

MINISTRY OF HEALTH OF BRAZIL  
Secretariat of Science, Technology and Strategic Inputs  
Department of Science and Technology

**METHODOLOGICAL GUIDELINES: HEALTH  
TECHNOLOGY ASSESSMENT APPRAISALS**

Series A. Norms and Technical Manuals

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## **ACRONYMS**

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ANS: National Agency for Supplementary Health

ANVISA: National Agency for Health Surveillance

HTA: Health Technology Assessment

CG-HTA: General Coordination of Health Technology Assessment

DECIT: Department of Science and Technology

WG-HTA/CCTI/MS: Permanent Work Group on Health Technology Assessment of the Science, Technology and Innovation Council of the Ministry of Health of Brazil

MS: Ministry of Health of Brazil

PNGTS: National Policy on Health Technology Management

SCTIE: Secretariat of Science, Technology and Strategic Inputs



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## **PRESENTATION**

The high quality evidence usage in Health Technology Assessment (HTA) processes was one of the main recommendations of the “Workshop on Priorities of Research in Health – Thematic Issues”, held in March 2006. This workshop has identified that it was needed to elaborate methodological guidelines for HTA appraisals, systematic reviews and studies on economic analysis fostered by the Ministry of Health of Brazil in order to promote these HTA products’ quality.

The establishment of HTA as a fundamental element in the technologies’ management and technology incorporation processes started with the discussion of the National Policy for Science, Technology and Innovation in Health and, more recently, with the National Policy on Health Technology Management (PNGTS).

The main objective of PNGTS is to “maximize health benefits from the available resources, assuring population’s access to effective and safe technologies in equitable conditions”. Among PNGTS’ principles, “Technologies’ management must use scientific evidences and consider the following attributes: efficiency, effectiveness, safety and economic, ethical, social and environmental impacts of the technologies” (BRASIL, 2006b).

The PNGTS discusses the importance of the HTA in the decision-making processes regarding the health technologies public coverage: “Using scientific evidence to subsidize the management process: Health Technology Assessment.” In this context, it was needed to elaborate methodological guidelines for health technology assessment studies, considering the specificities of each technology and its development stage.

The implementation of the technology management process in the Brazilian Health System started with the PNGTS. In this sense, it must significantly guide actions regarding Health Technology Assessment in the country and contribute to the way in which the demands increase for the Ministry of Health of Brazil, through technical reports based on high quality scientific evidences.

In order to attend this demand, the Methodological Guidelines Elaboration Project for Technical and Scientific Reports Elaboration

was agreed in the ambit of the Permanent Working Group on Health Technology Assessment of the Science, Technology and Innovation Council of the Ministry of Health of Brazil (WG-HTA/CCTI/MS). After that, a group of experts was formed due to the necessity of working in Health Technology Assessment and Evidence Based Medicine for the preparation of this document.

Having presented the proposal in the ambit of WG-HTA/CCTI/MS, some meetings with the Group of experts took place as a second stage of the project:

- 1st Meeting for the Elaboration of Methodological Guidelines for HTA Appraisals, in 27/04/06: basic objectives and principles were defined for the methodological guidelines, terms and experts to be invited to the Consensus Workshop, as well as elaborators and reviewers for the proposal document.

- Consensus Workshop for the Elaboration of Methodological Guidelines for HTA Appraisals, on 25/07/2006: the proposal document was analyzed by invited experts and the suggestions and critics were incorporated after the consensus.

Before the Guidelines' publication, in September 2007, there was an opportunity to test the application of the instruction contained in the guidelines. After this occasion, the first edition of the document was published in October 2007.

Fortunately, after their publication, the Guidelines started to be used in several contexts throughout Brazil, at federal, state and municipal levels of the Brazilian Unified Health System and Supplementary Health. The federal level experience, in the ambit of the Ministry of Health of Brazil, allowed the establishment of a flux production for HTA appraisals that includes: the elaboration by technical consultants, the search methodological revision and critical analysis of selected studies and the revision of specialists and health decision makers. The flowchart and revision criteria in all production stages of an HTA Appraisal by the Science and Technology Department are presented in Annex A.

In this context, with DECIT's know-how to use the Guidelines and on training workshops up to 2008, more than 100 people from technical departments of the Ministry of Health, State and Municipal Health Secretariats, hospitals, universities and medical insurance companies have evaluated the document regarding its usefulness,

validity and applicability. The opinions and suggestions proposed were used to update this document.

As a final stage for this new edition, researchers and stakeholders in health technology assessment, management, coverage, and evidence based medicine, and health economics were involved. Several structural and methodological aspects were discussed and updated for the construction of a new version, more didactic and complete.

In this way, we present the Methodological Guidelines for the Elaboration of HTA Appraisals, which importance is mainly delimited by the lack of similar previous publications in Brazil and also in the Ministry of Health of Brazil. The objective is to contribute to the reports' standardization elaborated by researchers as well as by the Ministry's technicians. In addition, it will help to qualify them and to establish criteria for quality assessment.

We hope that the Guidelines could be helpful for the several efforts that were undertaken for the structuring and the dissemination of Health Technology Assessment in Brazil.

**Ministry of Health of Brazil**



## 1 INTRODUCTION

As part of the advances in several knowledge fields, the medicine achieved satisfactory results during the past century, which include, among others, the reduction of mortality and morbidity taxes in infectious, prenatal, and cardiovascular diseases, the increasing of life expectancy, the rise of organ and tissue transplantations, the therapy with stem cells, and even the cure of some types of cancer.

At the same time, problems with the usage of technologies have been observed for a long time, through studies which did not find scientific evidences for widely used procedures as well as through those which found a substantial range in the use of technologies without improvements in the health outcomes (OFFICE TECHNOLOGY ASSESSMENT, 1994; GARBER, 2001). In other cases, it's already been demonstrated that technologies recognized as non effective, or with deleterious effects, continue to be widely used, while several efficient technologies present low utilization. Another very frequent matter is the use of technologies out of the conditions and indications in which they are more efficient.

The growth in technological innovation and utilization has also been intimately related to the increase in expenditure on health. In a scenario of increased expenditure, with restriction of health resources, and of services restructuring, aiming a greater efficiency and better utilization of public budget, decision-makers are being pressured. They need coherent and well-founded information regarding the benefits of health technologies and their impact on health services to be able to make rational decisions (PANERAI; MOHR, 1989). Within this context, the importance and interest in health technology assessment has grown.

Health Technology Assessment (HTA) is known as a great process, through which clinical, social and economic impacts of health technologies are assessed, considering aspects such as efficiency, effectiveness, safety, cost-effectiveness, among others (GOODMAN, 1998; HUNINK; GLASZIOU, 2001). HTA's main objective is to support health policy and decision makers in coherent

and rational decision-making for technologic incorporation in health systems (PANERAI; MOHR, 1989; HUNINK; GLASZIOU, 2001; CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT, 2006) Health technologies are drugs, equipment and technical procedures, organizational, informational, educational, and support systems, and support programs and guidelines through which health attention and care are provided to the population (BRASIL, 2005c).

