable description</td>
<td>mean (sd)</td>
<td>mean (sd)</td>
<td>Mean difference (CI 95%: x to x)</td>
<td>P</td>
</tr>
</tbody>
</table>

(*) If n is different for secondary endpoints or subgroup, please incluye it after the result.
(**) Calculators for continuous variables: R.Saracho.

sd: standard 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)

---

20
**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:**

<table>
<thead>
<tr>
<th>Study endpoint</th>
<th>Hazard ratio</th>
<th>p</th>
<th>RRR (CI95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>x (CI95 : x to x)</td>
<td>p</td>
<td>X% (x% to x%)</td>
</tr>
</tbody>
</table>

**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

\[
\text{HR} = 0.65, \text{then } 1 - 0.65 = 0.35 \\
\text{Instantaneous RRR} = 35 \%
\]

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)**

<table>
<thead>
<tr>
<th>Study endpoint and time</th>
<th>Treatment studied N (pts in time t)</th>
<th>Control treatment N (pts in time t)</th>
<th>ARR (CI 95%) Absolute Risk Difference</th>
<th>p</th>
<th>NNT (CI 95%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>%</td>
<td>%</td>
<td>% (CI95 : x% to x%)</td>
<td>p</td>
<td>X ( x to x)</td>
</tr>
</tbody>
</table>

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:

![Graph showing survival curves and variables](image)

**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)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment studied n</th>
<th>Control treatment n</th>
<th>ARR (CI95%) Calculated from HR (CI95%)</th>
<th>p</th>
<th>NNT (CI95%) Calculated from HR (CI95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Brief description of the variable</td>
<td>Cumulative probability b</td>
<td>Cumulative probability a</td>
<td>X % (x% to x%)</td>
<td>p</td>
<td>HR: x (x to x) NNT: x (x to x)</td>
</tr>
</tbody>
</table>

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


- 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 trial:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Apixaban N (9,120)</th>
<th>Warfarina N (9,081)</th>
<th>ARR (CI95%) at 1,8 year (*)</th>
<th>NNT (CI95%) at 1,8 year (*)</th>
<th>NNT (CI95%) Per patients-year (**) from HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke and syst. embolism</td>
<td>212 (1,27%)</td>
<td>265 (1,60%)</td>
<td>0,6% (0,13% a 1,06%)</td>
<td>168 (95 a 773)</td>
<td>HR:0,79 (0,66-0,95) NNT:300 (185-1260)</td>
</tr>
<tr>
<td>Stroke</td>
<td>199 (1,19%)</td>
<td>250 (1,51%)</td>
<td>0,6% (0,12% a 1,02%)</td>
<td>175 (98 a 832)</td>
<td>HR:0,79 (0,65-0,95) NNT:217 (190 - 1334)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>40 (0,24%)</td>
<td>78 (0,47%)</td>
<td>0,4% (0,2% a 0,7%)</td>
<td>238 (153 a 535)</td>
<td>HR:0,51 (0,35-0,75) NNT:435 (328 – 853)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>15 (0,09%)</td>
<td>17 (0,10%)</td>
<td>NS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Death for any causet</td>
<td>603 (3,52%)</td>
<td>669 (3,94%)</td>
<td>1,1% (0,8% a 1,8%)</td>
<td>132 (67-6951)</td>
<td>HR: 0,89 (0,80-0,998) NNT:235 (129-12948)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>90 (0,53%)</td>
<td>102 (0,61%)</td>
<td>NS</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

(*) 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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment studied N (nº pts)</th>
<th>Control treatment N (nº pts)</th>
<th>Difference in median survival</th>
<th>p</th>
<th>---</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>Mean or median b</td>
<td>Mean or median a</td>
<td>Mean or median difference b - a</td>
<td>p</td>
<td>---</td>
</tr>
</tbody>
</table>

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**:


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

**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 (e.g., mortality), it is possible and desirable to determine what exactly this probability value is. 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

Further information:


