Actualización de la Guía para la Incorporación de Nuevos Fármacos

Update of the Guide for the Introduction of New Drugs. *Full text*

INFORMES, ESTUDIOS E INVESTIGACIÓN 2007
MINISTERIO DE SANIDAD Y CONSUMO

AETSA 2006/03

MINISTERIO DE SANIDAD Y CONSUMO
Plan de Calidad para el Sistema Nacional de Salud
Ministerio de Sanidad y Consumo
Instituto de Salud Carlos III
AIeT Agencia de Evaluación de Tecnologías Sanitarias
JUNTA DE ANDALUCIA
CONSEJERÍA DE SALUD

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Actualización de la Guía para la incorporación de Nuevos Fármacos = To Review the Guide for the Introduction of New Drugs / Bernardo Santos Ramos, Sandra Flores Moreno, Eduardo Briones Pérez de la Blanca, Roberto Marín Gil, Sara Gallego Villanueva, Javier Bautista Paloma; [traducción al inglés de Mónica Murphy]. Sevilla, Agencia de Evaluación de Tecnologías Sanitarias de Andalucía; *Madrid; Ministerio de Sanidad y Consumo, 2007*

207 p.; 24 cm

1. Evaluación de Medicamentos 2. Adquisición en Grupo 3. Costos y Análisis de Costo 4. Análisis Costo-Beneficio I. Santos Ramos, Bernardo II. España. Ministerio de Sanidad y Consumo

Autores: Bernardo Santos Ramos, Sandra Flores Moreno, Eduardo Briones Pérez de la Blanca, Roberto Marín Gil, Sara Gallego Villanueva.
Dirección Técnica: Agencia de Evaluación de Tecnologías Sanitarias de Andalucía.

Edita:
Agencia de Evaluación de Tecnologías Sanitarias de Andalucía
Avda. de la Innovación s/n.
Edificio RENTA SEVILLA, 2ª planta.
41020 Sevilla
España - Spain

Este documento se ha realizado en el marco de colaboración previsto en el Plan de Calidad para el Sistema Nacional de Salud, al amparo del convenio de colaboración suscrito por el Instituto de Salud Carlos III, organismo autónomo del Ministerio de Sanidad y Consumo, y la Fundación Progreso y Salud de Andalucía

ISBN: 978-84-932545-8-2
NIPO: 354-07-0711-7
Depósito Legal: SE-2.813/2008
Imprime: Tecnographic, S.L.

http://publicaciones.administración.es
http://www.juntadeandalucia.es/salud/aetsa

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Executive Summary

Title: Update of the Guide for the Introduction of New Drugs.

Authors: Bernardo Santos Ramos, Sandra Flores Moreno, Eduardo Briones Pérez de la Blanca, Roberto Marín Gil, Sara Gallego Villanueva, Francisco Javier Bautista Paloma.

BACKGROUND. New drugs are constantly being approved, forcing hospitals to take decisions regarding whether to introduce them selectively into healthcare practice. These decisions are taken by Pharmacy and Therapeutics Commissions (CFyT, Spanish acronym) which includes professionals from several fields of expertise. Their decisions may be influenced by the existence of different[1] interests between clinical physicians, managers and funding agencies. In 1999, the Andalusian Agency for Health Technology Assessment (AETSA) published a Guide for the Acquisition of New Technologies (GANT) with the purpose of capitalising on using[2] evidence-based medicine (EBM) to establishas[5] a common ground which would streamline decision-making regarding new technologies. On the basis of that Guide, it was developed a new model to request the introduction of new drugs inte pharmaco-therapeutics Gruides (GFT). GINF is aimed at assisting requesting physicians in knowing the criteria applied by the Pharmacy Commission when selecting drugs while establishing that physicians should submit the evidence supporting the introduction of the requested drug in an orderly and rigorous fashion. For three years now the Guide is one of the quality standards included in the Framework Contract adhered to by Hospitals operating under the Andalusian Health Service, and it has been publicised informally among other hospitals and healthcare facilities in Spain, and even abroad. Since it was first drawn up, a total of six versions have been published, and circulated among Andalusian hospitals. The pros and cons of using the Guide in daily practice have been debated at length in a number of forums, providing opportunities to better understand how GINF works under real conditions. In the light of these experiences, various opportunities have been identified to improve this tool, confirming the need to draft a new version of GINF - which can be validated scientifically - on the basis of the experience gained by end users and their proposals, as well as by drawing from similar experiences in other countries.

OBJECTIVES

1. To assess the degree of GINF implementation in Andalusian hospitals.
2. To identify opportunities for improvements to the current version of GINF.
3. To draft a new version of GINF that incorporates any improvements identified.

METHODOLOGY

Objective 1: To assess the degree of GINF implementation in Andalusian hospitals.

All public hospitals in Andalusia were identified systematically and through semi-structured telephone surveys, it was assessed, namely the degree of GINF implementation, the year in which it was first incorporated as a Guide in the hospital, the version in use at the time of the interview, sections which had been modified at local level, criteria for using the Guide (in the event that it is not used for all drugs), usefulness of the tool as perceived by the user, and the impact of GINF on decisions taken by the Pharmacy and Therapeutics Committee (CFyT).

Objective 2: To dentify opportunities to improve.

Two procedures were rolled out to detect opportunities for improvement:

2.a Structured literature review on instruments available for the introduction of drugs into hospitals, difficulties encountered in work procedures, and opportunities for improvement.

2.b Telephone survey: Any modifications introduced locally by the various hospitals with regard to the official version endorsed by AETSA were noted down in the form of a register which was later completed with the proposals for improvement suggested by interviewees.

Once the survey and literature review were completed, a list was drafted containing all the opportunities for improvement identified through both the channels indicated above. To this purpose a cause – effect diagram was designed.

Objective 3: To draft a new version of GINF.

3.a Selecting modifications to be introduced: RAND/UCLA Methodology
We adopted the RAND/UCLA Appropriate Use Methodology as our basic technique. The following steps were taken:

- Drawing up a list of possible modifications: list of scenarios.
- Identifying an experts' group.
- Assessment of scenarios by the experts' group, in two successive rounds of discussion ("modified Delphi technique").

3.b Drafting a new version of GINF
Selection and application of the identified opportunities for improvement to up-date GINF.

OUTCOMES

Objective 1: To assess the degree of GINF implementation.

- The target population identified included 31 hospitals. The survey was carried out at 29 of these; the degree of implementation was 96.5% among the hospitals interviewed; implementation had taken place mostly in 2003-2004. Twenty-three out of the 28 hospitals used GINF for 100% of drugs; the version most used was the first to be published (version *1.2*). 26% of the hospitals had introduced local modifications to GINF, primarily in the section called "efficacy, effectiveness and safety", and 80% of interviewees made suggestions for improvement.

Objective 2: To identify opportunities to improve

- **Literature review**: Review of the literature yielded a total of 132 articles. Ultimately, it was selected 15 original articles and six guides dealing with requests for the introduction of drugs. The main modifications detected using this method were related to general procedural modifications and more specific structural changes.

- **Survey**: The hospitals interviewed suggested a total of 52 potential improvements which affected work methodology, the overall structure of the guide, and some specific sections.

Objective 3: To draft a new version of GINF

- After a first round of voting, without interaction among the experts' group, a second round was organised, with all present, to assess the scenarios. During the second round of voting, 41 scenarios were deemed appropriate, seven were deemed doubtful, and five inappropriate. The new version of GINF includes all the scenarios assessed as appropiate, and six of those deemed doubtful. Final drafting of the guide included the creation of new sections in the questionnaire, adding new questions, extending the scope of questions and/or changing the wording of existing sections.

CONCLUSIONS

1. The GINF guide is currently in place in the vast majority of public hospitals in Andalusia which consider it to be a useful tool in the work of their Pharmacy and Therapeutics Commissions (CFyTs). However, lack of knowledge regarding the existence of subsequent versions of the guide is notorious, and this has led to scarce implementation of the most recent versions.
2. A considerable number of opportunities for improvement have been identified, justifying the need to up-date GINF. Most of the opportunities detected are related to specific structural changes to the questionnaire, primarily in the section on efficacy, effectiveness and safety.
3. The need to establish channels of communication between the pharmaceutical industry and the CFyTs, through an adequate procedure, is blatantly clear. However, GINF was conceived as an educational instrument, to promote the necessary dialogue between clinicians and evaluators, and hence mechanisms need to be put in place to foster and guarantee that primary aim.
4. A new version of GINF has been produced. This new version includes an on-line electronic version, and an English language version of the pdf file, as well as complementary resources to the Guide.

Introduction

Selection of drugs has been defined by the World Health Organisation as a *continuous, multi-disciplinary and participatory process aimed at guaranteeing the availability of the necessary drugs to meet the therapeutic requirements of any given area, on the basis of efficacy, safety and cost criteria, while promoting their rational use*. So the need for drug selection is based on the premise that using a not too excessive number of drugs in a given area allows:

- Making available of comprehensive, reliable information in real time.
- Improving knowledge that health professionals and patients may have on the drugs routinely used.
- Establishing therapeutic protocols or consensus.
- Monitoring use and the positive or adverse effects of the drugs.

The above will guarantee the best possible conditions of safety in the use of medication[1,2].

The constant approval of new drugs forces hospitals to take decisions regarding elective introduction of medication in healthcare assistance practice. These decisions are taken by Pharmacy and Therapeutics Commissions (CFyTs) which have customarily designed the application forms used to request the introduction of new medication in the Hospital´s Pharmaco-Therapeutics Guides (GFT). In general, the application forms would briefly mention the main details enabling CFyTs to identify the drug and the requester, and there was a different application form in place at each hospital. The selection process entails striking the right balance between possible risks and benefits of the drug. This process – not always scientifically well-founded – must also bear in the mind the costs involved.

So the primary components for assessment and selection which are normally taken into account by hospitals are as follows[3-7]:

- Therapeutic contribution as opposed to other available alternatives.
- Magnitude of benefits as opposed to costs (cost-effectiveness ratio).
- Adequacy with the features and services delivered by the hospital as well as overall impact on pharmacy budgets, including costs incurred or avoided in primary healthcare.

CFyTs are currently under considerable pressure, so decision-making is increasingly complex and difficult. Some of the factors contributing to this state of play are:

- A clear increase in requesting the introduction of new drugs, especially in certain research and marketing areas.
- Lack of important information when adopting decisions.
- Clinicians and managers have difficulties in accessing objective, comprehensive and up-dated information. As a result of the rise in the number of scientific publications and the enormous volumes available, CFyTs are confronted with huge problems when attempting to locate and discern the relevant information. Since the data comes largely from the pharmaceutical industry, there is the additional difficulty, to interprete and assess the information in terms of the scientific validity of its possible application in view of the particular conditions of any given hospital facility.

With the purpose of streamlining this process while harmonising the criteria adopted by the various CFyTs, the Andalusian Agency for Health Technology Assessment (AETSA), in collaboration with the Pharmacy Service of University Hospital Virgen del Rocio, designed a Guide for formulary submissions in January 2002, known as the Guide on the Introduction of New Drugs (GINF) [8]. To produce this Guide, the authors based their work on the Guide for the Acquisition of New Health Technologies in Andalusia (GANT), also produced by AETSA[9]. The objectives to be met by producing GINF were as follows to: 5

- Foster systematic compilation of the necessary data to assist in decision-making on the introduction of new drugs, also considering available research outcomes.
- Provide methodological tools to assess the information available.
- Enhance the transparency of the process governing the introduction of new drugs to Pharmaco-Therapeutic Guides (GFT).

In addition, GINF was intended to encourage applicants/requesters to think carefully about their request, having compiled all the information required, urging them to anlyse the suitability of the application.

GINF includes four general sections, the most comprehensive of which is devoted to evidence regarding efficacy, effectiveness and safety, and it essentially intends to provide information on the following:

- Indication for which the drug is requested.
- Data on efficacy and safety for the requested indication, on the basis of clinical trials' outcomes.

- Advantages in terms of efficacy, safety or efficiency as opposed to drugs included in the Guide for the same indication.
- Data on number and characteristics of candidate patients, eligible to receive the treatment requested at the hospital in question.
- Economic data and cost-effectiveness ratio.