The HTA Appraisal is a support tool to management and decision-making, based on the same rationality of HTA, however with more simplified execution and content. Although they involve a less broad and extensive literature revision than a systematic review, and have quicker elaboration, the HTA Appraisal must present a systematized and comprehensive report of knowledge able to be provided in this context, contributing on qualifying the decisions to be made (CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT, 2003; NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE, 2004a; DANISH CENTRE FOR EVALUATION AND HEALTH TECHNOLOGY ASSESSMENT, 2005; CAMERON et al, 2007).

The Methodological Guidelines for HTA Appraisal have as their priority audience the technicians of the Ministry of Health and other management levels of the Brazilian Unified Health System and Supplementary Health who support the processes and decisions related to health technology assessment and public coverage. Whoever elaborates them must meet minimum pre-requisites such as: English reading, Internet skills, epidemiology and evidence based medicine knowledge, direct work with management and incorporation of technology, judicialization of health decisions, pharmaceutical assistance, rational use of drugs, diseases surveillance, primary and specialized health care and correlated issues. In addition, it is recommended that HTA Appraisal authors and reviewers declare their potential conflicts of interests, according to the form suggested in Annex B.

The objective of this document is to contribute to the standardization, qualification and assessment of HTA reports, based on scientific evidences, by external consultants as well as by technicians the Ministry and other management levels of the Brazilian Unified Health System and Supplementary Health.

## **2 METHODOLOGY TO BE APPLIED TO THE ELABORATION OF HTA APPRAISALS**

### **2.1 In which cases will an HTA Appraisal be elaborated?**

As previously mentioned, the HTA Appraisal is the first stage in the process of analysis of demands for the recognized non effective public coverage of new technologies - or new indication for technologies which already exist - in the health system. Actually, it is justified in those cases in which there are pressures for rapid decision-making by the Ministry of Health of Brazil regarding the incorporation of a given technology.

In this situation, the HTA Appraisal presents the results of an initial analysis aiming to attend rapidly to the primary questions regarding the technology: its efficacy, the population who will benefit from its use and possible consequences of its incorporation on health system. This preliminary evaluation may indicate that the available evidences are sufficient to support decision-making. Alternatively, the analysis may indicate that the evidences obtained are insufficient or inadequate, demanding more knowledge for better analysis of effects and clinical, economical and social impacts of the technology. In this case, the HTA Appraisal may suggest the elaboration of, among others, a Systematic Review or an Economic Analysis, studies which require more time for elaboration.

However, the use of the HTA Appraisal is not only limited to new technologies (understood as those not yet incorporated into the health system, even though they are already available for use in the country). It may and must be used for the analysis of health technology in any stage of its life cycle. Thus, the HTA Appraisal may also be a useful element for assessment of established technology, to which adaptations or new uses are proposed, as well as to those in potential obsolescence stage, through the incorporation of another more safe, effective and cost-effective one.

The HTA Appraisal must be a brief document, having to be written in approximately 20 pages (or 20,000 characters), excluding annexes, considering some important points: the question to be answered by the report; the description of epidemiological aspects of the health condition which the technology will be intended for; the description of the

technology, alternative technology and impact of the incorporation in the health system; results found and recommendations by the authors.

If necessary, details regarding report methods - including a full and detailed description of the search for scientific evidence, the inclusion and exclusion criteria of studies, classification criteria of studies according to the level of evidence quality and possible bias - may be presented in the annex.

The authors must remember that the HTA Appraisal will be intended for decision makers. Therefore, it must consider the language used, it is essential that the health decision makers can be able to understand and to access and use the results in their daily practice. The terminology used must be comprehensible to a non-specialized public. Acronyms must be avoided, except when they are broadly known (for example, AIDS, HIV). When there is no way to avoid acronyms, they must be provided unabbreviated in their first use. Names of drugs and interventions which may be internationally known must be used whenever possible.

The document must contain all elements which allow the reader to access the validity of the analysis, including information which allows: to understand the used methodology, to verify sources of evidence, to verify relevance of information, and to put the recommendations in the context in terms of implications on clinical practice, services and research. Further topics of research should be pointed, due to the results obtained in the analysis which may possibly serve for the establishment of priorities to be investigated.

An executive summary must be located at the beginning of the document, no longer than one page (1,000 characters) and written in a way that is accessible to a non-specialized reader. Thus, they are elements which must be present in this summary, always as concise as possible: intensity of recommendations, context (the purpose that motivated the elaboration of the report), question to be answered (including the analyzed technology and alternatives, the health condition to which it is indicated, and the outcome of interest), search and assessment of evidence quality, main results of the selected studies and recommendations. An example of an executive summary and topics which must be contained in a HTA Appraisal are presented at end of this document, in Chapter "HTA Appraisal General Structure".

## 2.2 Which steps are fundamental for the elaboration of a HTA Appraisal?

The steps which should be complied within the elaboration of HTA appraisals, according to the recommendations of the Ministry of Health of Brazil, are described below. The whole methodology approached in the following topics is based on internationally published methodological guidelines (CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT, 2003; NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE, 2004a, 2004b; DANISH CENTRE FOR EVALUATION AND HEALTH TECHNOLOGY ASSESSMENT, 2005; CAMERON et al.,2007).

### 2.2.1 How should the question of a HTA Appraisal be formulated?

The clarity and precision of the question elaboration is the main step for the construction of a HTA Appraisal. The following issues must be detailed: health condition which it applies to (population of interest), technology to be assessed, alternative technologies on comparison, and outcomes of interest (mortality, morbidity, adverse effects, incidence of complications, quality of life, etc). Question examples for each type of intervention are provided in Box 1.

**Box 1. Question example of an HTA Appraisal, according to intervention type**

|                  | Population  | Intervention  | Comparison  | Outcome  |
|------------------|---|---|---|--|
| <b>Treatment</b> | For patients with acute myocardial infarction with supra ST-segment...                        | ...use of Thrombolytic...                             | ...compared to angioplasty with stent...                              | does it decrease mortality?<br>does it decrease re-infarction?<br>does it improve quality of life?   |
| <b>Diagnosis</b> | For women between 25 to 60 years of age, with altered oncotoc cytology, CIN 1* or ASC-US**... | ...the Test for HPV*** detection by hybrid capture... | ...compared to the gold-standard (Colpocytology with Papanicolaou)... | is it accurate? (performance)  |
|                  |   | ...the Test for HPV detection by hybrid capture...    | ...compared to the gold-standard (Colpocytology with Papanicolaou)... | does it decrease mortality rate by cervical cancer?<br>does it decrease cervical cancer rate?<br>does it change therapeutic conduct? (utility) |

## 2.2.2 What should be contained in the Introduction?

### a) Epidemiological, demographic and social aspects

In this topic, the scenario of the country regarding health condition to which the technology is indicated (considering the indication contained in the question that the HTA Appraisal must respond), including prevalence, incidence, mortality and severity of health condition and burden of disease (if there is information about this parameter) must be described. Population characteristics which may be important in the assessment, such as different prevalence for gender, ethnicity, age, health condition severity, co-morbidity as well as factors which may be related to health inequality must also be mentioned.