**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**

<table>
<thead>
<tr>
<th>Variable description</th>
<th>Results binary variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>References</strong> &amp; <strong>Treatment studied N (nº pts)</strong> &amp; <strong>Control treatment N (n pts)</strong> &amp; <strong>ARR (IC 95%)</strong> &amp; <strong>p</strong> &amp; <strong>NNT (CI 95%)</strong></td>
<td></td>
</tr>
<tr>
<td>Trial 1 (ref) year &amp; % &amp; % &amp; % (CI95 : x% to x%) &amp; p &amp; X (x to x)</td>
<td></td>
</tr>
<tr>
<td>Trial 2 (ref) year &amp; % &amp; % &amp; % (CI95 : x% to x%) &amp; p &amp; X (x to x)</td>
<td></td>
</tr>
<tr>
<td>Trial 3 (ref) year &amp; % &amp; % &amp; % (CI95 : x% to x%) &amp; p &amp; X (x to x)</td>
<td></td>
</tr>
<tr>
<td>Trial 4 (ref) year &amp; % &amp; % &amp; % (CI95 : x% to x%) &amp; p &amp; X (x to x)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Calculators for binary variables: ARR, NNT and CI 95%. CASPe = SIGN
(**) If \( n \) is different for secondary endpoints or subgroup, please include it after the result.
(***) Indicate CI 95% and NNT only if the result is statistically significant: \( p < 0.05 \)

**Table 3.2**

<table>
<thead>
<tr>
<th>Variable description</th>
<th>Results continuous variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>References</strong> &amp; <strong>Treatment studied N (nº pts)</strong> &amp; <strong>Control treatment N (n pts)</strong> &amp; <strong>Mean difference (CI 95%)</strong> &amp; <strong>p</strong> &amp; <strong>---</strong></td>
<td></td>
</tr>
<tr>
<td>Trial 1 (ref) year &amp; mean &amp; mean &amp; Mean difference (CI95% : x to x) &amp; p &amp; ---</td>
<td></td>
</tr>
</tbody>
</table>

26
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

<table>
<thead>
<tr>
<th>Meta-analysis endpoint</th>
<th>Treatment studied N (nº pts)</th>
<th>Control treatment N (nº pts)</th>
<th>ARR, RR u OR (CI 95%)</th>
<th>P</th>
<th>NNT (CI 95%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>%</td>
<td>%</td>
<td>% (CI95 : x% to x%)</td>
<td>X ( x to x)</td>
<td></td>
</tr>
<tr>
<td>Secondary endpoint of interest</td>
<td>%</td>
<td>%</td>
<td>% (CI95 : x% to x%)</td>
<td>X ( x to x)</td>
<td></td>
</tr>
<tr>
<td>Subgroup results</td>
<td>%</td>
<td>%</td>
<td>% (CI95 : x% to x%)</td>
<td>X ( x to x)</td>
<td></td>
</tr>
</tbody>
</table>

* 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>
<thead>
<tr>
<th>Table 5.2.b.1</th>
<th>Unified table for bias from the Cochrane Collaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item</td>
<td>Description</td>
</tr>
<tr>
<td>Selection bias</td>
<td></td>
</tr>
<tr>
<td>Allocation sequence generation</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td></td>
</tr>
<tr>
<td>Realization bias</td>
<td></td>
</tr>
<tr>
<td>Staff and patients blinding</td>
<td></td>
</tr>
<tr>
<td>Detection bias</td>
<td></td>
</tr>
<tr>
<td>Clinical evaluator blinding</td>
<td></td>
</tr>
<tr>
<td>Result evaluator blinding</td>
<td></td>
</tr>
<tr>
<td>Attrition bias</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data management</td>
<td></td>
</tr>
<tr>
<td>Notification bias</td>
<td></td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td></td>
</tr>
<tr>
<td>Other sources of bias</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Support for assessment, evaluation based observations.</th>
<th>Assessment of risk of bias (High Risk, Low Risk, Risk unclear)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 study 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.

- 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

<table>
<thead>
<tr>
<th>5.2.b.2 Table 3</th>
<th>APPLICABILITY OF THE TRIALS TO HOSPITAL PRACTICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES/NO</td>
<td>JUSTIFY</td>
</tr>
<tr>
<td>Is the comparator the appropriate standard?</td>
<td>Drug, dose, posology, duration of the treatment</td>
</tr>
<tr>
<td>Do you consider the results clinically relevant?</td>
<td>Do you might consider the difference obtained as clinically relevant improvement?</td>
</tr>
<tr>
<td>Is the measured outcome appropriate?</td>
<td>Is the measured outcome evaluated routinely in the clinic?</td>
</tr>
<tr>
<td>Do you consider the inclusion and exclusion criteria adequate?</td>
<td>Are there similar patients who receive the drug in the hospital?</td>
</tr>
<tr>
<td>Are the results directly applicable to routine clinical practice?</td>
<td>Feasibility in our enviroment</td>
</tr>
<tr>
<td>Other limitations to external validity</td>
<td>Comments</td>
</tr>
</tbody>
</table>

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 (intermediate, 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%.