In our setting, no instruments similar to GINF has been identified that include a document to request the introduction of drugs based on available evidence, although there are similar tools in other countries[10]. The most noteworthy examples – on account of their methodological quality and their impact – are the PBAC guide (Pharmaceutical Benefits Advisory Committee) in Australia[11] and the guide produced by the Academy of Managed Care Pharmacy in the United States[12-14]. Unlike GINF, the latter guide is intended to encourage pharmaceutical companies to request the introduction of a drug at a hospital or, more commonly, in a series of hospitals, or for applications presented by a given healthcare assistance company. It has become the un-official standard for systematically dealing with requests for the introduction of new drugs in the hospital setting.

GINF has been introduced as a quality standard in the Programme Contract subscribed by hospitals operating under the Andalusian Health Service[15] and it has been diffused informally among other hospitals and healthcare centres in Spain and abroad. However, there is no data available on the genuine degree of implementation and the only case assessed to date was used at Virgen del Rocio University Hospital, where GINF completed during the period January 2002 – July 2003 were analysed – a total of 32 requests for 26 drugs. The conclusions drawn from this study show that the GINF is a useful tool to improve the quality of work of CFyTs in introducing new drugs and that the process by no means exclusively implies restraining costs. However, it is noted that healthcare professionals found that the work involved in searching for scientific evidence, summarising and interpreting it, was an extremely arduous and complex task[16].

Since initial publication of GINF, a total of six versions have been produced, the most recent of which is version 2.0. The possible pros and cons posed by GINF have been debated at length since it was taken on board by CFyTs in their daily work, providing opportunities to improve knowledge on how GINF works in real daily practice.

In the light of the experience gained to date, several opportunities for improvement of this tool have been detected, confirming the need to produce a new, scientifically-sound version of GINF.

Objectives

1. To assess the degree of GINF implementation in Andalusian hospitals.

2. To identify opportunities to improve the current version of GINF.

3. To draft a new version of GINF that incorporates any improvements identified.

Methodology

Objective 1: To assess the degree of GINF implementation

An assessment questionnaire was designed by a working group formed by three members of the CFyT at University Hospital Virgen del Rocio, namely the Secretary, a Hospital Pharmacist and an Internal Medicine Specialist Physician, along with an epidemiologist from AETSA. They had all actively taken part in producing the first version of the GINF Guide.

The questionnaire included the following items, in addition to issues on implementing GINF as a working document for the CFyT:

- Year when GINF was implemented/introduced at the hospital.
- Version currently in use.
- Modifications made at local level in the hospital.
- Criteria for using the Guide, in the event that it is not used for all drugs.
- Utitily of the tool, as perceived by the user.
- Impact of the GINF Guide on decisions taken by the CFyT

All in all, the questionnaire included twelve questions, eleven of which were closed questions. The last was an open question requesting information on any changes already introduced to the the Guide at local level, or proposals regarding potential changes which the interviewee deemed of interest for a future version. Previously, agreement was reached on how to codify the open question, and possible clarifications which might be necessary during the survey to curb information bias as far as possible. So the items were assessed by the interviewee using the qualitative Likert scale (high, average, low or null). The questionnaire is detailed in Appendix I.

All public hospitals in Andalusia were identified using the Regional Ministry of Health's Hospital Catalogue. It was decided that the Secretary of the CFyT at each hospital would be the person interviewed, although (s)he would be given the chance to nominate another CFyT member if (s)he so wished. AETSA sent an official letter by registered post to all CFyT Secretaries, announcing the undertaking of the project and the telephone interview, while also providing a summary of the project.

Telephone interviews were carried out one month after the letters were posted. Included in the study were all hospitals that had used GINF prior to January 1st 2006. Hospitals failing to respond to three telephone calls, or which refused to take part after receiving the call were excluded (Appendix II). The survey was carried out by two pharmacist interns specialising in Hospital Pharmacy at Virgen del Rocio University Hospital.

The period of study covered the first semester 2006, during which letters were sent out to the hospitals, and telephone interviews were conducted. The data were initially compiled using an Excel 2000, data sheet, and were later imported to the SPSS programme (Statistical Package for Social Sciences), version 12.0.

Descriptive analysis of the data was performed. Median and range were calculated for quantitative variables. The frequency distribution of the categorical qualitative variables included in the study was plotted. For the last question – regarding possible modifications to the GINF Guide – responses were divided into (i) procedural modifications for using the Guide or (ii) changing the structure of the guide; in this latter case, notes were made on the section of the guide for which the changes were suggested.

Dependent variables were also analysed (see Appendix I for a list), classified according to the following characteristics of the hospitals involved:

- Size: The biggest hospital, Medical Specialisations, The smallest Hospitals.
- Training Programme for Pharmacist Intern Residents, or not.
- Specialist hospital.
- Province where hospital is located.

To this purpose, we used the Ji squared Pearson test (with continuity correction) for comparison of qualitative variables. For comparison of the average number of drugs analysed using GINF, we applied the ANOVA test (analysis of variance) for analysis by type of hospital (three categories), along with Student's t test for dichotomic variables (Training Programme for Pharmacist Intern Residents and geographical location).

Objective 2. To identify opportunities to improve

Two different procedures were used to pinpoint opportunities to improve:

2.a Structured literature review

A structured literature review was carried out to identify the tools and instruments in place for introducing drugs at hospitals, as well as to detect difficulties in work procedures and opportunities for improvement. Various data-bases were scrutinised to find the information, which was extracted in an organised manner. Below are described the various activities carried out during the search:

2.a.1. Search on Medline

The search strategy was aimed at maximising sensitivity, given the difficulties and the sheer magnitude of the topic. No language restrictions were applied.

Search strategy

Period covered in the search: 1996-2006.

The Search on Medline was conducted using the Silverplatter interface, dated 15th March 2006.

Nº.	Application
1	(Formular* and guidelin*) in Ti
2	(hospital? and formular*) in Ti
3	"Formularies"/ without-subheadings, standards
4	"Formularies-Hospital"/ without-subheadings, standards
5	"Drug-Approval"/ methods
6	#3 or #4 or #5
7	"Guideline-" in MIME,MJME,PT
8	"Guideline-Adherence"/ without-subheadings, standards, trends
9	"Evidence-Based-Medicine"/ all subheadings
10	"Decision-Making"/ without-subheadings
11	"Choice-Behavior"/ without-subheadings
12	"Decision-Making-Organizational" in MIME, MJME, PT
13	"Economics-Pharmaceutical"/ without-subheadings, standards, trends
14	"Cost-Benefit-Analysis"/ without-subheadings, methods, organization-and- administration, standards, trends
15	"Pharmacy-and-Therapeutics-Committee"/ without-subheadings, standards, trends, utilization
16	#10 or #11 or #12 or #13 or #14 or #15
17	#1 or #2
18	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
19	(#6 in MJME) and #18
20	#17 or #19
21	#17 or #19

2.a.2 Web pages

The web sites of the following organisations and societies were checked, looking for information related to the study:

- Academy of Managed Care Pharmacy (AMCP)
- American Society of Health-System Pharmacy
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- International Network for Health Care Research,
- Institute for Health Economics
- Spanish Society for Hospital Pharmacy
- European Society of Clinical Pharmacy
- Blue Cross and Blue Shield Association-Technology Evaluation Center

3. Search on INAHTA

4. Handy searches

Reference lists contained in the documents identified.

Once the search was completed, documents were selected bearing in mind previously established inclusion/exclusion criteria, as follows:

Inclusion criteria:

1. Articles referring to documents or guides for submissions at individual hospitals, groups of hospitals, medical insurance companies, the biggest hospital or national healthcare systems (first inclusion criterion).
2. Articles referring to request procedures in place at individual hospitals, groups of hospitals, insurance companies, the biggest hospital or national healthcare systems (second inclusion criterion).

Exclusion criteria:

1. Articles referring to individual drugs or groups of drugs that do not contribute relevant outcomes in terms of the general method for request of introduction.
2. Articles referring to marketing authorisation.

Inclusion/exclusion criteria were applied by revising the titles and abstracts of the articles or reading the complete texts in the event of doubt. All the abstracts selected were reviewed separately by two researchers to ensure compliance with the criteria established. When disagreement arose on the references, they were subsequently reviewed jointly by both, to reach consensus.

2.a.5. Extracting the data

Three of the researchers produced two different types summary tables containing the main information items to be obtained from each of the documents identified. The tables covered various aspects, depending on the type of document. For original articles, the items to be noted were: title, authors, year, use of the guide (mission), characteristics of the application procedure, main difficulties encountered in the introduction of new drugs in Pharmaco-Therapeutic Guides (GFT), relevant issues or aspects not contained in GINF, and any other observations. The following information was compiled for analysis of the guides: date of publication, author(s) affiliation, statement regarding conflict of interests, main goal, recipients, scope of application of decisions, standard application form included, and schedule for revision.

Data were extracted by two of the researchers.

2.b Telephone interviews

Telephone interviews enabled researchers to identify and systematically register all the modifications carried out locally with respect to the official version established by AETSA. The project's researchers registered the information, classifying each modification according to the section and subsection in GINF, as well as the related question in the questionnaire. The register was completed with interviewee's suggestions for improving GINF.

In parallel, the Heads of Pharmacy Units in other hospitals in Spain, which, according to existing evidence, have also implemented GINF (Appendix III), were likewise approached by telephone. They were interviewed to respond to the questionnaire (Appendix I) this time with the aim of identifying other opportunities for improvement.

2.c Cause-effect diagram

Once the interviews and literature review were completed, a list was drawn up including all the opportunities for improvement detected via both procedures. A cause-effect diagram was designed to enable envisaging how the various opportunities for improvement pinpointed would affect use of the Guide. The various causes were grouped into categories according to affinity between them, thus coming up with a unified list of opportunities for improvement.

Objective 3. To draf a new version of GINF

3.a Selecting modifications to be made: RAND/UCLA Methodology

3.a.1 List of scenarios

On the basis of the improvements described in the cause-effect diagram, a list of hypothetical scenarios or possible changes was drawn up, divided into chapters according to the various aspects of GINF that were assessed (Appendix IV). The scenarios identified both in the literature review and telephone interviews with Pharmacy Sevices using GINF, were fine-tuned to draw relevant, feasible and mutually excluding changes. The final list was produced by the research team.

The scenarios were grouped under three different chapters:

- Changes to the procedure.
- Changes to the overall structure of the guide.
- Changes to specific sections in the current guide.

The last chapter – on changes to specific sections – was sub-divided into the following: applicant's information, data on the drug, efficacy, effectiveness and safety, economic assessment, conclusions and classification of requests.

Lastly, for each of the modifications proposed, researchers tried to reproduce the scenario in which they might appear. To do so, panellists received a copy of the latest version available of the GINF guide (version 2.0) in which the modifications proposed under the last chapter referred to above were clearly highlighted (in blue, and with the relevant identification code).

3.a.2 Experts' Group

The experts' group included twelve professionals from different autonomous regions in Spain, with ample experience in decision-making regarding the introduction of drugs in hospital Pharmaco-Therapeutics Guides. The group also included requesters of new drugs, along with members of Pharmacy and Therapeutic Committees. Their meeting took place in Seville in November 2006.

3.a.3 Assessment of the scenarios

Once the experts had been selected, they were e-mailed the literature review and the list of proprosals of improvement, one month before the meeting. They were asked to firstly assess whether it was convenient to make the proposed changes, by rating each using a score from 1 to 9 where 1 denotes that the change is extremely inappropriate, and 9 that it is highly appropriate. During this first round, scores were assigned individually by the experts, either at home or work and no interaction took place between group members.

Later, using the scores assigned by experts, scenarios were classified according to the degree of agreement and appropiateness, on the basis of the following definitions:

Degree of Agreement

- Agreement: no more than two participants assess the indication outside the 3 point tranche (1-3; 4-6; 7-9) of the median score.
- Disagreement: at least three participants assess the indication within the 1-3 tranche, and at least three assess it in the 7-9 tranche.

Degree of Appropriateness

- Appropriate: 7-9 group median, no disagreement.
- Uncertain: 4-6 group median, or any other median with disagreement.
- Inappropriate: 1-3 group median, no disagreement.

Subsequently, during a second round, members of the group met along with two moderators who are well versed in the use of the method. During this second stage, each member of the group received an individualised assessment sheet, showing the frequency of responses that each indication archieved the first round, along with a symbol indicating the particular member's response. The idea was to give participants the opportunity to discuss their assessments knowing how their colleagues had scored during the first round. During the meeting, group members debated the various scenarios, focussing primarily on areas where disagreement had arisen. They were invited to modify the preliminary list of scenarios and/or definitions. After commenting on each, they re-classified each scenario individually. So, each indication was re-classified as "appropriate", "uncertain" or "inappropriate", on the basis of the same criteria used in the previous case.