In order to obtain this information, authors must consult some existing databases, such as the websites available in Annex C. Additionally; the authors may use other sources of information, as estimates, inquiries and other studies. It must be highlighted if the information used has a state, regional or international context. All sources of information must be referred.

### b) Description of the technology to be assessed

The technology to be assessed must be described, clarifying first whether it has or has not been registered in the Brazilian regulatory agency (National Agency for Health Surveillance – Anvisa) or in regulatory agencies of other countries, and in which conditions it may be used according to such registrations.

If the question to be answered by the HTA Appraisal is regarding a new indication of the technology, to which it is not registered, this must be clearly specified. In order to know if a given technology has or has not been registered in Anvisa, the author needs to visit the website of the mentioned agency (BRASIL, 2006a), according to instructions contained in Box 2.

## Box 2. Instruction for consultation of drugs and health products registered by the National Agency for Health Surveillance



The following information must be mentioned: the type of technology under assessment (diagnostic, preventive, therapeutic, in terms of its function in the process of care; drugs, vaccines, equipments, clinical or surgical procedures, regarding the type of technology), its basic characteristics, previous uses, different indications, contraindications and risks already known and described in the literature regarding this subject.

In case of a drug, when necessary, pharmacokinetic and pharmacodynamic aspects of its structure and application, presentation form, posology and other aspects common to such substances must be approached. This information may be available on the website of ANVISA (BRASIL, 2006a), in the space intended for the instructions of registered drugs and, when not available on this source, MICROMEDEX (MICROMEDEX..., 2008) must be used for pharmacological information (restricted access).

In case of equipments and devices, technical characteristics and the infrastructure needed for its adequate use must be mentioned. On ANVISA's website, when regarding equipments, there are documents related to the instructions similar to drugs label. The directions for consultation to these documents are provided in Box 3. In case of clinical and surgical procedures, the description of the requirements regarding training, skills and abilities of the professionals for the performance of the procedure is also important.

**Box 3. Consulting instructions' usage of the National Agency for Health Surveillance registered equipments.**

It must also be mentioned the space for practice where the technology is being or will be used, as well as the professional training needs for its use, and the existence of other conditions that are related to the use of technology and that what should be considered (other associated technologies requirements – diagnostic or therapeutic–, special ambiance necessity, etc).

The price by each unit of an analyzed technology and of the alternatives under comparison must be mentioned. For the technologies in use by the health system, this value must be estimated by the average price of the previous years, through the values available in the Health Price Base (Annex D). If these prices are not available, the proposed price for the use of a technology must be presented. In the case of drugs, the proposed price must be presented by the Drug Market Regulation Chamber – CMED (Annex D), more specifically the Factory Price 18%.

When the unit price is not sufficient for the first comparison for the health system expenses, the usage cost of a technology must be estimated. For this, it is necessary to inform the potential demand, the standard usage, and when necessary, the additional expense with technologies and supplementary procedures, investment in infrastructure and principal costs. All calculations made should be consolidated in a table. When these values are not available, the possible sources of expenditures must be mentioned and described as presented above. For more detailed analysis of costs, a full economic analysis must be recommended.

### c) Alternative technologies' Description

Existing alternative technologies must be described as well as those considered comparative gold-standard for the health conditions in vogue and those already well accepted by the scientific community of clinical practice. In case in which the assessed technologies are new or are still not available in the health system, the comparison must be the technology (ies) available in the Brazilian Unified Health System or Supplementary Health, if necessary, for the same indication. Alternative technologies must be described considering the same criteria presented for the technology under assessment.

The indications, the unit prices, the technology characteristics, and discrepancy points between them must be compared, in addition to identify adequate comparison outcomes.

### **2.2.3 How should we do the research and the quality critical analysis of scientific evidences for the HTA Appraisal elaboration?**

The methods used in HTA Appraisal elaboration must be described clearly and detailed. Although the literature research and the evidence quality assessment scope are typically more limited in an HTA Appraisal than in a systematic review, they must still be systematized, in order to ensure an overview of the best available evidence and prioritizing evidences according to the studies' methodological quality.

#### a) Search for evidence

The second step for the preparation of a HTA Appraisal consists of describing the strategy of searching evidences, considering the electronic bases used, the description of the algorithm used, including describers, key-words and the use of MeSH (Medical Subject Heading) terms in the electronic search.

Authors must consider some reference bases in the search for qualified scientific evidence as contained in the search strategy presented in Annex E. At each stage of evidence search process, how many studies were obtained and how many were selected must be provided, according to the proposed search strategy table presented in Annex F.

## b) Articles' selection and exclusion criteria

Criteria for selection of studies must be clearly mentioned in the HTA Appraisal, from the search described in the previous item. Some selection criteria which may be used are:

- Study design: randomized clinical trials, or non-randomized ones, systematic reviews, cohort studies, case-control studies, etc. It is important to highlight that in a HTA Appraisal it must be prioritized studies of greater methodological quality available for the subject to be analyzed;

- Population or subgroups of interest: health problem, problem severity, age, gender and ethnicity;

- Intervention or assessed technology;

- Outcomes (health results): mortality, morbidity, incidence of complications, quality of life, etc.

Similarly to the selection criteria, the exclusion criteria for the studies must be described with the number of selected and excluded studies at each search stage. Besides that, it must be mentioned in this topic (Annex F) the motives explaining the sorting reasons.

## c) Evidence quality methodological analysis

By the characteristics of the document itself and by the previously mentioned indications, the methodological rigidity for the elaboration of an HTA Appraisal may be less than that required for a systematic review. Therefore, the report may include interest topic analysis for the decision makers, even if those topics present sub-optimum evidences, particularly, in the technology's initial life cycle stage.

It is generally accepted that a hierarchy of evidence is used in studies' quality assessment, when higher values are defined to systematic reviews of high quality randomized clinical trials (RCT) and randomized clinical trials adequately designed, while lower levels contemplate non-randomized studies, cohort, case-control and case series studies. This document provides two suggestions in order to analyze the evidences found: the Classification of Evidence Level of the Oxford Centre for Evidence Based Medicine and the Classification of Grading of Recommendations Assessment, Development and Evaluation – GRADE (Annex G). However, the author may use other sources, if he wishes to, but he has to mention them.

Although there is strong preference for decision-making based on systematic reviews or RCT, it is important to realize that several technologies or interventions (such as surgical procedures or health programs) are rarely investigated by this type of study, common for drugs. Thus, other types of studies must be considered if they are the only option and the higher quality available for the intervention analyzed.

In addition, the level of evidence is not the only factor that must be considered when assessing the selected studies. A low quality randomized clinical trial may provide less information than other non-randomized, even if it is well designed. In this context, it is important that this analysis of evidence involves the most important determinant parameters of quality and is always performed and mentioned.