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.

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Level of evidence</th>
<th>Degree of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Evidence”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equivalence and non-inferiority RCTs</td>
<td>1</td>
<td>High</td>
</tr>
<tr>
<td>“Estimation”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equivalence RCTs without clinical</td>
<td>2</td>
<td>High</td>
</tr>
<tr>
<td>relevance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superiority RCTs without statistical</td>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>significancace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCTs vs a common comparator</td>
<td>4</td>
<td>Moderate</td>
</tr>
<tr>
<td>RCTs vs a different comparator</td>
<td>5</td>
<td>Low</td>
</tr>
<tr>
<td>Observational studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Support”</td>
<td></td>
<td>“Support to levels above”</td>
</tr>
<tr>
<td>Reviews, CPGs, recommendations, expert opinions, clinical judgement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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:


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, Rocio 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>
<thead>
<tr>
<th>ITEMS TO DEFINE THE DIFFERENCE</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Statistically significant difference?</td>
<td>2. ARR, OR, RR or HR exceed delta value?</td>
</tr>
<tr>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>
Table 3
RECOMMENDED POSITIONING

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

* 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.

<table>
<thead>
<tr>
<th>Reference:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
</tr>
<tr>
<td>Brief description of the meta-analysis</td>
</tr>
<tr>
<td>N. of trials N. of patients</td>
</tr>
<tr>
<td>Inclusion and exclusion criteria of trials:</td>
</tr>
<tr>
<td>Active treatment group and control group:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meta-analysis endpoint</th>
<th>Treatment studied N (nº pts)</th>
<th>Control treatment N (nº pts)</th>
<th>ARR, RR u OR (CI 95%)</th>
<th>NNT (CI 95%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>%</td>
<td>%</td>
<td>% (CI 95: x% to x%)</td>
<td>X (x to x)</td>
</tr>
<tr>
<td>Secondary endpoint of interest</td>
<td>%</td>
<td>%</td>
<td>% (CI 95: x% to x%)</td>
<td>X (x to x)</td>
</tr>
<tr>
<td>Subgroup results</td>
<td>%</td>
<td>%</td>
<td>% (CI 95: x% to x%)</td>
<td>X (x to x)</td>
</tr>
</tbody>
</table>

(*) Indicate CI 95% and NNT only if the result is statistically 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 (χ², 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:


- 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


**5.3.b Indirect comparisons (IC)**

**5.3.b.1 Published indirect comparisons**
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:

<table>
<thead>
<tr>
<th>Reference:</th>
<th>RCTs comparison</th>
<th>NON-ADJUSTED IC</th>
<th>ADJUSTED IC</th>
<th>Network metanalysis</th>
</tr>
</thead>
</table>

**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)

**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 COMPARISONS:**
- YES
- NO

**METHODS USED FOR THE INDIRECT COMPARISON**
- Bucher
- Bayesian
- Frequentist
- Non SPECIFIED
- Otro

**Bias adjustment 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 authors 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
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.
Internal validity analysis for IC

Reference of the assessed IC:

Table 5.3.b.1.2
Internal validity analysis for IC

<table>
<thead>
<tr>
<th>YES/NO</th>
<th>JUSTIFY</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Is it appropriate to the method used for indirect comparison? Reject comparisons “naive” made with point estimates derived from different controlled trials or different active arms of controlled trials</td>
<td></td>
</tr>
<tr>
<td>- Is clearly stated how they conducted the search and selection of trials for inclusion?</td>
<td></td>
</tr>
<tr>
<td>- A full description of the methods of analysis / synthesis of the evidence is made? Bias Management</td>
<td></td>
</tr>
<tr>
<td>- 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</td>
<td></td>
</tr>
<tr>
<td>- Is there results concordance? The result is the same regardless of the chain of comparisons used to obtain it</td>
<td></td>
</tr>
<tr>
<td>- 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</td>
<td></td>
</tr>
<tr>
<td>- Other biases or limitations found in the study</td>
<td></td>
</tr>
</tbody>
</table>