Moderators worked with two documents to prepare and stage the group's meeting:

- The summarised assessment form: shows the frequency of responses for each indication like the individualised docoment for each indication. In addition, it includes other information to assist the moderator in deciding which scenarios should be emphasised during the discussion, namely the median, degree of agreement for indication assessment (agreement, undetermined, disagreement) and assessment of appropiateness (appropriate, uncertain, inappropriate).
- Detailed assessment form for each participant: this document shows the scores given by each particular expert for each scenario.

3.b Drafting GINF

After the second round, a list was compiled with the scenarios assessed by experts as appropriate or uncertain. The final draft of the new version of GINF includes:

- All the scenarios under chapter 3, assessed as appropriate.
- Some scenarios under chapter 3, assessed as uncertain, depending on the criteria adopted by the research team.

At the same time, the outcomes and conclusions of two similar projects were also assessed namely, the Guide for the Acquisition of New Health Technologies (GANT)[9] and Guide for Decision-Making on the Introduction of Genetic Tests in the National Health Service (GEN guide). Both were up-dated by AETSA at roughly the same time, and share a number of aspects in common with GINF.

The drafting of the new GINF guide was conducted in two successive stages. Firstly, once all the scenarios to be introduced were identified, a member of the research team drafted the new version of GINF, which was later studied and commented on by the rest of the team during a series of successive meetings. Subsequently, having gathered all the contributions made, two researchers fine-tuned the final version. Finally, the Guide was subject to external review by contacting other Technology Assessment Agencies in Spain.

Following external review, the final document was produced, including a web version, to enable working with the Guide on-line, as well as English language version.

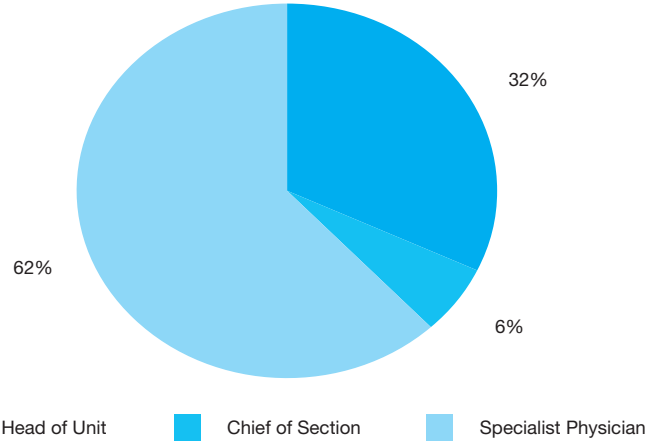
Outcomes

Objective 1. To assess the degree of GINF implementation

The target population identified was 31 hospitals in Andalusia, 29 of which took part in the survey (93,5% response rate). Two hospitals were dismissed because they failed to respond after three scheduled telephone calls; both fell under the category "the smallest hospitals".

The survey included interviews with specialists working in Hospital Pharmacy Units – primarily Assistant Pharmacists (62,1%) – and in most cases (25/28) they officially belonged to the Hospital's Pharmacy Commission. In eight of the cases, the person interviewed was the hospital's Head of Pharmacy (Figure 1).

Figure 1. Interviewee's position



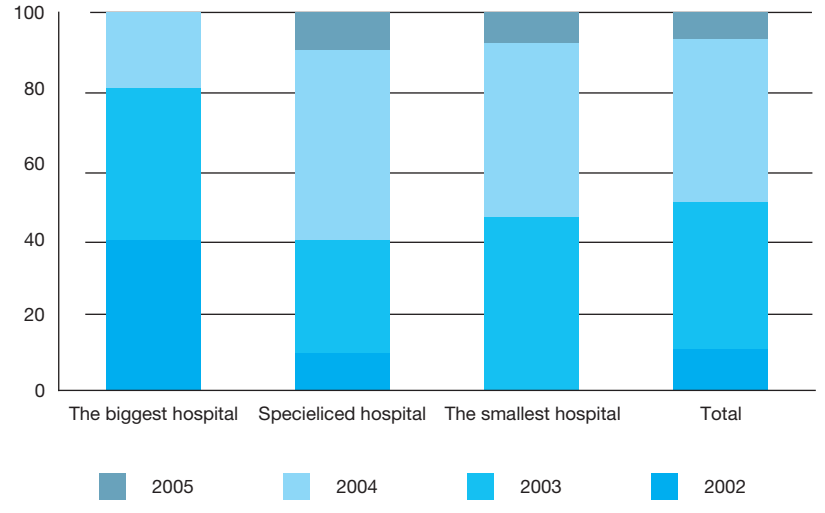
At the time of the survey, GINF was already in place in 28 out of the 29 hospitals interviewed. The degree of implementation is therefore 96,5% in responding hospitals. The hospital GINF was not implemented in belonged, once again, to the smallest hospital category. Analysis of variables was conducted on those 28 hospitals using GINF, whose features are tabled below (Table 1).

Table 1. Characteristics of the sample of hospitals where GINF had been implemented

Hospitals	No. (%)
Total	**28 (100)**
Type of hospital	
The biggest	5 (18)
Specialist	10 (36)
The smallest	13 (46)
Location	
Western Andalusia	12 (43)
Eastern Andalusia	16 (57)
Training Programmes for Pharmaceutical Intern Residents	
Yes	13 (46)
No	15 (54)
Person interviewed	
Head of Unit	9 (32)
Deputy Head	19 (68)

Implementation began in 2002 at the biggest hospitals only; GINF was introduced in over 80% of hospitals in the period 2003-2004, and the remainder implemented the guide in 2005 (Table 2).

Figure 2. Time-progression of GINF implementation according to type of hospital

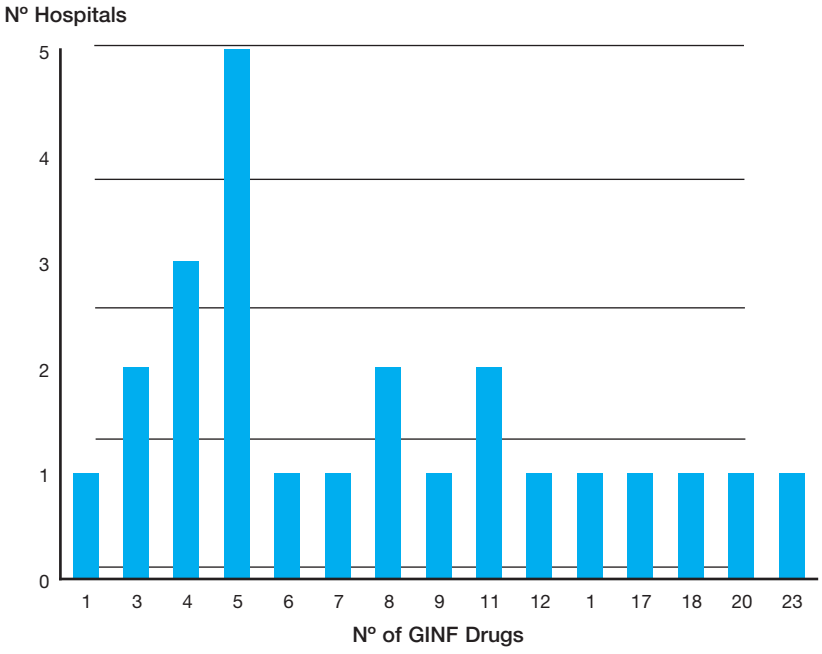


As to the precise version of GINF in place at the hospitals, 14 out of 28 were not sure which they were using since the Guide could not be identified properly. In the other half of hospitals, the first version was the one mostly used (version 1.2), which was found in ten hospitals (36% of the total). Moreover, only seven hospitals had used different versions of the GINF guide; the remainder had always employed the version they received initially, and were unaware of the existence of subsequent or more recent versions.

As to the degree of use of the Guide once it was introduced at the hospital, 23 affirmed that they applied the Guide when introducing all innovative drugs, without exception; the other five only use the Guide partially, depending on the therapy group (anti-neoplastic and anti-retroviral drugs were primarily excluded from the GINF methodology).

In terms of the volume of drugs for which the GINF Guide was used in 2005, there is great variability. The range covers 1 to 23 drugs, with a median of eight drugs assessed per Hospital using GINF (Figure 3).

Figure 3. Volume of Drugs Assessed using GINF



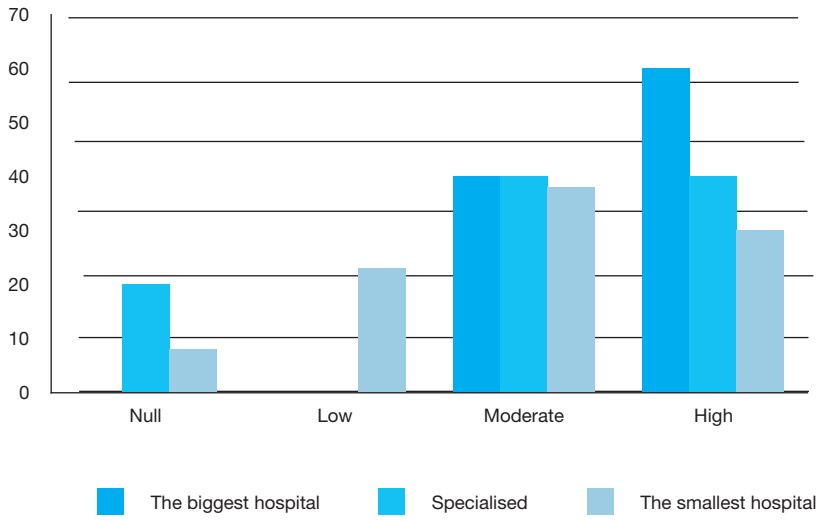
Analysis of dependent variables, as indicated in Table 1, shows that depending on the characteristics of each hospital, statistically significant differences were only found in the following cases:

a. Hospitals delivering medical training to resident interns (n=14) used different versions of GINF more frequently than hospitals that do not deliver training (n=14): 35% vs. 7% (p=0.049).
b. Hospitals located in Western Andalusia (n=14) used different versions of GINF more frequently than hospitals located in Eastern Andalusia (n=14): 45% vs. 0% (p=0.004).
c. The average number of drugs assessed using GINF was significantly higher in the biggest hospital hospitals than in less complex hospitals (p=0.001).
   The biggest Hosp. (n=3), average = 16.33 (SD = 4.73)
   The smallest Hosp. (n=12), average = 4.67 (SD = 2.17)
   Specialised Hosp. (n=8), average = 8.13 (SD = 4.05)
d. The average number of drugs assessed using GINF was significantly higher in hospitals delivering training programmes to resident medical interns than those which do not - 10.90 vs. 4.69 (p = 0.001).

GINF was modified or adapted at local level in six hospitals, of which two were the biggest hospital, three for medical specialisations, and one a the smallest hospital. Four hospitals introduced changes to the original Guide, in the section called: "efficacy, safety and effectiveness"; within this group, only one of the hospitals had introduced changes to various sections in the guide. The only section that was left unchanged by all hospitals was that named "economic assessment".

Utility, as perceived by users of the Guide, was null in three cases, low in another three, average in twelve cases and high in ten. The impact of GINF on decision-making within Pharmacy and Therapeutics Committees (CFyT) was considered by users as null in three cases, low in six, average in eight cases, and high in eleven. Figure 4 shows the distribution of responses according to type of hospital. It is worth noting here, that there is a difference in perceived utility among medical training hospitals and those that do not deliver medical training; in the first group, GINF is seen as a moderately to highly useful tool in 92% of cases, whereas only 66% of hospitals in the second group consider GINF as being moderately to highly useful.

Figure 4. Perceived utility of the Guide by Users according to the Hospital category they belong to



With regard to proposals for improvement, almost 80% of interviewees proposed one or more changes. A total of 52 proposals were received, 31 in relation to the lay-out or structure of the guide, and 21 referring to the procedure for using the guide. The number of proposals per hospital ranged between zero and six. The main areas of improvement suggested were as follows:

- Limit or regulate access of Pharmaceutical Companies to the GINF Guide, for example, by rejecting applications completed by them and/or introducing those questionnaires which show a potential conflict of interests of the applicant(s).
- Increase dissemination of future versions of the guide and raise introducing regarding GINF by creating an easily accessible, electronic version, together with teacher-training material on GINF methodology.
- New concepts should be introduced in the Guide, particularly the critical assessments taken from clinical trials reviewed.
- Introduce new sections and broaden existing sections on qualitative assessment by the requesting physician with respect to the drug requested and advantages that it poses.