It is necessary, therefore, to describe the method used for assessment of the evidence found, including quality parameters for each type of selected study in the HTA Appraisal, as well as the source selected, considering that the parameters may vary according to the considered authors (GUYATT et al., 2008a, 2008b, 2008c; GUYATT; RENNIE, 2006; SACKETT et al., 2003; OXMAN; COOK; GUYATT, 1994). A standard model suggested regarding how to assess quality of evidence selected in a HTA Appraisal is presented in Annex H, which contains tables with assessment parameters for clinical trials for therapeutic and diagnostic interventions and systematic reviews.

#### **2.2.4 How should the Results be presented?**

##### **a) Selected studies' results**

The results of the studies considered in the analysis must be presented in a data table format, which must contain the study's identification, country where it was performed, number of participants, study type, performed intervention and comparison alternatives, description of outcomes and obtained results. The results data table must contain a space delimited between the selected studies, for the description of biases and limitations. A data table example containing these information is presented in Annex I.

It is also recommendable to critically discuss the limitations of literature found and, when applicable, to justify the studies' usage of a lower methodological quality.

##### **b) Interpretation of results**

After the presentation of the selected studies and their results, the interpretation of these results must be performed, always considering the question which guides the HTA Appraisal and its importance to decision-making about the technology. The results' statistical and clinical significance must be considered, making observations concerning the statistical and association measures (relative risk, odds ratio, number needed to treat, number needed to harm). Also the size of the effect and the confidence interval of analyzed measures must be taken into account.

Furthermore, as the majority of clinical trials are performed outside of Brazil, the real benefit to Brazilian reality must be discussed. In this context, population and epidemiology differences, the necessary conditions and the viability of technology implantation in the Brazilian context, such as human resources training, infrastructure and maintenance capacity, among others, must be considered.

In this topic, the authors must comment and discuss the technological implantation conditions, as well as the negative factors for use in the Brazilian reality or contributing factors for different results and performance of those findings in international evaluations.

### **2.2.5 Recommendations**

The HTA Appraisal authors will be able to, if required, elaborate considerations regarding the technology coverage and usage in the Brazilian reality and its foreseen impact in health services, relations with the specific care policies for the health condition in question, other factors which contribute to the identification of inequalities in health and the promotion of equity in the access of technology.

Furthermore, it will be essential that the author compares their recommendations with those formulated by the international Health Technologies Assessment agencies. The websites where these types of study are available may be found in Annex E.

The report must be concluded concerning the implications of its results to clinical practice, health services and research. Concerning this last topic, it is worth highlighting the importance of suggesting subjects for studies that can come to complete knowledge gaps.

In this context, when conclusions of the report show the existence of many available evidences or, on the contrary, when there is no sufficient evidence for decision-making, the elaboration of other

studies, such as a systematic review or a clinical trial, must be recommended, respectively. If it is necessary, the elaboration of a full economic analysis may be another indicator that can be presented with the recommendations made by the authors.

### **2.2.6 References**

At the end of the appraisal, all studies, bases and sources of data used must be provided. References used in the elaboration of the appraisal must be presented based on the instructions and rules of ABNT (Brazilian Association of Technical Rules) or other traditional existing rules.



### **3 FINAL CONSIDERATIONS**

To readers who would like to obtain full HTA Appraisals, prepared by the Ministry of Health's technicians and based on these guidelines, we recommend accessing the website of the Brazilian Health Technology Assessment Network ([www.saude.gov.br/rebrats](http://www.saude.gov.br/rebrats)).

To give your opinion on this document, in Annex J there is a form for the assessment of clarity, concepts and methods of the "Methodological Guidelines for the Elaboration of HTA Appraisals". All users (decision makers, health professionals, consultants and technicians of the Ministry of Health of Brazil, their agencies and other management levels of Brazilian Unified Health System and Supplementary Health) are invited to complete the form and send it via e-mail to [ats.decit@saude.gov.br](mailto:ats.decit@saude.gov.br), aiming the reassessment of the document periodically and the guarantee of its quality.

The Working Group for Elaboration and Updating of Methodological Guidelines for HTA Appraisals appreciate the participation of all and we hope that these guidelines are useful for professional practice.



## 4 HTA APPRAISAL GENERAL STRUCTURE

The tables below bring a summary of the suggested format to the elaboration and composing of HTA Appraisals and its executive summary:

| <b>HTA Appraisals</b>  |
|--|
| Cover (theme of the HTA Appraisal, authors and reviewers with title and institution)   |
| Executive summary  |
| Context  |
| Question   |
| Introduction (epidemiological information, technology description, its indication, risks, prices and alternative technologies descriptions): <ul style="list-style-type: none"> <li>• Epidemiologic, demographic and social aspects</li> <li>• Description of the evaluated technology and alternatives</li> </ul> |
| Database and search strategy   |
| Articles' selection and exclusion criteria   |
| Selection and exclusion criteria   |
| Methodological quality analysis  |
| Results of the selected studies (main findings, study result table, biases and limitations): <ul style="list-style-type: none"> <li>• Presentation of study results</li> <li>• Results interpretation</li> </ul>   |
| Recommendations (implications to clinic practice, to services and research)  |
| Bibliographic references   |
| <b>Annex containing the Method's details</b>   |

## HTA Appraisal Executive Summary

Intensity of recommendations:

Technology:

Indication:

Technology's Characteristic:

Question:

Search and analysis of scientific evidence:

Summary of the selected study results:

Recommendations:

- Intervention highly recommended – conclusive evidence regarding benefits
- Intervention recommended with reservations – evidences suggest benefit, but more studies are necessary
- Non-recommended intervention – evidences are conclusive regarding the absence of benefit or harm of the intervention
- Non-recommended intervention – evidences suggest absence of benefit or harm of the intervention, but more studies are necessary
- Non-recommended intervention – non available studies

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## GLOSSARY

**Health Technology Assessment (HTA):** comprehensive process, through which clinical, social and economic impacts of health technology are assessed considering aspects such as efficiency, effectiveness, safety and cost-effectiveness, among others (GOODMAN, 1998; HUNINK; GLASZIOU, 2001). Its main objective is to support health stakeholders on coherent and rational decision-making regarding the utilization and coverage of health technologies (PANERAL; MOHR, 1989).

**Economic analysis:** comparative analysis of different health technologies, regarding their costs and effects on health condition (BRASIL, 2005d).

**Health cost:** value of resources employed in the use of a therapeutic alternative, of a health program or service, during a period of time (BRASIL, 2005d).

**Aggregated cost:** amount paid for the technology, regarding the demand usage (considers the entire population which will actually benefit from the use of the technology) (BRASIL, 2005d).

**Cost-benefit:** type of economic analysis which values costs and consequences (results) in monetary terms (BRASIL, 2005d).

**Cost-effectiveness:** type of economic analysis in which the consequences (results) of the health technologies are measured in natural health units, such as years of life gained or clinical events avoided; this term is also used many times to refer to all types of economic analysis (BRASIL, 2005d).