Applicability analysis for IC

Table 5.3.b.1.3
APPLICABILITY ANALYSIS FOR IC

<table>
<thead>
<tr>
<th>YES/NO</th>
<th>JUSTIFY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you consider the / comparators appropriate? Is common comparator the usual treatment in our environment?</td>
<td></td>
</tr>
<tr>
<td>Are the results clinically significant?</td>
<td></td>
</tr>
<tr>
<td>Is the variable used adequate?</td>
<td></td>
</tr>
<tr>
<td>Are the inclusion criteria and / or exclusion of patients appropriate?</td>
<td></td>
</tr>
<tr>
<td>Generalization of the findings (Population of patients in the trials and between trials)</td>
<td></td>
</tr>
<tr>
<td>Do you think that the results can be directly applied to clinical practice?</td>
<td></td>
</tr>
<tr>
<td>Other biases or limitations found in the study</td>
<td></td>
</tr>
</tbody>
</table>

E.g. Table for IC:


<table>
<thead>
<tr>
<th>Comparison BvITV versus RnITV</th>
<th>OR (CI 95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients improved more than 2 lines (10 letters) on the ETDRS BCVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab: 21/77 (27%) Laser: 6/73 (8%)</td>
<td>Ranibizumab: 60/152 (39%) Laser: 19/148 (12,8%)</td>
<td>0,95 (0,23-4,34)</td>
</tr>
</tbody>
</table>
**Table 12. Results of the studies included in the IC by Ford et al:**

<table>
<thead>
<tr>
<th>COMPARISONS OF RCTs</th>
<th>NON-ADJUSTED IC</th>
<th>ADJUSTED IC</th>
<th>NETWORK METAANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A: Bevacizumab (BvITV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference, Type of study, design, eyes (patients), country…</td>
<td>Intervention A (N) (dose, treatment duration)</td>
<td>Control(N) (dose, treatment duration)</td>
<td>Patients characteristics (age, genre…)</td>
</tr>
<tr>
<td>BOLT study Michaelides et al 2010</td>
<td>1.25 mg BvITV (n=42) weekly for 6 weeks (n of injections, range 3-9)</td>
<td>Laser (n=38) Monthly treatment (range 1-4)</td>
<td>Difference in mean BCVA at 12 months</td>
</tr>
<tr>
<td>Sohelian et al 2009</td>
<td>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</td>
<td>Laser + simulated injection (retreatment every 12 weeks if indicated) (n=50) Retreatment in 3 eyes y 3rd tt in 1 eye</td>
<td>Difference in mean BCVA (logMAR) at 6 months</td>
</tr>
<tr>
<td>Drug B: Ranibizumab (RnITV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference, Type of study, design, eyes (patients), country…</td>
<td>Intervention A (N) (dose, treatment duration)</td>
<td>Control(N) (dose, treatment duration)</td>
<td>Patients characteristics (age, genre…)</td>
</tr>
<tr>
<td>RESTORE study 2011</td>
<td>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).</td>
<td>Laser (monthly if needed) + simulated injection (n=110)</td>
<td>Mean change in BCVA (month 1 to 12 vs basal)</td>
</tr>
<tr>
<td>Nguyen et al 2009</td>
<td>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).</td>
<td>Laser months 0 y 3, if needed (n=42). Mean change in BCVA (month 6 vs basal). Until 24 months in the extension study</td>
<td>Mean change in BCVA (month 6 vs basal). Until 24 months in the extension study</td>
</tr>
</tbody>
</table>
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


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

<table>
<thead>
<tr>
<th>Reference:</th>
<th>Brief description of the trial and design</th>
<th>Safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety endpoint evaluated in the study</td>
<td>Treatment</td>
</tr>
<tr>
<td></td>
<td>N (pt)</td>
<td>treated</td>
</tr>
<tr>
<td>-Variable description</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>-Variable description</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>-Variable description</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>-Variable description</td>
<td>%</td>
<td>%</td>
</tr>
</tbody>
</table>

(*) 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](http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/Calculadoras.htm)

Instructions:

Expose in section 6.1.b the general safety profile

**Recommendation 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.

**Recommendation 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).

**Recommendation 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

**Recommendation 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: 

\[ LHH = \frac{1/NNT}{1/NNH} \]

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 additional 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