- Introduce more questions on local aspects that may impact on drug request: local incidence/prevalence of the disease; profile of local sub-groups and criteria; diagnostic tests or additional tests required for recruitment/follow-up of proposed patient sub-groups.

Objective 2. To identify opportunities to improve

2.a Literature search

A total of 132 articles were retrieved, of which ultimately fifteen original articles and six guides for the introduction of new drugs were selected. It was possible to access the complete text of all articles.

- **Description of original articles**

The fifteen original articles have been grouped into two tables, shown below, according to the inclusion criteria met by each. The tables also provide a brief description of each of the papers, with the aim of helping readers understand the utility of each and its contribution to the project.

Table 2. Articles that meet the first inclusion criterion

Articles referring to documents or guides for request of drugs at individual hospitals, groups of hospitals, medical insurance companies, the biggest hospital or national healthcare services.

Title	1st Author; Year	Brief description
Incorporating Clinical Outcomes and Economic Consequences into Drug Formulary Decisions: A Practical Approach	Mather D.B. 1999	The paper explains the process followed to gather and review economic, clinical data and other outcomes as part of the process to adopt the drug formulary in the largest healthcare insurance company in Washington called Regence Blue Shield (Regence).
Formulary Submission Guidelines for Blue Cross and Blue Shield of Colorado and Nevada Structure, Application and Manufacturer Responsibilities	Langley P. 1999	The paper describes the guidelines that apply to Blue Cross and Blue Shield guides or formularies, and explains how drug manufacturers are expected to meet the needs for information of the healthcare sytem when presenting new products to the Pharmacy and Therapeutics Committee.
Meeting the Information Needs of Drug Purchasers: The Evolution of Formulary Submission Guidelines	Langley P. 1999	The paper analyses the various roles of guides in management of healthcare systems, examining and comparing two types of opposing guides, namely, the Australian Guides, published in 1992, and the Guides for Blue Cross and Blue Shield of Colorado and Nevada (US).

Table 2. Articles that meet the first inclusion criterion. (Continuación)

Articles referring to documents or guides for request of drugs at individual hospitals, groups of hospitals, medical insurance companies, the biggest hospital or national healthcare services.

Title	1st Author; Year	Brief description
Evidence-Based Decision Making: Using Submission Guidelines to Inform Formulary Approvals	Anis A. 1999	Assessment of the Mather et al. report, which describes experience in using the guides, while providing an approach in terms of information requirements to be met by pharmaceutical companies, in order to ease decision-making when introducing drugs in the State of Washington.
Using economic evaluations to make formulary coverage decisions So much for guidelines	Aslam A. 2000	This paper highlights the fact that it is mandatory, for Canadian drug manufacturers who request inclusion of their drug formularies under the British Columbia Provincial Plan, to submit an economic-pharmacological analysis in accordance with published guides. The article also assesses concordance of the studies presented with the specific criteria laid out in the Guides.
The Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions: An Evolving Standard—A Foundation for Managed Care Pharmacy Task Force Report	Fry R. 2003	Assessment and detailed coverage of the requirements contained in version 2.0 of the AMCP Guide. The paper also elaborates on certain key points raised by some users and drug manufacturers vis-à-vis the utility of the guide since it was published in October 2000.
Ontario's Formulary Committee How Recommendations Are Made	Paus . Jenssen A. 2003	In 1996, Ontario's provincial government (Canada) demanded that drug manufacturers, requesting introduction of their drugs in the provincial formulary, submit a cost-effectiveness analysis regarding their products. The paper describes how the Ontario Commission decides to list products in their formulary and, more specifically, how they apply economic analysis to the process.
Priority setting in a hospital drug formulary: a qualitative case study and evaluation	Martin D. 2003	It describes the process established to prioritise and include new drugs in the formulary of a hospital in the US.
Evidence-Based and Valued-Based Formulary Guidelines	Neumann P. 2004	It describes the process through which various healthcare organisations have begun to implement the guides published by AMCP (Academy of Managed Care Pharmacy), which demand that Pharmaceutical Labs submit a standard dossier containing detailed information not only on effectiveness and safety of the drug, but also on economic value vis-à-vis alternative therapy options.

Table 3. Articles that meet the second inclusion criterion

Papers addressing submission procedures at individual hospitals, groups of hospitals, medical insurance companies, the biggest hospital or national healthcare services.

Title	1st Author; Year	Brief description
Understanding, Creating, and Working with Formulary Systems	Quinn C. 1999	The aim of this paper is to help physicians and pharmacists to design and implement formularies.
Application of Pharmacoeconomics to Formulary Decision Making in Managed Care Organizations	Dong-Churl S. 2002	This paper describes the need that healthcare organisations introduce and apply pharmaco-economic studies in their decision-making processes regarding Guides for introduction of drugs.
What constitutes evidence in hospital new drug decision making?	Jenkings N. 2003	In UK National Health Service Hospitals, the introduction of new drugs is controlled by a local Drugand Therapeutics Committee, DTC) which is expected to apply evidence-based medicine principles. This study observed, recorded and analysed the work of DTCs with the aim of determining what precisely is considered as evidence and how it is used in decision-making.
Cost-Effectiveness Analysis and the Formulary Decision-Making Process	Wang Z 2004	Review of cost-effectiveness analysis, its limitations and applications in formulary decision-making with a view to promoting enhanced utility of formularies for pharmacists.
The Arrival of Economic Evidence in Managed Care Formulary Decisions The Unsolicited Request Process	Neumann P. 2005	Analysis on how to use economic evidence in decision-making regarding new drug formularies and the implications of unsolicited requests which arise as a result of the AMCP format.
The Evolving Use of Cost-Effectiveness Analysis in Formulary Management Within the Department of Veterans Affairs	Aspinall S. 2005	Assessment of cost-effectiveness analysis for management of formularies in decision-making at the VHA (Veterans Health Administration), which supervises the largest comprehensive healthcare service in the US, providing assistance to all Veterans enrolled in the Veterans Affairs Department.

Description of the guides

The following six guides were selected:

- Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee (Australia)
- Common Drug Review Submission Guidelines for Manufacturers (Canada)
- Academy of Managed Care Pharmacy Format for Formulary Submissions (USA)
- Drug Submission Guidelines for New Products, New Indications and New Formulations (USA)
- NICE Guidelines for Manufacturers and Sponsors (England and Wales)
- Guidance to Manufacturers: Notes for Completion of the New Product Assessment Form (Scotland)

From each of these guides, a detailed description was drawn up on the following aspects:

- Date of publication.
- Authors' affiliation.
- Statement on conflict of interests.
- Primary aim.
- Recipients.
- Scope of application of decisions taken.
- Standard application form included.
- Schedule for revision.

The aspects included in this section were taken from the ISPOR guidelines (**International Society for Pharmacoeconomics and Outcomes Research**) regarding assessment of pharmaco-economic guides, and submissions for the introduction of new drugs.

Finally, a table was drawn up to compare the items included (or not) in the main sections of the guides for requesting new drugs (general information on the drug/disease, clinical and economic assessments).

Summary of each of the guides:

1. Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee (Australia).

PBAC GUIDELINES

Date of publication	September 2002
Authors' affiliation	Pharmaceutical Benefits Advisory Committee (PBAC)
Authors' statement on conflict of interests	No
Primary aim	To provide Pharmaceutical Labs with a guide to prepare the clinical and economic data required for PBAC submissions
Recipients	Pharmaceutical Companies/Labs, Scientific Societies and healthcare professionals
Scope of application of decisions taken	Australia
Standard application form included	Yes
Includes a schedule for revision	Yes

2. Common Drug Review Submission Guidelines for Manufacturers (Canada).

CDR GUIDE

Date of publication	May 2006
Authors' affiliation	CDR Section (Common Drug Review) within the Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA).
Authors' statement on conflict of interests	Yes
Primary aim	Standard Guide for submissions regarding new drugs with subsequent, centralised assessment which will serve as a non-binding benchmark for regional agencies in various states in Canada.
Recipients	Pharmaceutical Labs
Scope of application of decisions taken	Not directly applicable. Decision is not binding.
Standard application form included	Yes
Includes a schedule for revision	No

3. Academy of Managed Care Pharmacy Format for Formulary Submissions (USA).

AMCP GUIDE

Date of publication	April 2005
Authors' affiliation	Academic experts from a variety of scientific societies.
Authors' statement on conflict of interests	Yes
Primary aim	To standardise the format for submissions regarding new drugs. To provide a guide that may be used by a wide range of institutions.
Recipients	Pharmaceutical Labs specialising in new drugs' submissions.
Scope of application of decisions taken	Undetermined. This is a framework guide made available to institutions that may wish to adopt it.
Standard application form included	Yes
Includes a schedule for revision	Yes

4. Drug Submission Guidelines for New Products, New Indications and New Formulations (USA)

WELLPOINT GUIDE

Date of publication	September 2005
Authors' affiliation	Wellpoint Pharmacy Management (US Insurance Company with more than 34 million insurance holders).
Authors' statement on conflict of interests	No
Primary aim	To provide a standardised guide for submissions requesting the introduction of new drugs in the company's healthcare coverage.
Recipients	Pharmaceutical Labs.
Scope of application of decisions taken	Patients/Individuals insured by Wellpoint.
Standard application form included	Yes
Includes a schedule for revision	No

5. National Institute for Clinical Excellence (NICE) Guidelines for Manufacturers and Sponsors (England and Wales)

NICE GUIDE

Date of publication	June 2001
Authors' affiliation	National Institute for Clinical Excellence.
Authors' statement on conflict of interests	No
Primary aim	To create a common framework for submissions regarding new health technologies, and to streamline identification of clinically and cost-effective technologies for the British healthcare system.
Recipients	Pharmaceutical Labs.
Scope of application of decisions taken	British Healthcare System (England and Wales).
Standard application form included	Yes
Includes a schedule for revision	Yes

6. Guidance to Manufacturers Notes for Completion of the New Product Assessment Form (Scotland)

SMC GUIDE

Date of publication	May 2006
Authors' affiliation	Scottish Medicines Consortium (Scottish Centre for Health Technology Assessment).
Authors' statement on conflict of interests	Yes
Primary aim	Guide for the pharmaceutical industry which includes precise and relevant information vis-à-vis new drug submissions.
Recipients	Pharmaceutical Labs
Scope of application of decisions taken	British Healthcare System (Scotland)
Standard application form included	Yes
Includes a schedule for revision	No

Below are four tables for comparison of more specific items, included (or not) in the main sections of each of the guidelines for new drugs' submissions, grouped according to the section in question.

Table 4. Items on General Information of the Drug/Disease as included in the Guides.

	PBAC	CDR	AMCP	WELL POINT	NICE	SMC
Pharmacological Group and action of drug	■	■	■	■		
Indications	■	■	■	■		■
Detailed treatment approach	■			■		
New concomitant treatments	■		■	■		
Concomitant treatments that will cease to be used	■		■	■		
Justified selection of main comparator	■	■	■	■	■	■
Comparative table new drug/comparator	■	■	■	■		
Epidemiological data			■	■	■	
Prevalence/incidence	■	■	■	■	■	■
General treatment approach/ scheme	■	■	■	■	■	■
Presentation and clinical progression	■		■	■	■	■
Socio-economic impact of the disease	■		■		■	
Description of sub-population groups eligible for treatment	■	■	■	■	■	■
Clinical, diagnostic or genetic markers for sub-population groups		■	■	■		■

Table 5. Items on Clinical Assessment included in the Guides.

	PBAC	CDR	AMCP	WELL POINT	NICE	SMC
Detailed reference search						
Clinical Trials' inclusion/exclusion criteria in submissions						
Trial design						
Description of randomisation process						
Inclusion/exclusion criteria for patients recruited for trials						
Patients' demographic profiles						
Patient follow-up (ITT analysis, withdrawals...)						
Clear differentiation of primary and secondary variables						
Rationale justifying selection of final variables						
Ditto for intermediate variables						
External validity of trials						
Adaptability of outcomes to the local setting						

Table 6. Items on Economic Assessment included in the Guides.