**Unitary cost:** amount paid per unit of the technology (BRASIL, 2005d).

**Cost-utility:** type of economic analysis in which consequences (results) of the health technologies are measured as preferences related to health, frequently expressed as Quality Adjusted-Life Years - QALY (BRASIL, 2005d).

**Effectiveness:** probability that the individuals from a certain population obtain benefit from the use of a health technology directed at a determined problem in real use conditions (OFFICE OF TECHNOLOGY ASSESSMENT, 1978).

**Efficacious:** probability that the individuals from a certain population obtain benefit from the use of a health technology directed at a determined problem in controlled use conditions (OFFICE OF TECHNOLOGY ASSESSMENT, 1978).

**Randomized controlled clinical trial:** clinical trials in which patients are random selected (HULLEY et al., 2006).

**Non-randomized controlled clinical trial:** clinical trials without random selection of patients (HULLEY et al., 2006).

**Equity:** absence of unfair, avoidable or remediable differences in public health or groups defined with social, economical, demographic or geographic criteria (ORGANIZAÇÃO MUNDIAL DE SAÚDE, 2005).

**Standard Error:** a statistic standard deviation (CALLEGARI-JACQUES, 2003).

**Cohort study (follow-up study):** longitudinal study where the researcher, after distributing the individuals as exposed and non exposed to a given factor of study, follows them up during a certain period of time in order to check the incidence of a disease or clinical condition between the exposed and non exposed individuals (HULLEY et al., 2006).

**Confidence interval:** margin error, regarding a statistic (CALLEGARI-JACQUES, 2003).

**Meta-analysis:** techniques which apply protocols and use statistical methods to critically review and interpret the combined results from relevant primary investigations which were performed, in order to obtain quantitative syntheses on the effects of the health technologies which will guide the decisions (KHAN et al., 2005).

**Morbidity:** ratio of patients with a specific disease during a given year per a given population unit (FLETCHER, R.; FLETCHER, S.; WAGNER, 1982).

**Mortality:** all deaths observed in a population (FLETCHER, R.; FLETCHER, S.; WAGNER, 1982).

**HTA Appraisal:** a support tool to management and decision-making based on the same rationality which involves an HTA, however, with a more simplified execution and content.

**Quality of life:** combination of physical, mental and social well being of the individual, and not only the absence of a disease.

**Systematic Review:** review of a theme from a clearly formulated question which uses systematic and explicit methods to critically identify, select and assess relevant studies, and collect and analyze data of studies included in the review (COCHRANE COLLABORATION CENTER, 2001).

**Health technology:** drugs, equipment and technical procedures, organizational, informational, educational and support systems, and support programs and protocols through which health attention and care are provided to the population (BRASIL, 2005a).

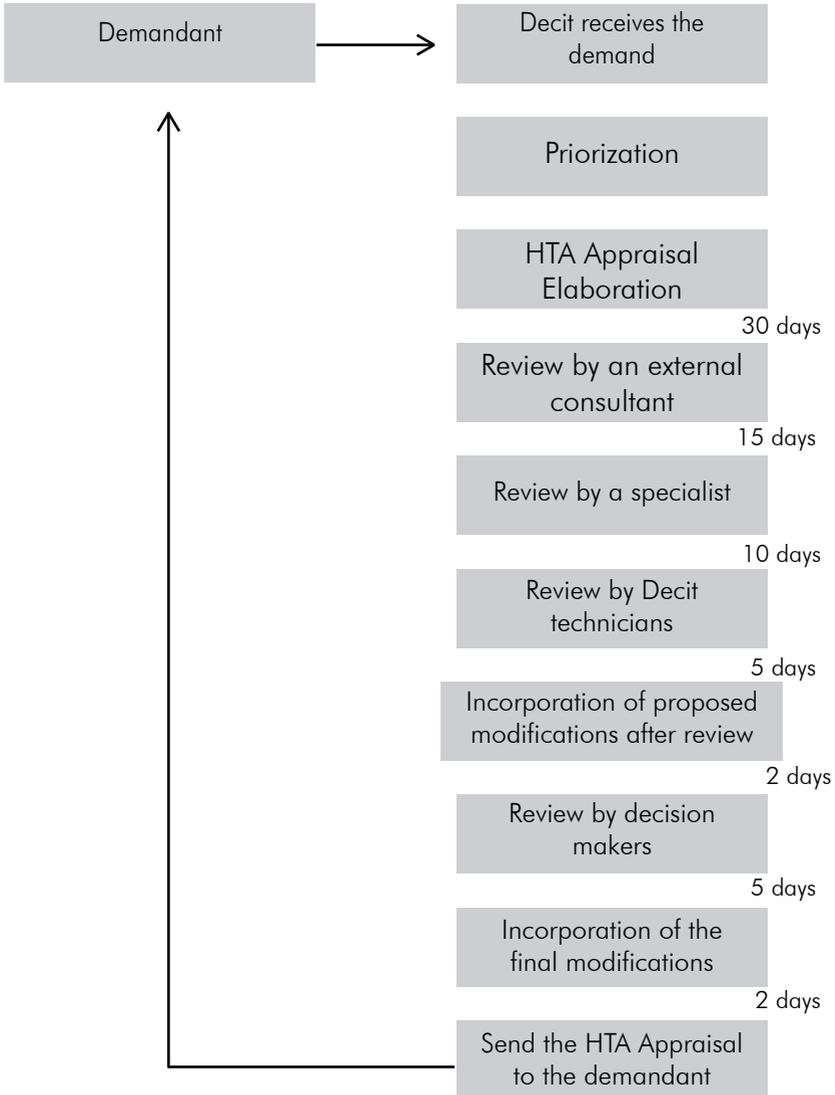
**Biases:** any process, in any inference stage, which tends to produce results and conclusions, which systematically differ from the truth. Its effect is to distort the estimative of a variable, for example, increasing the mean of a variable or decreasing the prevalence of a characteristic (FLETCHER, R.; FLETCHER, S.; WAGNER, 1982).



# ANNEX

## Annex A

Workflow of HTA Appraisal elaboration and criteria of review adopted by Decit/SCTIE/MS



### **HTA Appraisals' review criteria**

- External consultants' and DECIT technicians' Review
  - To verify the internal coherence of the text;
  - To re-do the search, paying attention to the adequacy of keywords and descriptors;
  - To verify if the selected articles, according to selection and exclusion criteria, and if the quality evaluation are adequate;
  - In case of non-adequacy of the keywords, to propose a new search and indicates which articles should be selected, justifying each step;
  - To verify the applicability and adequacy of the author's recommendation.

### **The specialist's review**

- To analyze the content, concerning the clinical component of the health condition;
  - To verify epidemiological information about health condition, technology indications and alternatives of appropriate outcomes;
  - To verify if the main studies about the theme are included;
  - To verify the applicability and adequacy of the author's recommendation.

### **Management review**

- To check the agreement among reviewers;
  - To analyze the clarity of result measures;
  - To check information about prices;
  - To check information about conflicts of interest;
  - To verify the clarity and coherence between results and recommendations.