**Recommendation 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

<table>
<thead>
<tr>
<th>Safety endpoint evaluated in the study</th>
<th>Treatment studied N (nº pt)</th>
<th>Control treatment N (nº pt)</th>
<th>ARR (CI 95%) Absolute Risk Difference*</th>
<th>P</th>
<th>NNH (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main safety endpoint -Variable description</td>
<td>% ( N)</td>
<td>% (N)</td>
<td>% (CI95 : x% to x%)</td>
<td>X (x to x)</td>
<td></td>
</tr>
<tr>
<td>Safety results by subgroups -Subgroup 1</td>
<td>% (n1)</td>
<td>% (n1)</td>
<td>% (CI95 : x% to %)</td>
<td>X (x to x)</td>
<td></td>
</tr>
<tr>
<td>-Subgroup 2</td>
<td>% (n2)</td>
<td>% (n2)</td>
<td>% (CI95 : x% to x%)</td>
<td>X (x to x)</td>
<td></td>
</tr>
<tr>
<td>-Subgroup 3</td>
<td>% (n3)</td>
<td>% (n3)</td>
<td>% (CI95 : x% to x%)</td>
<td>X (x to x)</td>
<td></td>
</tr>
</tbody>
</table>

(*) 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:**

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.

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

* 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.**

<table>
<thead>
<tr>
<th>Other efficacy and safety results</th>
<th>Palifermin (N =106)</th>
<th>Placebo (N =106)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of Total Parenteral Nutrition (% patients)</td>
<td>31%</td>
<td>55%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total Days Total parenteral nutrition</td>
<td>459</td>
<td>761</td>
<td></td>
</tr>
<tr>
<td>NPT required for mucositis</td>
<td>11%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Total days with TPN in patients who required PN for mucositis</td>
<td>158</td>
<td>569</td>
<td></td>
</tr>
<tr>
<td>Use of opioids in mg of morphine (median range))</td>
<td>212 (0-9418)</td>
<td>535 (0-9418)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Patients with febrile neutropenia</td>
<td>75%</td>
<td>92%</td>
<td>&lt; 0.001 (CI 95% of the difference 7-27)</td>
</tr>
<tr>
<td>Infections hematologic</td>
<td>15%</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Palifermin</th>
<th>No treatment of mucositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit price (ex-factory price plus VAT) *</td>
<td>781.5 € / vial of 6.25 mg</td>
</tr>
<tr>
<td>Posology</td>
<td>60 mcg/kg/day x 6 doses</td>
</tr>
<tr>
<td>Full treatment cost</td>
<td>4689 €</td>
</tr>
<tr>
<td>Costs associated approximate parenteral Nutrition</td>
<td>4,33 days x 60 €/day = 259.8 €</td>
</tr>
<tr>
<td>-75% (0.75 x 350 € ) = 262.5€</td>
<td>92% (0.92 x 350€) = 322 €</td>
</tr>
<tr>
<td>15% (0.15 x 350 €) = 52.5€</td>
<td>25% (0.25 x 350 €) = 87.5 €</td>
</tr>
<tr>
<td>212 mg x 1 € = 212€</td>
<td>535 mg x 1 € = 535 €</td>
</tr>
<tr>
<td>TOTAL costs associated</td>
<td>787€</td>
</tr>
<tr>
<td>Overall cost</td>
<td>5476€</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>4100€</td>
</tr>
</tbody>
</table>

* 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 pharacoeconomic 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

<table>
<thead>
<tr>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Type of study:</td>
</tr>
<tr>
<td>- Source of data: clinical trial, observational study Markov model ...</td>
</tr>
<tr>
<td>- Perspective:</td>
</tr>
<tr>
<td>- Population of the base case:</td>
</tr>
<tr>
<td>- Main outcome:</td>
</tr>
<tr>
<td>- Time horizon:</td>
</tr>
<tr>
<td>- Costs included in the study:</td>
</tr>
<tr>
<td>- Costing (DRGs, e-Health, ...):</td>
</tr>
<tr>
<td>- Discount rate applied to costs and health outcomes.:</td>
</tr>
<tr>
<td>- Utility values considered:</td>
</tr>
<tr>
<td>- Sensitivity analysis:</td>
</tr>
<tr>
<td>- Conflict of Interest:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COSTS (1)</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Incremental costs (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment cost (3)</td>
<td>xx €</td>
<td>xx €</td>
<td>Incremental cost of treatment xx €</td>
</tr>
<tr>
<td>Patient cost (4)</td>
<td>xx €</td>
<td>xx €</td>
<td>Incremental cost by patient xx €</td>
</tr>
</tbody>
</table>
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.