	PBAC	CDR	AMCP	WELL POINT	NICE	SMC
Type of preferential analysis defined						
Justification of assumptions						
Temporal horizon						
	PBAC	CDR	AMCP	WELL POINT	NICE	SMC
Costs included	Direct and Indiret cost	Direct and Indiret cost	Direct costs	Direct costs	Direct and Indiret cost	Direct costs
Systematic review of economic evidence						
Sensitivity analysis						
Pharmaco-economic modelling						
Incremental cost-effectiveness ratio						
Analysis of budgetary impacts						
Overall costs						
Number of patients to be treated						
Sub-population analysis						

Table 7. Other Aspects in the Guides.						
	PBAC	CDR	AMCP	WELL POINT	NICE	SMC
Final check-list	■	■	■			
Specific format for re-assessment	■	■				
Classification of requests	■	■				
Evidence scale for the studies analysed	■			■	■	
Glossary of terms	■	■	■			
Request of relevant clinical practice guides			■			

*In Tables 4, 5, 6 & 7, boxes in grey indicate that the guide includes the corresponding item/section.

Outcomes regarding identification of opportunities for improvement

In each of the studies and guides, we identified relevant aspects or issues that had not been included in GINF, while also homing in on how the items that are included in GINF are developed in the said guides. Starting from these key concepts, we identified categories classifying improvement opportunities. The categories are as follows:

- *Changes to the procedure:* Submission and assessment circuits, elective rejection of guides on account of completion of application forms, guidelines for streamlining the use of the Guide.
- *Changes to the overall structure of the guide:* preparing other products to facilitate submissions of the Guide, produce a digital format of the Guide, together with interactive aid tools, manuals for implementation, and training material for dissemination of the GINF methodology.
- *Changes to specific section in the current guide:* Introduction of new data on efficacy, effectiveness and safety, assessment of the internal validity of clinical trials, introduction of economic issues, broadening categories for classification of submissions.

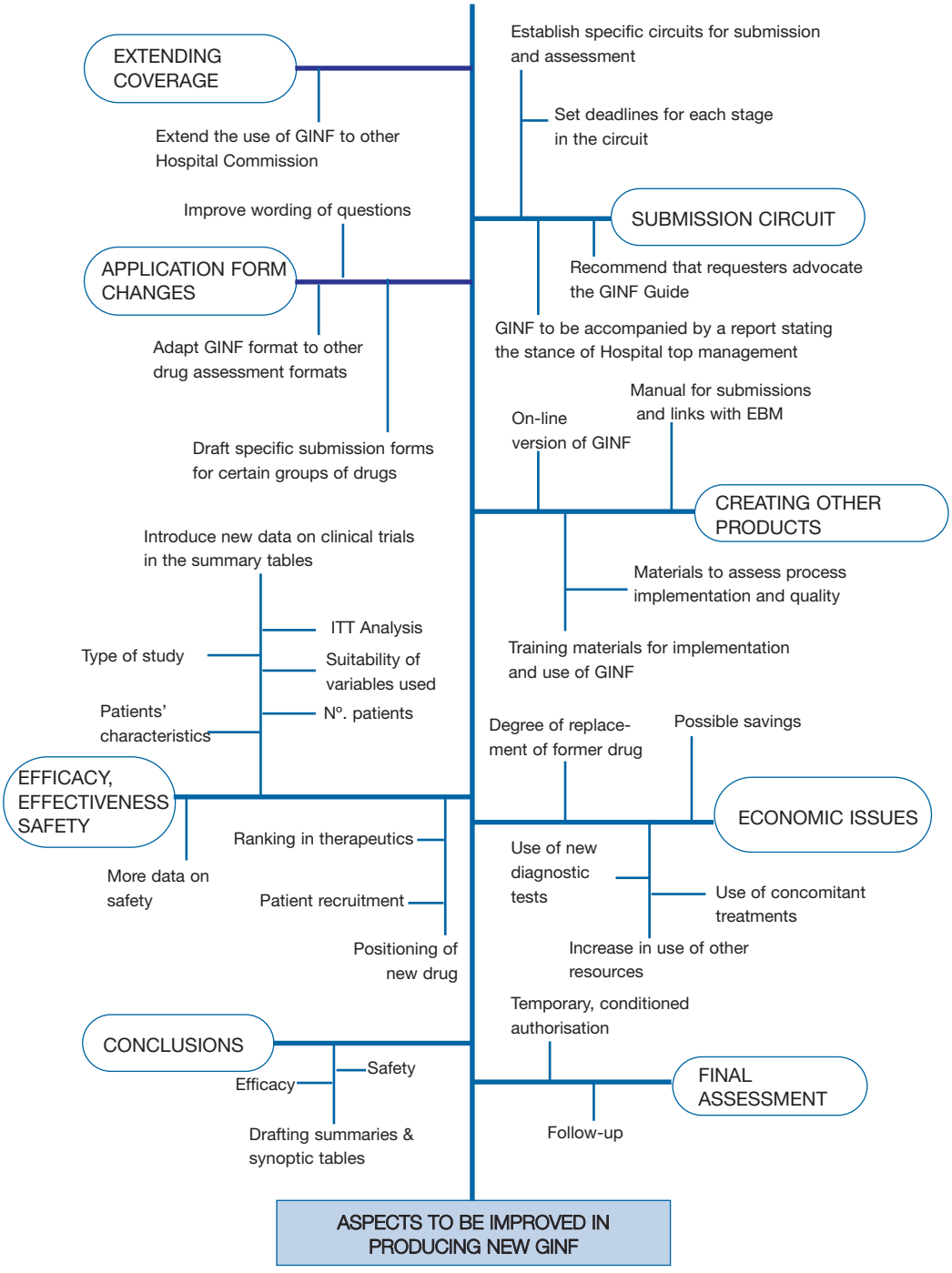
2.b.Hospitals' Survey

The hospitals surveyed proposed a total of 52 potential improvements which have an impact on working methodology, the overall structure of the guide, or specific sections. The main areas of improvement relate to the following:

- *Restrict or regulate access of Pharmaceutical Labs* to the GINF Guide, by rejecting submissions that have been prepared by the Pharmaceutical Industry and the introduction of a questionnaire on requesters' conflict of interests.
- *Implement measures for dissemination of the Guide and improve information on the Guide* by creating an easily accessible electronic version and by preparing training material on GINF methodology.
- *Introduce in the Guide* new *concepts for critical assessment* of the clinical trials presented to back the submissions.

Appendix IV provides a complete list of the opportunities for improvement identified through the literature review and the survey conducted with hospitals.

2.c Cause-Effect Diagram



Objective 3. To draft a new version of GINF

3.a Selecting final modifications. RAND/UCLA Methodology

3.a.1 List of scenarios

Scenarios were classified separately in chapters, according to the type of modification proposed and the section in GINF to be changed. Three different chapters were created, each with its own Excel® sheet, comprising a total of 46 scenarios distributed as indicated in the Table below:

CHAPTER	**Number of scenarios**
1 : Changes to the procedure	11
2 : Changes to the overall structure of the guide	10
3 : Changes to specific section in the current guide	25

Each of these three chapters was sub-divided according to the areas affected by modifications. The final drafting of the list of scenarios which was forwarded to expert panellists was structured as follows:

Chapter 1. Changes to the procedure
- Extending coverage. ..... item 3
- Submission circuit. ..... item 8

Chapter 2. Changes to the overall structure of the guide
- Modifications to GINF ..... item 3
- Creation of other products. ..... item 7

Chapter 3. Changes to specific section in the current guide
- Applicant's information and data of the drug ..... item 2
- Efficacy, effectiveness & safety ..... item 15
- Economic Assessment ..... item 6
- Conclusions ..... item 1
- Classifying requests/submissions ..... item 1

3.a.2 Appointing the experts' group

A total of twelve experts – nine men, three women – were appointed, from five different autonomous communities in Spain, namely Andalusia, Catalonia, the Balearic Islands, Valencia and Madrid. All have ample experience in management of the GINF tool since all belong – or have belonged in the past – to Hospital Pharmacy and Therapeutics Committees, or routinely use the Guide, as requesters.

Depending on their clinical field of expertise, the group was formed by:

- 6 specialists in Hospital Pharmacy.
- 2 specialists in Medical Oncology.
- 2 specialists in Internal Medicine.
- 1 specialist in Epidemiology.
- 1 specialist in Clinical Pharmacology.

Of the twelve experts selected, finally nine (Appendix V) gave ratings to the list of scenarios, while ten attended the meeting held on November 5th in Seville.

3.A.3 Assessment of scenarios

1st ROUND

Depending on the degree of agreement:

- 30 scenarios were classed as Agreement (A)
- 3 scenarios were classed as Disagreement (D)
- 13 scenarios were classed as Undetermined (U)

Depending on adequacy:

- 39 scenarios were classed as Appropriate (A)
- 1 scenario was classed as Inappropriate (I)
- 6 scenarios were classed as Uncertain (D)

With the results of voting during round 1, two working documents were drawn up for the moderators, along with an individual assessment sheet for each of the group's members.

Assessment of responses depending on each of the sections is detailed in the tables below. Horizontal rows show item number, according to the degree of agreement whereas columns show the degree of appropriateness.

Chapter 1. Changes to the procedure.

Extending coverage: 3 scenarios

	Appropriate	Uncertain	Inappropriate
Agreement	2		
Disagreement			
Undetermined		1	

Submission circuit: 8 scenarios

	Appropriate	Uncertain	Inappropriate
Agreement	3		
Disagreement		2	
Undetermined	2		1

Chapter 2. Changes to the overall structure of the guide.

Changes to the GINF: 3 scenarios

	Appropriate	Uncertain	Inappropriate
Agreement			
Disagreement		1	
Undetermined	2		

Creation of other products: 7 scenarios

	Appropriate	Uncertain	Inappropriate
Agreement	4		
Disagreement			
Undetermined	2	1	

Chapter 3. Changes to specific section in the current guide.

Applicant's information and data of the drug: 2 scenarios

	Appropriate	Uncertain	Inappropriate
Agreement	2		
Disagreement			
Undetermined			

Efficacy, effectiveness and safety: 14 scenarios

	Appropriate	Uncertain	Inappropriate
Agreement	10		
Disagreement			
Undetermined	3	1	

Economic assessment: 6 scenarios

	Appropriate	Uncertain	Inappropriate
Agreement	6		
Disagreement			
Undetermined			

Conclusions: 1 scenario

	Appropriate	Uncertain	Inappropriate
Agreement	1		
Disagreement			
Undetermined			

Classifying requests/submissions: 1 scenario

	Appropriate	Uncertain	Inappropriate
Agreement	1		
Disagreement			
Undetermined			

2nd ROUND

Meeting dynamics

During the meeting, group members debated the assessments, primarily focussing on those scenarios where disagreement arose during the first round of voting. In addition, a short discussion was held for each of the proposed scenarios. Group members also discussed the comments and/or suggestions put forward by experts during the first round.

Subsequently, after commenting on each chapter for the list of scenarios, the experts were invited to modify the original list of definitions. A new questionnaire was tabled, including all the new proposed modifications. During the same meeting, each scenario was rated once again individually, and classed as "appropriate", "uncertain" or "inappropriate", according to the scores delivered.

New scenarios

Eleven new scenarios emerged both as a result of the debate among experts and their comments during the first round. They were assigned to each of the different chapters as follows.

Chapter 1.
Request circuit..... 2 new scenarios

Chapter 3.
Applicant's information and data of the drug..... 2 new scenarios
Efficacy, effectiveness & safety ..... 4 new scenarios
Miscellaneous ..... 3 new scenarios

As a result of introducing these modifications and of re-formulating several scenarios of the first round, experts took a second vote on a final list including 53 scenarios.

The final results of this second round of votes were as follows:

As to the degree of agreement reached:

34 scenarios were classed as Agreement (**A**)
4 scenarios were classed as Disagreement (**D**)
15 scenarios were classed as Undetermined (**I**)

With regard to appropriateness:

41 scenarios were classed as appropriate (**A**)
5 scenarios were classed as Inappropriate (**I**)
7 scenarios were classed as Uncertain (**D**)

Below are indicated in detail for each scenario, the average score obtained, along with the degree of agreement and appropristeness. In addition, Appendix VI describes the number of participants that gave each of the scores.

Chapter 1. Changes to the procedure.