## Annex B

### Declaration of Potential Conflicts of Interest

1 – In the last five years did you accept what follows from any institution or organization that could somehow benefits or be financially injured by the results of your activity?

- a) Reimbursement for attendance in a symposium? Yes ( ) No ( )
- b) Honorarium to presentation, conference or lecture? Yes ( ) No ( )
- c) Honorarium to organize teaching activity? Yes ( ) No ( )
- d) Financial to the realization of research? Yes ( ) No ( )
- e) Resources of financial support to a team member? Yes ( ) No ( )
- f) Honorarium to consultancy? Yes ( ) No ( )

2 – During the last five years did you work to any institution or organization that could somehow benefit or be financially injured by the results of your activity? Yes ( ) No ( )

3 – Do you have policies or shares of any institution that could somehow be benefited or be financially injured by the results of your activity?

Yes ( ) No ( )

4 – Did you act as assessor about any subject of your activity?

Yes ( ) No ( )

5 – Do you have another financial conflicting interest with your activity? Yes ( ) No ( )

If necessary, please, specify:

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6 – Do you have an intimate relationship or a strong antipathy for someone which interests could be affected by the results of your activity? Yes ( ) No ( )

7 – Do you have an academic connection or rivalry with someone which interests could be affected by the results of your activity? Yes ( ) No ( )

8 – Do you have a deep personal or religious conviction that could compromise what you will be writing and that should be of knowledge of the decision makers in the applicability of the results of your activity? Yes ( ) No ( )

9 – Do you participate on a politic party, non-governmental organization or any other group of interest that could influence the results of your activity? Yes ( ) No ( )

In case you have answered “yes” to any of the previous questions, please declare here the conflicting interest:

\_\_\_\_\_

\_\_\_\_\_

Name: \_\_\_\_\_

Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

\_\_\_\_\_

Signature

## Annex C

### Links of epidemiologic databases

Sistema de Informação Ambulatorial e Sistema de Informação Hospitalar (Ambulatory Information System and Hospital Information System):

<http://w3.datasus.gov.br/siasih/siasih.php>

Caderno de Informações de Saúde (Health Information Journal):

[http://tabnet.datasus.gov.br/tabdata/cadernos/BR/Brasil\\_GeralBR.xls](http://tabnet.datasus.gov.br/tabdata/cadernos/BR/Brasil_GeralBR.xls)

Inter-Agency Health Information Network (RIPSA):

<http://portal.saude.gov.br/portal/saude/ripsa/default.cfm>

Basic Data and Indicators:

<http://tabnet.datasus.gov.br/cgi/idb2004/matriz.htm?saude=http%3A%2F%2Ftabnet.datasus.gov.br%2Fcgi%2Fidb2004%2Fmatriz.htm&obj=%24VObj&botaoook=OK>

Health Information – Epidemiologic and Morbidity:

<http://w3.datasus.gov.br/datasus/datasus.php?area=359A1B624C4D0E0F359G9H011Jd4L24M0N&VInclude=../site/infsaude.php>

Information on Mortality and Born Alive:

[http://w3.datasus.gov.br/site/visualiza\\_texto.php?noticia=4770](http://w3.datasus.gov.br/site/visualiza_texto.php?noticia=4770)

World Health Organization:

<http://www.who.int/research/en/>



## **Annex D**

### **Links to Health Price Search**

Drugs:

Chamber of Drug Market Regulation (CMED/ANVISA):  
[http://www.Anvisa.gov.br/monitora/cmed/legis/comunicados/06\\_04\\_anexo1.pdf](http://www.Anvisa.gov.br/monitora/cmed/legis/comunicados/06_04_anexo1.pdf)

Price Bank in Health - BPS of the Ministry of Health of Brazil:  
[www.saude.gov.br/banco](http://www.saude.gov.br/banco)

Procedures:

Brazilian Hierarchy Classification of Medical Procedures, of the Brazilian Medical Association:  
[www.amb.org.br](http://www.amb.org.br)



## Annex E

### Strategy of Scientific Evidences Search

#### Strategy:

After the formulation of the question (**Table 1**), the terms adopted to the question formulation should be used to search the official vocabulary of the search tools and its synonyms (non-official vocabulary) - **MeSH, DeCS, Emtree**.

- **MeSH:** <http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh>
- **DeCS:** <http://decs.bvs.br/>
- **EMTREE:** <http://www.embase.com/>

1. Search for Systematic Reviews and Reports with evaluated quality.

#### a) **Cochrane Library**

<http://cochrane.bvsalud.org/portal/php/index.php>

- Systematic reviews of Cochrane (complete)
- Systematic reviews non Cochrane with evaluated abstracts

#### b) **Pubmed**

– Select the Systematic Reviews data base

#### c) **Others sources**

|                              |   |  |      |
|------------------------------|---|--|------|
| CRD                          | Centre for Reviews and Dissemination – University of York               | <a href="http://www.york.ac.uk/inst/crd">www.york.ac.uk/inst/crd</a>   | FREE |
| Bandolier                    | Oxford University   | <a href="http://www.jr2.ox.ac.uk">www.jr2.ox.ac.uk</a>   | FREE |
| HTAi                         | Health Technology Assessment International                              | <a href="http://www.htai.org/">www.htai.org/</a>   |      |
| INAHTA                       | International Network of Agencies for Health Technology Assessment      | <a href="http://www.inahta.org/">www.inahta.org/</a>   |      |
| Ministry of Health of Brazil | Systematic reviews promoted by the Department of Science and Technology | <a href="http://portal.saude.gov.br/portal/saude/visualizar_texto.cfm?idtxt=25514">portal.saude.gov.br/portal/saude/visualizar_texto.cfm?idtxt=25514</a> | FREE |

2. Search by other studies with available evidences in bibliographic database.

|                    |  |                  |
|--------------------|--|------------------|
| COCHRANE LIBRARY   | <a href="http://cochrane.bvsalud.org/portal/php/index.php">cochrane.bvsalud.org/portal/php/index.php</a><br><a href="http://www.thecochranelibrary.com">www.thecochranelibrary.com</a> | FREE<br>RESTRICT |
| PubMed             | <a href="http://www.pubmed.gov">www.pubmed.gov</a>   | FREE             |
| LILACS             | <a href="http://www.bireme.br">www.bireme.br</a>   | FREE             |
| EMBASE             | <a href="http://www.embase.com">www.embase.com</a>   | RESTRICT         |
| Specialized bases: |  |                  |

Elaborated by Cochrane Center of Brazil team.

|                |  |            |
|----------------|--|------------|
| CINAHL         | <a href="http://www.cinahl.com">www.cinahl.com</a>                 | RESTRICT * |
| PsycINFO       | <a href="http://www.pubmed.gov">www.pubmed.gov</a>                 | RESTRICT * |
| Web of Science | <a href="http://scientific.thomson.com">scientific.thomson.com</a> | RESTRICT * |