**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 |


**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:

<table>
<thead>
<tr>
<th>Recommendations and checklists</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference</strong></td>
<td></td>
</tr>
</tbody>
</table>

**For further information**

**Other checklists of interest:**


**BMJ:**


**Check-lists for a model:**


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 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 further information:


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 España? Gac Sanit 2002;16:334-43

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 probabilidad 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:**


**International:**


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

<table>
<thead>
<tr>
<th>Incremental Cost Effectiveness Efficacy Ratio</th>
<th>Continuous variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference x</strong></td>
<td><strong>Endpoint</strong></td>
</tr>
<tr>
<td>Main population</td>
<td>Ef A units</td>
</tr>
</tbody>
</table>
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 €...

<table>
<thead>
<tr>
<th>Subgroup 1</th>
<th>Subgroup 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference y Main population</td>
<td></td>
</tr>
<tr>
<td>Subgroup 1</td>
<td></td>
</tr>
<tr>
<td>Subgroup 2</td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
<th>Maximum ICER</th>
<th>Minimum ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI95% of the result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment cost</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average (or median) number of cycles (Onco)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring costs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)

\[
\text{ICER} = \frac{(\text{Cost per patient of option A} - \text{Cost per patient of option B})}{(\text{Efficacy of A} - \text{Efficacy of B})}
\]

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:

\[
\text{ICER} = \text{NNT} \times (\text{cost per patient of option A} - \text{Cost per patient of option B})
\]

**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"

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 (e.g. 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:

<table>
<thead>
<tr>
<th>Estimated number of patients considered for treatment in the hospital every year, annual estimated cost and annual efficacy units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual number of patients</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>A</td>
</tr>
</tbody>
</table>

57
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 |
| A | | | |
| B | | | |

**BUDGET IMPACT OF THE SUBSTITUTION**

| Total DDD of drug B per year: N x | DDD Cost difference: d |
| Budget impact of a 100% substitution per year: N x d |
| Budget impact of a 5 |
| % substitution per year: (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.

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 increasing 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.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong></td>
<td>THE DRUG IS NOT INCLUDED IN THE GFT for lack of some basic requirements.</td>
</tr>
<tr>
<td>A-1.</td>
<td>NOT INCLUDED IN THE FORMULARY: it is not possible an adequate assessment of the application information.</td>
</tr>
<tr>
<td>A-2.</td>
<td>NOT INCLUDED IN THE FORMULARY: it is indicated in a condition that does not require hospitalization or served from Units Day</td>
</tr>
<tr>
<td><strong>B.</strong></td>
<td>NOT INCLUDED IN THE FORMULARY: insufficient evidence that there is a better relationship efficacy/safety compared with current treatment is performed in the hospital.</td>
</tr>
<tr>
<td>B-1.</td>
<td>NOT INCLUDED IN THE FORMULARY: the evidence indicates a worse profile efficacy/safety compared to current treatment performed in the hospital.</td>
</tr>
<tr>
<td><strong>C.</strong></td>
<td>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.</td>
</tr>
<tr>
<td>C-1.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>D.</strong></td>
<td>INCLUDED IN THE GFT with specific recommendations.</td>
</tr>
<tr>
<td>D-1.</td>
<td>INCLUDED IN THE GFT with specific recommendations and a commitment to reassessment of the same after the PTC period appropriate.</td>
</tr>
<tr>
<td><strong>E.</strong></td>
<td>INCLUDED IN THE GFT no specific recommendations.</td>
</tr>
</tbody>
</table>

### 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 Monitoring 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.