Extending coverage: 3 scenarios

Modification	Median score	Degree of Agreement	Degree of Appropriateness
A1: Include a recommendation for GINF to be implemented in Commissions on Infections and Anti-biotherapy, if the Commission is responsible for selecting anti-bacterial drugs.	8	Agreement	Appropriate
A2: Include a recommendation for GINF to be implemented in the Nutrition Commission so that it may be used in selecting artificial nutrition products.	6	Undetermined	Uncertain
A3: Include a recommendation for GINF to be implemented in other Hospital Commissions when they take part in decision-making on introducing drugs or healthcare products.	8	Agreement	Appropriate

Submissions/requests circuit: 8 scenarios

Modification	Median score	Degree of Agreement	Degree of Appropriateness
A4: Recommend that each hospital establish an appropriate circuit for GINF submissions and assessments.	9	Agreement	Appropriate
A5: Recommend that deadlines be established for each of the stages in the submission and assessment circuit.	8	Agreement	Appropriate
A6: Recommend refusal of GINF submissions that (THREE OPTONS)			
Option A. Application forms where at least 1 of the sections has not been completed.	2	Agreement	Appropriate
Option B. Those in which more than three sections have not been completed.	2	Undetermined	Inappropriate
Option C. Those in which one of the following sections in version 2.0 have not been completed: 1, 2, 3, 4, 6, 9 & 15	7	Agreement	Appropriate
Option D: Same as C but requesting help from the Commission and providing clinical trials.	8	Undetermined	Appropriate
Option E: Same as option C but not including the drug's technical sheet.	8	Undetermined	Appropriate
A7: Recommend that requesters defend their GINF submission before the Pharmacy and Therapeutics Committee(s).	7	Undetermined	Appropriate
A8: Recommend automatic rejection of any GINF submissions if there is unequivocal evidence that it has been completed by a Pharmaceutical Lab/Company.	7	Undetermined	Inappropriate
A9: Recommend that it is mandatory to accompany GINF with an assessment report by Managing Director or Financial Director when drugs may have considerable budgetary impacts.	3	Disagreement	Inappropriate

Chapter 2. Overall structural modifications

Modifications of GINF: 3 scenarios

Modification	Median score	Degree of Agreement	Degree of Appropriateness
B1: Harmonising the main sections of the GINF submissions guide and the GENESIS group assessment report, so that the questions are worded in the same way.	7	Agreement	Appropriate
B2: Simplify the grammar in some of the sentences of the guide, without deleting sections or changing the meaning of those sentences, indicating which sections have been modified.	7	Agreement	Appropriate
B3: Prepare a specific GINF guide for assessment of anti-neoplastic drugs, due to the stark difference between these and other drugs.	3	Agreement	Appropriate

Creation of other products: 7 scenarios

Modification	Median score	Degree of Agreement	Degree of Appropriateness
B4: Production of an explanatory annex guide, to explain more precisely how to complete the various sections, highlighting the importance of those that are most relevant for assessment, providing basic EBM concepts and tools for calculations.	8	Agreement	Appropriate
B5: Production of a GINF version in digital/ electronic format with interactive help tools for any sections that may require clarification, or those that are extremely relevant for assessment, or which may require calculations to be performed.	8	Agreement	Appropriate
B6: Production of a Manual for GINF Implementation explaining how to conduct the implementation process at each hospital.	7	Agreement	Appropriate
B7: Production of training material to be made available to GINF users, and dissemination of GINF methodology.	7	Agreement	Appropriate
B8: Production of material to assess the quality of GINF applications, to be made available to GINF users.	7	Agreement	Appropriate
B9: Production of material to assess requesters' satisfaction at any given hospital to be made available to GINF users.	7	Agreement	Appropriate
B10: Setting up a Web page containing all the documents stated above, along with relevant bibliography and other products which may be generated as a result of daily practice.	8	Agreement	Appropriate

Chapter 3. Specific structural modifications

Data on requester and drug: 4 scenarios

Modification	Median score	Degree of Agreement	Degree of Appropriateness
C1: Introduction of a brief questionnaire on potential conflict of interests of requesters.	9	Agreement	Appropriate
C2: Ask which sections of GINF have been completed with help from others.	9	Agreement	Appropriate
C3: Ask which sections/items have been complete by the pharmaceutical industry.	9	Agreement	Appropriate
C4: Introduction of a new section requesting a brief summary of the disease's epidemiology, especially with regard to relevant treatment aspects, and for those cases in which the introduction of a new drug may be especially relevant.	8	Agreement	Appropriate

Efficacy, effectiveness and safety: 15 scenarios

Modification	Median score	Degree of Agreement	Degree of Appropriateness
C5: Introduction, in the summary tables, of new data on the clinical trials used.			
C5A: Type of study	9	Undetermined	Appropriate
C5B: Number of patients	8	Undetermined	Appropriate
C5C: ITT Analysis	9	Undetermined	Appropriate
C5D: Study duration	7	Undetermined	Appropriate
C5F: Inclusion/exclusion criteria	8	Undetermined	Uncertain
C6: Quality assessment with closed items	8	Agreement	Appropriate
C6A: Relevance of standard treatment	5	Disagreement	Uncertain
C6B: Relevance of main variable	5	Disagreement	Uncertain

Efficacy, effectiveness and safety: 15 scenarios (Continuación)

Modification	Median score	Degree of Agreement	Degree of Appropriateness
C6C: Relevance of secondary variables.	4	Disagreement	Uncertain
C7: Introduction of a new line in the summary table for each trial to carry out rapid safety assessment.	8	Agreement	Appropriate
C8: Requesting clinical practice guides, published by official institutions, which include the use of the drug assessed for the indication requested.	8	Agreement	Appropriate
C9: Introduction of a new question regarding patients with special profiles who may benefit more especially from the requested treatment.	8	Agreement	Appropriate
C10: Criteria, diagnostic tests, additional tests which may be required for recruitment/follow-up of the proposed sub-patient groups.	8	Agreement	Appropriate
C11: Brief description of the ranking of the drug in therapeutics, should it achieve introduction. Line of treatment, prior treatments.	9	Agreement	Appropriate

Economic assessment: 6 scenarios

Modification	Median score	Degree of Agreement	Degree of Appropriateness
C12: Include a new question to address the degree of replacement of formerly used drug by new drug (Patients switch).	7	Agreement	Appropriate
C13: Prevalence and staging of the disease for which the new drug is requested by the hospital.	7	Undetermined	Appropriate
C14: Incidence (No. of new cases/year) and staging of the disease for which the new drug is requested by the hospital.	7	Agreement	Appropriate
C15: Include a new question regarding the use of new concomitant treatments, not used before.	8	Agreement	Appropriate
C16: Include a new question on the lesser use of concomitant treatments used before.	7	Agreement	Appropriate
C17: Structuring and broadening possible savings that may arise as a result of using the new drug.	7	Agreement	Appropriate

Conclusions: 1 scenario

Modification	Median score	Degree of Agreement	Degree of Appropriateness
C18: Introduction of a synoptic table presenting the conclusions of the request, in terms of efficacy, effectiveness, safety and cost.	6	Disagreement	Uncertain

Classification of requests/submissions: 1 scenario

Modification	Median score	Degree of Agreement	Degree of Appropriateness
C19: Introduction of a new classification category for requests/submissions which foresees review of the drug after an initial period of application.	8	Agreement	Appropriate

Miscellaneous: 3 scenarios

Modification	Median score	Degree of Agreement	Degree of Appropriateness
C20: Include a question on healthcare assistance impact at Primary Care level.	8	Agreement	Appropriate
C21: Include a question on repercussions in terms of Healthcare Service indicators.	4	Undetermined	Uncertain
C22: Include the current concept regarding off-label / compassionate use in the GINF guide	7	Undetermined	Appropriate

3.b To draft the new version of GINF

A new GINF version was drafted, including:

- The 23 scenarios under chapter 3, assessed as appropriate after the second round of voting.
- All the uncertain scenarios under chapter 3 save for that recommending the introduction of a synoptic summary table including all the conclusions.

Once the scenarios to be included were selected, one of the researchers drafted an up-dated version of GINF. Via a series of successive rounds, the remaining members of the research team critically assessed the new draft, and fine-tuned the definitive version. The new GINF includes all improvements, in terms of:

- Introducing new sections in the questionnaire.
- Drafting and including questions that were not contained in the guide before.
- Broadening the scope of questions.
- Some of the sections in the current questionnaire were re-drafted and changed.

So, the definitive version includes:

1. A new section at the beginning of GINF called "Applicants Data". Here are included questions regarding conflict of interests, plus an explicit question asking which part of GINF has been completed by the pharmaceutical industry.
2. A new question under section A: "Description of the drug and its indication(s)" where the requester is to provide a brief description of the natural history of the disease.
3. The summary table – containing the main features of the clinical trials put forward for assessment – has been modified.
4. The summary table on evidence has been broadened and modified. It now includes detailed assessment of any issues related to the internal validity of the trials and the new drug's safety, via a series of items, as follows:

Modifications with respect to version 2.0, sections 4 & 5, were carried out by grouping both together in a table, as shown below:

New GINF version

Author and year.					
Study design					
Randomized Yes No Open Yes No Placebo Yes No ITT Analysis Yes No	Base-line characteristics of patients:			Number of patients: % Withdrawals Duration of study:	
Treatment of active group		Treatment of control group			
Efficacy and Safety Outcomes					
Variables assessed in the study (indicate)	**Outcome for TREATMENT Group**	**Outcome for CONTROL Group**	**Absolute Difference**	**p**	
Primary efficacy endpoint					
Other efficacy endpoint					
Other efficacy endpoint					
Primary safety endpoint					
Other complications / adverse reactions					
Applicability / Relevance of outcomes					
❑ Is the control treatment the best therapeutic alternative available? ❑ Are dosage, posology and duration of treatment adequate? For the control group, are these the same as those routinely applied in clinical practice? ❑ Are the patients included in the trial similar to those in clinical practice?			Do you consider the endpoints measured to be clinically relevant? ❑ Is the magnitude of outcomes clinically relevant?		

5. In the section on "Effectiveness and Applicability" sub-sections on patient recruitment, diagnostic or additional tests and therapeutics ranking of the requested drug have been modified.
6. In the section on "Economic Assessment", a new question is included regarding possible repercussions in healthcare delivery at primary care level; changes have also been made to the number of target patients eligible for the new treatment. In addition, requesters are asked to provide more detail on estimates of possible savings should the new drug be introduced.
7. In the section on "Final Classification of Request", there is a new possibility of assigning the request to new categories which suggest re-evaluation at six months, or in the event that new evidence emerges.

The opportunities for improvement identified, which affected procedural modifications, and not the GINF format itself – that is, those pertaining to chapters 1 & 2 – have been incorporated in the form of Appendices containing recommendations for completing the Guide or as guidelines and future working proposals for the present report.

Once the new version of GINF was ready, Agencies and/or services involved in Assessment of Health Technologies in Spain were asked to review it externally. Following external review, the definitive version was drawn up, including a web format which enables working directly online, as well as an English language version.

Conclusions

Objective 1: To assess the degree of implementation in Andalusia

- The GINF guide has been implemented in the majority of public hospitals in Andalusia, only four years after its publication. It is used intensively both in terms of type and number of drugs to be introduced, depending of course on the precise activity of the Pharmacy and Therapeutics Committee (CFyT) of the hospital, and on complexity. This illustrates how flexible GINF is as a tool that can be applied regardless or the type of hospital of the volume of drugs under assessment.

- The main problem identified in hospitals using GINF is lack of knowledge on the part of users regarding the existence of later versions, and scant implementation of the most recent ones. This fact may be related to the high rate of local modifications detected, especially in sections regarding efficacy and effectiveness assessment. It could be argued that the absence of new versions has led to local modifications being made which, in general terms, tally with the modifications carried out institutionally on successive versions. This problem appears to be due to the lack of a sound strategy for scheduled implementation, dissemination and communication more than to deficiencies inherent to the Guide itself. It is therefore necessary to design implementation strategies to be rolled out following the publication of future versions. In addition, once implemented, it is recommended that each hospital define the circuits and establish deadlines for GINF submissions and assessment.

Objective 2: To identify opportunities to improve

- A considerable number of opportunities for improvement have been identified which fully justify up-dating GINF. The main modifications detected are related to specific, structural modifications to the questionnaire, especially in the section on efficacy, effectiveness and

safety. The guide should periodically be subject to reviews which take into account evidence-based research in the field, as well as data from implementation processes and/or legal and regulatory developments which may arise.

Objective 3: To draft a new version of GINF

- Implementation of GINF in other Hospital Quality Commissions is recommendable, when their decisions have to do with selection of drugs or healthcare products.