\*Bases with access through CAPES web Portal

**A. Wide search – sensible: disease x intervention x type of the study**

**PUBMED**

**Disease: Psoriasis**

("Psoriasis"[Mesh]) OR (Psoriasis) OR (Psoriasis) OR (Pustulosis of Palms and Soles) OR (Pustulosis Palmaris et Plantaris) OR (Palmoplantar Pustulosis) OR (Pustular Psoriasis of Palms and Soles) OR (severe plaque psoriasis) OR (severe psoriasis) OR (Erythrodermic psoriasis)

**AND**

**Intervention: Infliximab**

("infliximab "[Substance Name]) OR (Infliximab) OR (monoclonal antibody cA2) OR (MAb cA2) OR (Remicade) OR (Schering-Plough brand of infliximab) OR (Schering brand of infliximab) OR (Centocor brand of infliximab) OR (Essex brand of infliximab)

**AND**

**Type of the study**

((randomized controlled trial [pt]) OR (controlled clinical trial [pt]) OR (randomized [tiab]) OR (placebo [tiab]) OR (drug therapy [sh]) OR (randomly [tiab]) OR (trial [tiab]) OR (groups [tiab])) AND (humans [mh])

**B. Simple search (tool resources) – Only MeSH terms or only synonyms: disease X intervention X type of the study**

(psoriasis) AND (infliximab) AND (randomized clinical trial)

3. Optimized search at INAHTA members web sites developed at Google laboratory: <http://www.google.com/coop/cse?cx=015151609256227371949%3Aodk1sr9rtis&hl=pt-BR>

Put the search terms and automatically it will search in the 45 agencies (with available web site) that are part of INAHTA.

When putting the search terms with a well structured question (disease, intervention, comparison, outcomes) the results should be very satisfactory.

Even though there are sites in Portuguese and Spanish, the best results are recovered when the search is done in English.



## Annex F

### Example of Table describing the search strategy

| Base   | Terms  | Results | Selected studies | Available studies |
|--|--|---------|------------------|-------------------|
| Medline (via Pubmed <sup>1</sup> )                       | ((everolimus or certican) and (heart or cardiac) and (transplant or transplantation)) and systematic[sb]   | 1       | 0                | 0                 |
|  | ((everolimus or certican) and (heart or cardiac) and (transplant or transplantation)) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) | 9       | 2                | 2                 |
| Centre for Reviews and Dissemination (CRD <sup>2</sup> ) | (everolimus or certican) and (heart or cardiac) and (transplant or transplantation)  | 4       | 0                | 0                 |
| The Cochrane Library (via Bireme <sup>3</sup> )          | (everolimus or certican) and (heart or cardiac) and (transplant or transplantation)  | 29      | 1                | 1                 |

<sup>1</sup>Medline (via Pubmed). Available at: <<http://www.ncbi.nlm.nih.gov/sites/entrez>>. Accessed: 10th July 2008.

<sup>2</sup>Center for Reviews and Dissemination. Available at: <<http://www.crd.york.ac.uk/crdweb>>. Accessed: 10th July 2008.

<sup>3</sup>The Cochrane Library (via Bireme). Available at: <<http://cochrane.bvsalud.org/portal/php/index.php?lang=pt>>. Accessed: 07th July 2008.



## Annex G

### Classification of Levels of Evidence of Oxford Centre for Evidence-based Medicine<sup>1</sup>

| Level | Therapy/<br>Prevention/<br>Aetiology/Harm                                 | Prognosis  | Diagnosis   | Differential<br>diagnosis/symptom<br>prevalence study |
|-------|---|--|---|---|
| 1a    | SR (with homogeneity) of RCTs   | SR (with homogeneity) of inception cohort studies; CDR validated in different populations  | SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres                      | SR (with homogeneity) of prospective cohort studies   |
| 1b    | Individual RCT (with narrow Confidence Interval)                          | Individual inception cohort study with > 80% follow-up; CDR† validated in a single population  | Validating cohort study with good reference standards; or CDR tested within one clinical centre                               | Prospective cohort study with good follow-up          |
| 1c    | All or none   | All or none case-series  | Absolute SpPins and SnNouts   | All or none case-series                               |
| 2a    | SR (with homogeneity) of cohort studies                                   | SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs                                     | SR (with homogeneity) of Level >2 diagnostic studies  | SR (with homogeneity) of 2b and better studies        |
| 2b    | Individual cohort study (including low quality RCT; e.g., <80% follow-up) | Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR or validated on split-sample only | Exploratory cohort study with good reference standards; CDR† after derivation, or validated only on split-sample or databases | Retrospective cohort study, or poor follow-up         |
| 2c    | “Outcomes” Research; Ecological studies                                   | “Outcomes” Research  |   | Ecological studies                                    |

|    |  |  |  |  |
|----|--|--|--|--|
| 3a | SR (with homogeneity) of case-control studies  |  | SR (with homogeneity*) of 3b and better studies  | SR (with homogeneity) of 3b and better studies   |
| 3b | Individual Case-Control Study  |  | Non-consecutive study; or without consistently applied reference standards                                       | Non-consecutive cohort study, or very limited population   |
| 4  | Case-series (and poor quality cohort and case-control studies)   | Case-series (and poor quality prognostic cohort studies)<br>All or none case-series                              | Case-control study, poor or non-independent reference standard   | Case-series or superseded reference standards  |
| 5  | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" |

<sup>1</sup>Adapted from Oxford Centre for Evidence-based Medicine Levels of Evidence produced by PHILLIPS, B., BALL, C., SACKETT, D., BADENOCH, D., STRAUS, S., HAYNES, B., DAWES, M., 1998, reviewed in 2001. Published online: <http://www3.interscience.wiley.com/cgi-bin/fulltext/118508068/PDFSTART>.

Notes: SR: systematic review; RCT: randomized controlled trial;

| <b>Grades of Recommendation</b> |   |
|---------------------------------|---|
| A                               | consistent level 1 studies  |
| B                               | consistent level 2 or 3 studies or extrapolations from level 1 studies            |
| C                               | level 4 studies or extrapolations from level 2 or 3 studies                       |
| D                               | level 5 evidence or troublingly inconsistent or inconclusive studies of any level |

Classification of Scientific Evidence Level of Grading of  
Recommendations Assessment, Development and Evaluation –  
GRADE

<http://www.gradeworkinggroup.org/>



## Annex H

Data table containing parameters about how to evaluate the methodological quality of therapy randomized clinical trials<sup>1</sup>

| Parameters  | Study 1 | Study 2 | Study 3 |
|---|---------|---------|---------|
| Were patients randomized?   |         |         |         |
| Was randomization concealed (blinded or masked)?  |         |         |         |
| Were patients analyzed in the groups to which they were randomized?                                 |         |         |         |
| Were patients in the treatment and control groups similar with respect to known prognostic factors? |         |         |         |
| Did experimental and control groups retain a similar prognosis after the study started?             |         |         |         |
| Were patients aware of group allocation?  |         |         |         |
| Were clinicians aware of group allocation?  |         |         |         |
| Were outcome assessors aware of group allocation? Was follow-up complete?                           |         |         |         |
| How large was the treatment effect?   |         |         |         |
| How precise was the estimate of the treatment effect?   |         |         |         |
| Were the study patients similar to those of interest?   |         |         |         |
| Were all clinical important outcomes considered?  |         |         |         |

<sup>1</sup>Adapted from GUYATT, G.; RENNIE, D. *Diretrizes para utilização de literatura médica: fundamentos para a prática clínica da medicina baseada em evidências*. Porto Alegre: Artmed, 2006.