PARTICIPANTS in Phase 1

Brainstorming phase to identify new scenarios MADRE
March - April 2011

Mª Reyes Abad Sazatornil. H U Miguel Servet. Zaragoza
José Luis Alonso Romero. H U Virgen de la Arrixaca. Murcia
Vicente Arocas Casañ. H U Virgen de la Arrixaca. Murcia
Rocío Asensi Díez. H R U Carlos Haya. Málaga
Beatriz Calderón Herranz. Hospital Son Llàtzer. Palma de Mallorca
Cecilia Calvo Pita. Servei de Salut de les Illes Balears. Palma de Mallorca
Andrés Carrillo. H U Son Espases. Palma de Mallorca
Raúl Díez Fernández. H U de Getafe. Getafe
Mª Esther Durán García. H G U Gregorio Marañón. Madrid
María Dolores Fraga Fuentes. C H La Mancha Centro. Alcázar de San Juan
Mª Queralt Gorgas Torner. C. Sanitari Parc Taulí. Sabadell
Juan Carlos Juárez. H U Vall D'Hebron. Barcelona
Eduardo López Briz. H U P La Fe. Valencia
Ana Lozano Blázquez. Hospital de Cabueñes. Asturias
Mª Antonia Mangues. H Santa Creu i Sant Pau. Barcelona
Roberto Marín Gil. H U Virgen del Rocío. Sevilla
José Antonio Martín Conde. H La Candelaria. Tenerife
Icíar Martínez López. H U Son Espases. Palma de Mallorca
Noemí Martínez López de Castro. Hospital Meixoeiro. Vigo
Andrés Navarro Ruiz. Hospital General U de Elche. Alicante
Ana Ortega Eslava. Clínica Universidad de Navarra. Pamplona
Ramon Pla Poblador. H U Mutua de Terrassa
Maite Pozas del Río. Hospital Niño Jesús. Madrid
Francesc Puigventos Latorre. H U Son Espases. Palma de Mallorca
Teresa Requena Caturla. Servicio Madrileño de Salud
Bernardo Santos Ramos. H U Virgen del Rocío. Sevilla
Jaime Torelló Iserte. Centro Andaluz de Farmacovigilancia. HU Virgen Rocío. Sevilla
Pere Ventaloy Bosch. H U Son Espases. Palma de Mallorca
Montse Vilanova Boltó. Hospital Son Llàtzer. Palma de Mallorca

PARTICIPANTS in Phase 1

Expert panel
January-March 2012

Iñigo Aizpurúa. CEVIME. Osakidetza. Joint Committee member. Euskadi
Emilio Alegre. Hospital Pharmacy (Drug Evaluation). Andalusia
Eduardo Briones. EBM and HTA. Andalusia
Cecilia Calvo. Primary Care Pharmacy (Drug Evaluation). Madrid
María José Carreras. Hospital Pharmacy (Pharmacy Oncology). Catalunya
Ana Clopés. Hospital Pharmacy (Pharmacy Oncology). Catalunya
Ana Lozano. Hospital Pharmacy (Drug Evaluation). Asturias
Javier Mar. Economic evaluation of health technologies. Euskadi
Meneu Ricard. Evaluation of Health Services. Valencia
Alfonso Muriel. EBM and Biostatistics. Madrid
Juan Oliva. Health Economics. Castilla La Mancha
Mª José Otero. Hospital Pharmacy (Drug Safety). Castilla Leon
Galo Sanchez. EBM. Drug evaluation. Estremadura
Javier Soto. Pharmacoeconomics and Health Outcomes Research. Madrid
Jaime Torelló. Clinical Pharmacology (Pharmacovigilance). Andalusia
**Version nº 3.0 September 2005:**

Revised by the Working Group of the SEFH GENESIS:

- Joan Altimiras. Health Corporació Parc Taulí. Sabadell
- Ana Clopés. H Duran i Reynolds.ICO. Hospitalet. Barcelona
- Esther Duran. H General Universitario Gregorio Marañón. Madrid
- Maria Jose Martinez Bengoechea. H. Galdakano
- Juan Pablo Ordovás. H General Universitario de Alicante.
- Ana Ortega. University Clinic of Navarra. Pamplona
- Mª Ángeles Porta. Canalejo Hospital Complex. La Coruna
- Francesc Puigventós. H. Dureta University. Palma Mallorca.
- Teresa Requena. H. Universitario La Paz Madrid
- Bernardo Santos. H. Universitario Virgen del Rocio. Seville.
- Montse Vilanova. H. Llàtzer. Palma Mallorca

**Previous Versions 2003-2004:**

- Pharmacy Department Son Dureta Hospital: Francesc Puigventós Latorre, Pere Ventayol Bosch, Manel Pinteño Blanco, Francisco Campoamor Landín, Olga Delgado Sánchez, Joan Serra Devecchi.

- Pharmacy Department Virgen del Rocio Hospital: Bernardo Santos Ramos, Francisco Javier Bautista Paloma.