- The need to establish communication channels between the pharmaceutical industry and CFyTs through an appropriate mechanism appears to be blatantly clear. However, GINF was not designed as such; it was conceived as an educational instrument to promote the necessary dialogue between requesters and evaluators and hence there should be added focus on developing the mechanisms that facilitate and ensure that ultimate goal.

- An up-dated version of GINF has been produced which includes the changes that affect both the format of the questionnaire and its contents. This new Guide includes paper formats, in Adobe Acrobat documents, on-line electronic formats and an English language version of the pdf document.

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Guide for the Introduction of New Drugs in the Pharmaco-Therapeutics

Guide (GINF)

Version 3.0

Pharmacy and Therapeutics Commission
Hospital _____

APPLICATION FORM

WHAT IS THE APPLICATION FORM?

This questionnaire is used to request the introduction of a drug in a Hospital's Pharmacy and Therapeutics Guide.

The introduction of drugs in healthcare assistance delivery carries clinical, organizational and economic repercussions and hence it is required to be preceded by evidence-based assessment. Pharmacy and Therapeutics Commissions (CFyT) have the final say in terms of approval of the evaluation; however it is the requester's responsibility to make available to the Commission the necessary data, since it is the requester who is best acquainted with the medication in question.

Following this premise, this Guide has been conceived as an instrument to assist petitioners in compiling, in an orderly fashion, all the information required to ensure sound assessment of the drug. The role of evaluators, in this case, essentially involves helping physicians with management of the Guide, and to co-ordinate any number of requests regarding the same drug, that may have been put forward by various healthcare facilities.

This Guide has been developed using as a starting point the Guide for Decision-Making regarding the Acquisition of New Technologies in Andalusia - called as the GANT Guide – produced by the Andalusian Agency for Health Technology Assessment (AETSA).

RECOMMENDATIONS FOR COMPLETING THE APPLICATION FORM

1. The application form has been designed as an in-house document for Hospitals, to be used for communication between requester and the Pharmacy Commission. In the past, it has been noted that some GINFs have been completed by the drug manufacturer. Manufacturers may be a valuable source of information for the petitioner, but it is the petitioner who is responsible for assessing clinically useful information, and putting that data forward in this Guide.

2. The application form is available in paper format and electronically, accessible via the Hospital's intranet or by request to the Pharmacy Unit. If the paper format is used, the space provided in some of the sections may be insufficient. In this case, please provide any further information in the form of annexes.

3. It is important to fill- in the application form in the most thorough and detailed manner possible, using easily comprehensible language. Lack of information may prevent appropriate assessment of the request.

4. The application form has been conceived to assess a standard drug, so some of the questions may not be applicable. If the requester deems it appropriate, this may be stated in the relevant sections.

5. Some of the terms employed may be subject to several interpretations, or may seem ambiguous. In the event of doubt, petitioners should use the operational definition that they believe is most appropriate and specify this at the end of the application form in the form of final clarifications. If using acronyms, indicate the equivalence in full the first time they are used.

6. Some of the data requested may require a more detailed study, or they may not be available at the time of completing the application form. Requesters should explain this in an annex, putting forward a proposal to obtain the information or conduct the study.

Update of the Guide for the Introduction of New Drugs

REQUESTER

Information on the requester

Name:
Department:
Professional category:
The request is made:

- ❑ Individually
- ❑ Following consensus with peers in Department
- ❑ Following consensus with peers, and with the go ahead of the Head of Department

Indicate if you received external assistance to prepare this request:

- ❑ No
- ❑ Yes, from members of the Pharmacy and Therapeutics Commission
- ❑ Yes, from members of the Pharmacy Departament
- ❑ Yes, from the manufacturer (pharmaceutical laboratory)

If you responded affirmatively, for which sections precisely did you receive external assistance?

Statement of circumstances that may pose a potential conflict of interests:

1. Has the requester taken part in a clinical trial involving the requested drug?
   - ❑ YES
   - ❑ NO
2. Does the requester have a personal, commercial or professional relationship with the pharmaceutical laboratory that manufactured the requested drug?
   - ❑ YES
   - ❑ NO
3. Does the requester participate in a research project funded by the pharmaceutical laboratory that manufactured the requested drug?
   - ❑ YES
   - ❑ NO
4. Do you believe there are any other circumstances that may jeopardise your professional judgement?
   - ❑ YES
   - ❑ NO

If you have answered YES to any of the above, please be more specific.

Date of application: **Signature:**

A. DESCRIPTION AND INDICATION OF THE DRUG

THE DRUG

1. International Common Denomination (ICD), or generic name of active principle

2. 2. Is the drug being commercialised in Spain?
   - ❑ YES
   - ❑ NO

   Please specify the commercial presentations of the medication and the Pharmaceutical Company(s) that markets the drug (in the case of a international drug, specify which countries have it on the market)

3. Indication (s) for which the drug is requested in our hospital.

4. Therapeutic indications. [1]

5. Patients for whom the drug is requested are normally attended to ...

❑ ... Hospitalization / Emergency room

❑ ...At Hospitals/ Units outpatient facilities (or similar) / At home ...

❑ ... As out-patients. In this case, is the drug administered exclusively at hospital [2]
   - ❑ YES
   - ❑ NO

[1] The indications approved are listed on the drug's technical sheet. In the case of requesting a drug from abroad, list the indications approved in country of origin.

[2]The category "drug exclusively administered at hospital" **(H)** features in the drug's technical sheet.

6. Do you think that any other clinical unit/division, functional unit, or medical specialisation unit may be interested in using this drug? If so, which? Do you think the Pharmacy and Therapeutics Commission could contact anyone in particular for consultation on the introduction of the drug at our Hospital?

INDICATION

7. Please provide a brief description of the clinical problem to be addressed with the requested drug (incidence and prevalence, staging, progression, treatment sub-groups, survival, quality of life, etc.).

8. With which other drugs or alternative treatments and regimens is the indication - for which the new drug is requested - being treated?

   If there is a protocol or clinical practice guidelines available in writing at your Unit which includes the pharmacological treatments available for this particular indication, please attach a photocopy.

9. According to your own criteria, please describe the advantages posed by the new drug as opposed to other alternatives approved at present by the Pharmacy and Therapeutics Commission.

   ❑ Greater effectiveness

   ❑ Greater safety

   ❑ Enhances compliance/adherence

   ❑ Improves delivery: posology / pathway of administration.

   ❑ Others:

B. EFFICACY AND SAFETY

List below the clinical trials on which you base your request and which you consider of greater quality. Select **only** those which have been conducted to assess the indication for which you are requesting the drug. Please complete the table below. **Complete <u>one table for each</u> of the clinical trials selected.** Please attach a legible photocopy of each of the trials/studies.

Author and year.

Study design

Randomized	Yes	No	Base-line characteristics of patients:	Number of patients:
Open	Yes	No		% Withdrawals
Placebo	Yes	No		Duration of study:
ITT Analysis	Yes	No		

Treatment of active group	Treatment of control group

Efficacy and Safety Outcomes

Variables assessed in the study (indicate)	Outcome for TREATMENT Group	Outcome for CONTROL Group	Absolute Difference	p
Primary efficacy endpoint				
Other efficacy endpoint				
Other efficacy endpoint				
Primary safety endpoint				
Other complications / adverse reactions				

Applicability / Relevance of outcomes

❑ Is the control treatment the best therapeutic alternative available? ❑ Are dosage, posology and duration of treatment adequate? For the control group, are these the same as those routinely applied in clinical practice? ❑ Are the patients included in the trial similar to those in clinical practice?	Do you consider the endpoints measured to be clinically relevant? ❑ Is the magnitude of outcomes clinically relevant?

10. Are there any other studies – not clinical trials - that may contribute with information of interest, and which you may wish to put forward for any reason?

- ❑ Meta-analysis
- ❑ Systematic Review
- ❑ Clinical Practice Guidelines (official organisations)
- ❑ Observational Study
- ❑ Assessment conducted by official organisations
- ❑ Others.

Indicate the reference, provide a brief summary and explain why you believe this study is important for the assessment process.

C. EFFECTIVENESS AND APPLICABILITY

11. Do you think that the conclusions drawn by the clinical trials noted above can be extrapolated to habitual caring at our hospital? [3]

- ❑ YES
- ❑ NO

12. In your view, is there any sub-group of patients that may benefit more especially from the treatment requested?

13. Should the drug be introduced at our hospital, which would be its ranking in therapeutics?[4]

D. ECONOMIC ASSESSMENT

14. Are there any studies on economic assessment, such as cost-effectiveness, cost-utility, etc. for the requested drug? Please provide reference and attach a photocopy.

[3] In other words, are there any factors that may jeopardise the effectiveness of treatment? For instance, lack of diagnostic tests or measures to support patients, clinical or social characteristics that differ, in the clinical trials, from those of our own patients, learning curve effects, etc.?

[4] For instance, line of treatment proposed, clinical conditions to be met by candidates, rescue treatment, etc.

❑ YES
❑ NO.

REFERENCE(S)
1.
2.

15. For the proposed indication, and in your field of specialisation, please state whether you think the drug will

❑ Completely replace current treatment.
❑ Partially replace current treatment (some sub-groups of patients will benefit from the new drug, while others will continue with their usual treatment)
❑ Be added to the current treatment for the vast majority of patients.
❑ Be added to the current treatment for some patient sub-groups.

16. In the event of not achieving total replacement of current treatment, or if the new treatment can only be applied to certain patient sub-groups, which percentage of patients will use the new drug?

17. Which is the current prevalence and incidence of the clinical disease/condition for which this drug is indicated in our Hospital?

PREVALENCE (Total number of patients CURRENTLY eligible candidates to receiving this treatment at our hospital):

INCIDENCE (Nº. of new patients each year):

18. Please complete the table below[5]:

	Cost of treatment	**Difference(s) with respect to current treatment**
Current treatment		_____
Requested treatment		

[5] If drug is for chronic use, specify cost per month; if duration of treatment is highly variable, specify cost per day; in the case of chemotherapy, indicate the cost for entire treatment, etc.

19. Will the introduction of the new drug involve altering use of concomitant treatments? If the answer is affirmative, please elaborate and give more details

❑ YES.
❑ NO.

20. Which are the possible repercussions of introducing the drug in terms of prescriptions for outpatients (Primary Care, External Consultations, etc)?

21. If applicable, indicate and elaborate on the savings that could be made by introducing the new drug:

❑ In medication
❑ In duration of hospital stays
❑ Other healthcare costs
❑ Non-healthcare related costs

CLASSIFICATION OF REQUESTS

Requests will be classified according to the procedure described below, following a decision based on the contents of the table featuring in the next page.

1. Total absence of data or insufficient data in the most important sections (questions 1, 2, 3, 17 and/or Table in Section B) may be considered a reason for rejection, given that this implies the absence of essential requirement(s) and virtually forces ruling out the request, thus including it under Category A-1. If the request is considered relevant, the Commission may ask for more information, or suggest the necessary modifications so as to ensure that the basic requirements are met, for the request to be re-evaluated.

2. If the indication for which the drug is requested is treated in the outpatient setting, the drug is not for Hospital use (question 5) and does not require delivery during hospitalisation, the request will be classified under Category A-2.

3. If the questions regarding efficacy, effectiveness and safety (Section B) lack the support of clinical trials, or are based on trials that pose considerable methodological problems, or trials with clinically irrelevant outcomes, the request will be classified under Category B-1.

4. If the questions regarding efficacy, effectiveness and safety (Section B) are based on good quality clinical trials, with clinically relevant outcomes, that report that the new drug has a worse efficacy/safety profile as opposed to the currently existing alternative at the hospital, the request will be classified under Category B-2.

5. If the questions regarding efficacy, effectiveness and safety (Section B) lack the necessary criteria to make a choice between the new drug and alternative treatments, and there is no difference in the cost-effectiveness ratio, the new drug may be considered as a therapeutic equivalent to existing treatment options and it will be classified under Category C. This decision may be due to two circumstances:
   - There are clinical trials that compare the drug with the alternative treatment, which demonstrate that they are therapeutically equivalent.
   - OR there are clinically relevant outcomes from parallel trials for each alternative, comparing with a third option whose methodology, target population in the study, outcome variable and other relevant characteristics are similar in nature.

Market conditions and the implications for hospital management that may arise from the introduction (or not) of a new equivalent alternative will lead, depending on each case, to classification under Category C-1 or Category C-2.

6. If clinical trial outcomes on efficacy, effectiveness and safety present significant clinical advantages as opposed to the therapeutic option currently available at the hospital, OR if the cost-effectiveness ratio is clearly favourable, the drug will be included in the Guide, and the alternative drug may or may not be withdrawn.