**Data table containing parameters about how to evaluate the methodological quality of diagnosis randomized clinical trials<sup>2</sup>**

| Parameters  | Study 1 | Study 2 | Study 3 |
|---|---------|---------|---------|
| Did clinicians face diagnostic uncertainty?   |         |         |         |
| Was there a blind comparison with an independent gold standard?   |         |         |         |
| Did the results of the test being evaluated influence the decision to perform the gold standard?          |         |         |         |
| What likelihood ratios were associated with the range of possible test results?                           |         |         |         |
| Will the reproducibility of the test result and its interpretation be satisfactory to the health service? |         |         |         |
| Are the results applicable to patients of interest?   |         |         |         |
| Will the results change my management strategy?   |         |         |         |
| Will patients be better off as result of the test?  |         |         |         |

<sup>2</sup>Adapted from GUYATT, G.; RENNIE, D. *Diretrizes para utilização de literatura médica: fundamentos para a prática clínica da medicina baseada em evidências*. Porto Alegre: Artmed, 2006.

**Data table containing parameters about how to evaluate the methodological quality of systematic reviews evidence<sup>3</sup>**

| Parameters  | Study 1 | Study 2 | Study 3 |
|---|---------|---------|---------|
| Did the review explicitly address a sensible clinical question? |         |         |         |
| Was the search for relevant studies detailed and exhaustive?    |         |         |         |
| Were the primary studies of high methodological quality?        |         |         |         |
| Were assessments of studies reproducible?                       |         |         |         |
| Were the results similar from study to study?                   |         |         |         |
| What are the overall results of the review?                     |         |         |         |
| How precise were the results?                                   |         |         |         |

<sup>3</sup>Adapted from GUYATT, G.; RENNIE, D. *Diretrizes para utilização de literatura médica: fundamentos para a prática clínica da medicina baseada em evidências*. Porto Alegre: Artmed, 2006.



## Annex I

**Example of how to present a data table with the results of selected studies** (Results of selected studies about the long term use of  $\beta$ 2-agonist in the treatment of Moderate Persistent Asthma)

| STUDIES  | TYPE OF THE STUDY / POPULATION  | OUTCOMES   | RESULTS (CI 95%)   |
|--|---|--|--|
| Ni Chroinin et al., 2004   | <ul style="list-style-type: none"> <li>• Systematic review</li> <li>• 9 RCT (n = 1061)                             <ul style="list-style-type: none"> <li>• Adults</li> </ul> </li> <li>• Light to moderate non-controlled Asthma, first-time treatment with IC patients</li> <li>• Intervention: <math>\beta</math>2-ALD + IC (400 <math>\mu</math>g to 800 <math>\mu</math>g/day)</li> <li>• Control: IC in the same dosage</li> </ul>  | 1 or more exacerbation, being necessary systemic corticosteroid<br>FEV1<br>Withdrawal<br>Adverse effects (oral candidiasis, headache and shaking)  | $\beta$ 2-ALD + IC vs IC<br>RR = 1,2 (0,8 – 1,9)<br>WMD = 0,21 L (0,12 – 0,3)<br>RR = 0,9 (0,6 – 1,2)<br>RR = 1,1 (0,8 – 1,5)  |
| Limitations of the study: the authors of the systematic review have conflict of interest. The primary study did not consider mortality as outcome. |   |  |  |
| Gibson et al., 2005  | <ul style="list-style-type: none"> <li>• Systematic review</li> <li>• 7 RCT (n = 2625)                             <ul style="list-style-type: none"> <li>• Adults</li> <li>• Stable Asthma</li> <li>• Comparison:                                     <ul style="list-style-type: none"> <li>&gt; 4 studies: salmeterol 100 <math>\mu</math>g/day + fluticasone 200 <math>\mu</math>g/day vs fluticasone 500 <math>\mu</math>g/day</li> <li>&gt;3 studies: formoterol 9-24 <math>\mu</math>g/day + budesonide 160-200 <math>\mu</math>g/day vs budesonide 400-800 <math>\mu</math>g/day</li> </ul> </li> </ul> </li> </ul> | 1 or more exacerbation, being necessary systemic corticosteroid<br>Exacerbation with need of hospitalization<br>FEV1<br>Withdrawal<br>Adverse effects (oral candidiasis, headache and shaking) | $\beta$ 2-ALD + IC vs IC<br>RR = 1,0 (0,76 – 1,32) Did not occur in both groups in the 2 studies that reported this closing<br>WMD = 0,1 L (0,07 – 0,12)<br>RR = 0,97 (0,74 – 1,28)<br>RR = 0,92 (0,79 – 1,07) |

Limitations of the study: even though the study demonstrates that the use of  $\beta$ 2-ALD favors the diminishing of corticosteroid dosage, which would reduce the importance adverse effects related to this drug (as the diminishing of growing, adrenal suppression and osteopenia), no study has evaluated these effects.

The primary study did not consider mortality as outcome.

The authors of the systematic review have conflict of interest.

RCT = Randomized controlled clinical trial; IC = Inhalant corticosteroids;  $\beta$ 2-ALD = long term  $\beta$ 2-agonist; FEV1 = forced expiratory volume in the first second; AR = Absolute Risk; RR = Relative Risk; WMD = weighted mean difference; CI = Confidence interval.

## Annex J

### Evaluation form of Methodological Guidelines for the Elaboration of HTA Appraisals

|                     |                |                        |
|---------------------|----------------|------------------------|
| Identification      |                |                        |
| Name:               |                |                        |
| Agency/Institution: |                |                        |
| Address:            |                |                        |
| Zip code:           | City:          | State:                 |
| Email:              |                |                        |
| Home Phone: (    )  | Mobile: (    ) | Business Phone: (    ) |

#### Mark with a X

| Criteria to be assessed  | Inadequate* | Partially adequate* | Adequate |
|--|-------------|---------------------|----------|
| Can these guidelines orient the reader to well elaborate a HTA Appraisal?                    |             |                     |          |
| Do the guidelines present the concepts in an easy and adequate way?                          |             |                     |          |
| The Methods described and proposed to the HTA Appraisal elaboration are adequate?            |             |                     |          |
| Was the guidelines clearly written?  |             |                     |          |
| * If inadequate or partially adequate, please, justify, indicating points that need changes. |             |                     |          |

|  |  |
|--|--|
| Open questions                             |  |
| General comments:                          |  |
| Positive points:                           |  |
| Negative points:                           |  |
| How many copies does the institution need? |  |



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