7. Classification under Category D or E will depend on (i) the need to prevent adverse effects, (ii) guarantee that the new drug will only be administered by the most experienced clinicians; (iii) ensure that only those patient sub-groups for which the drug has been subject to trials are treated with it; (iv) or any other circumstance that may ensure the most efficient use of the drug.

   Bearing in mind the criteria above, the Pharmacy and Therapeutics Commission will classify the drug under one of the following categories and these will feature explicitly in the minutes of the Commission's meeting.

A- THE DRUG IS NOT INCLUDED IN THE Pharmaco-Therapeutics Guide (PTG) due to the absence of basic requirements.

A-1- IT IS NOT INCLUDED IN PTG because it is impossible to assess given that the information provided in the submission is insufficient.

A-2- IT IS NOT INCLUDED IN PTG because the drug is indicated for treatment of a pathology that does not require assistance via hospitalisation or delivery at day healthcare facilities.

B-1- IT IS NOT INCLUDED IN PTG given that there is insufficient evidence to suggest a better efficacy/safety ratio compared with the treatment currently delivered at the hospital.

B-2- IT IS NOT INCLUDED IN PTG because existing evidence suggests that the efficacy/safety profile is worse than that of the treatment currently delivered at the hospital.

C-1--The drug's efficacy and safety are comparable to existing alternatives for the proposed indications. Moreover, it does not improve the cost-effectiveness ratio, or improve organisation or management of services. It is hence NOT INCLUDED IN PTG.

C-2- The efficacy and safety of the drug is comparable to existing alternatives for the proposed indications. Moreover it does not improve the cost-effectiveness ratio. However, its introduction to purchasing procedures could pose managerial advantages.
Hence, IT IS INCLUDED IN THE GUIDE AS A THERAPEUTIC EQUIVALENT to the existing options and the precise drug in place at any given time will be that selected as a result of public purchase procedures.

D.1- IT IS INCLUDED IN PTG <u>with</u> specific recommendations.

D.2 IT IS INCLUDED IN PTG <u>with</u> specific recommendations and with a commitment to re-assess the drug after an initial period of use, to be set by the Pharmacy and Therapeutics Commission.

E.- IT IS INCLUDED IN PTG <u>without</u> specific recommendations.

Appendices

Appendix I: Telephone survey

GINF PROJECT

GINF for telephone interviews:

Name and surname of interviewee:

Status of interviewee:
Head of Unit, Chief of Section, Specialist Physician, others.....

Member of the Pharmacy and Therapeutics Commission (CFyT):
a) Yes
b) No

Information on the Hospital:

a) Type: □ The biggest hospital □ Specialised □ The smallest hospital
b) No. of beds:
c) Training of Resident Pharmaceutical Interns: □ Yes □ No
d) Province:

1. Does the Pharmacy and Therapeutics Commission currently use the GINF Guide?

   a) Yes (Question 2)
   b) No (Ask which document they use)

2. In which year was the Guide implemented?

   2002
   2003
   2004
   2005

3. Have you used different versions of the GINF Guide?

    a) Yes
    b) No

4. Which version of GINF is currently in use?

    a) 1.0
    b.) 1.1
    c.) 1.2
    d.) 1.3
    e.) 1.4
    f.) 2.0
    g.) Other/Unknown

5. Have you modified or made specific alterations to the official version so as to adapt it to your hospital?

    a) Yes
    b) No

6. In the event of alternations, which sections were modified?

    a) Information on the drug
    b) Efficacy, effectiveness and safety
    c) Economic assessment
    d) Classification of requests

7. Do you use the GINF Guide for introduction of all drugs?

    a) Yes
    b) No

8. In the event of partial use of GINF, which are the criteria used to request (or not) completion of GINF?

    a) Cost
    b) Therapy Group
    c) Others .....

9. How many drugs were assessed by the Pharmacy and Therapeutics Commission during 2005? In how many cases was the GINF Guide used?

10. Do you consider the GINF Guide to be a useful tool?

    a.) Yes, very useful.
    b.) Yes, fairly useful.
    c.) Yes, useful sometimes.
    d.) No

11. How frequently do you think the GINF Guide is used for decision-making regarding new drugs?

    a) Very frequently
    b) Frequently
    c) Average frequency
    d) Low frequency
    e) Very low frequency

12. Which improvements have you made, or which would you introduce?

Appendix II: Andalusian hospitals surveyed

The biggest Hospitals
Virgen del Rocío (Seville)
Virgen Macarena (Seville)
Virgen de las Nieves (Granada)
Reina Sofía (Cordoba)
The biggest hospital in Malaga
Specialised Hospitals
Valme (Seville)
Puerta del Mar (Cadiz)
Jerez de la Frontera (Cadiz)
Puerto Real (Cadiz)
San Cecilio (Granada)
Virgen de la Victoria (Malaga)
Juan Ramón Jiménez (Huelva)
Complejo Hospitalario de Jaén (Jaen)
Torrecárdenas (Almeria)
The smallest Hospitals I
Infanta Margarita - Cabra (Cordoba)
Public Company- Costa del Sol Hospital - Marbella (Malaga)
Infanta Elena (Huelva)
San Agustín - Linares (Jaen)
San Juan de la Cruz - Úbeda (Jaen)
The smallest Hospitals II
Virgen de la Merced-Osuna Healthcare Management District- (Seville)
La Línea de la Concepción - Campo de Gibraltar Healthcare Management District - (Cadiz)
Baza (Granada)
Santa Ana - Motril (Granada)
Valle de los Pedroches - North Cordoba Healthcare Management District – Pozoblanco (Cordoba)
Antequera (Malaga)
Serranía de Ronda (Malaga)
Axarquía - Vélez-Málaga (Malaga)
La Inmaculada - Huércal-Overa (Almeria)
Public Company Poniente Hospital-El Ejido (Almeria)

Appendix III: Hospitals surveyed in the rest of Spain

1. TXAGORRITXU HOSPITAL. VITORIA. ÁLAVA
2. CORPORACIÓN PARC TAULÍ. SABADEL. BARCELONA
3. DE CRUCES HOSPITAL. GALDAKAO. BILBAO
4. LA MANCHA CENTRO HOSPITAL. CIUDAD REAL
5. GUADALAJARA UNIVERSITY HOSPITAL. GUADALAJARA
6. MÓSTOLES GENERAL HOSPITAL. MÓSTOLES. MADRID
7. SON DURETA UNIVERSITY HOSPITAL. PALMA DE MALLORCA
8. SON LLÁTZER HOSPITAL. PALMA DE MALLORCA
9. NUESTRA SEÑORA DE LA CANDELARIA HOSPITAL. SANTA CRUZ DE TENERIFE
10. VIRGEN DE LA SALUD HOSPITAL. TOLEDO

Appendix IV: Joint list of opportunities for improvement identified via surveys and literature review

Below is a joint list of opportunities, grouped under three chapters:

1- Changes to the procedure.
2- Changes to the overall structure of the guide.
3- Changes to specific section in the current guide

CHAPTER 1: CHANGES TO THE PROCEDURE

Extending Coverage

- Include a recommendation for implementation of GINF in Commissions on Infections and Antibiotherapy, if the commission is responsible for introducing anti-bacterial drugs.
- Include a recommendation for implementation of GINF in the Nutrition Commission, so that it is used when selecting artificial nutrition products.
- Include a recommendation for implementation of GINF in other hospital commissions, when they take part in decision-making regarding drugs or healthcare products.

Submission Circuit

- Recommend that each hospital establish an appropriate circuit for GINF submissions and assessment, and that it be made explicit to all clinicians.
- Recommend that dead-lines be set for each stage in the GINF submissions and assessment circuit, and that the Pharmacy and Therapeutics Commission commit to complying with them.
- Recommend that no GINF submissions be admitted for assessment if there are gaps in application form completion; there are three different options to follow, depending on which sections are mandatory and have not been completed:

  Option A. At least one of the sections has not been completed.

  Option B. More than three sections have not been completed.

  Option C. One of the following sections of version 2.0 has not been completed: 1, 2, 3, 4, 6, 9 & 15.

- Recommend that the petitioner defend the GINF submission by delivering a brief oral presentation to the Pharmacy and Therapeutics Commission.
- If there is unequivocal evidence to suggest that the GINF submission has been prepared by a Pharmaceutical Company, recommend automatic rejection.
- Recommend that it is mandatory to accompany GINF with an assessment report stating the stance of the Hospital's Managing Director or Head of Finance when the proposed drug is foreseen to have a significant budgetary impact.

CHAPTER 2: CHANGES TO THE OVERALL STRUCTURE OF THE GUIDE

Modifications to the GINF

- Harmonising the main sections of GINF submissions guidelines and the assessment report published by the GENESIS Group (Group for Assessment of Innovation, Standardisation and Research in Drug Selection) to ensure that questions are worded in the same way and that petitioner's responses can be transferred directly to the GENESIS format.
- Grammatical simplification of some of the sentences in the Guide, without deleting sections or changing the context/meaning of sentences or sections.
- Producing a specific GINF Guide to assess anti-neoplastic drugs given the stark difference between these and other drugs.

Creation of other Products

- Preparation of an explanatory guide (as an annex) describing how to complete the application form and the various sections correctly, highlighting the importance of the most important sections in terms of assessment, providing basic EBM concepts (efficacy, effectiveness, ITT, NNT...) and the necessary tools for calculations to be made.
- Production of an electronic format for GINF, with interactive aid available for any sections that may require clarification, or which are highly relevant for assessment of the drug, or those that call for calculations to be made.
- Production of a Manual for GINF Implementation that includes the best evidence on how to conduct the implementation process in a hospital.

- Preparation of training material to be made available to GINF users, and also for dissemination of GINF methodology – e.g. ppt. sessions, examples of GINF models, cases and work-shop materials.
- Preparation of material to assess the quality of a GINF requesting process - to be made available to GINF users – drawing from the experience gained at Virgen del Rocio University Hospital in previous assessment processes.
- Preparation of material to assess the satisfaction of petitioners at any given hospital also to be made available to GINF users.
- Setting-up a Web Page containing all the documents/currently described above, along with relevant bibliography and other products that are currently being produced.

CHAPTER 3: CHANGES TO SPECIFIC SECTION IN THE CURRENT GUIDE

Applicant's information and data on the drug

- Introduction of a brief application form regarding potential conflict of interests affecting petitioners.
- Introduction of a new section requesting a brief summary of the epidemiology of the disease for which the new drug is requested, placing special emphasis on issues regarding treatment of the disease, and on how switching to or introducing the new drug may be especially relevant.

Efficacy, effectiveness and safety

- Introduction of new information in the tables summarising the clinical trials used to support the request:

    1. 1.Type of study
    2. No. of patients
    3. ITT Analysis
    4. Study duration
    5. Inclusion/exclusion criteria
    6. Patient's base-line characteristics

- Introduction of a new line in the evidence summary table for each clinical trial, in which the requester should provide a brief qualitative assessment of the issues that (s)he wishes to emphasise for each of the trials.

- Introduction of a new line in the evidence summary table for each clinical trial, in which the requester should provide a brief qualitative assessment on safety.
- Requesting clinical practice guidelines published by official organisations, which include the use of an assessed drug for the same indication as requested here.
- Brief justification regarding the suitability of the standard treatment used in the clinical trials backing the request.
- Brief justification regarding relevance of the primary variable used in the clinical trials backing the submission.
- Introduction of a new question regarding secondary or intermediate variables used in the trials, which may be relevant for assessment of the drug.
- Introduction of a new question regarding patients with special features who may benefit more especially from the requested treatment.
- Criteria, diagnostic or additional tests that may be required for recruitment/ follow-up of the proposed patient sub-groups.
- Brief description of the new drug's ranking in therapeutics should it be introduced. Line of treatment, prior treatments, and rescue treatments.

Economic assessment

- To include a new question on the degree of replacement of the previously used drug by the new drug (Patients switch).
- Prevalence of the disease /disease staging for which the new drug is requested at the hospital.
- Incidence (No. of new cases/year) of the disease/staging of the disease for which the new drug is requested at the hospital (Note: this and the preceding question would substitute the current question regarding number of foreseeable patients).

* (NOTE: the two latter questions would replace the current question regarding the number of foreseeable patients).

- To include a new question regarding use of new concomitant treatments not applied before.
- To include a question on the lesser use of concomitant treatments applied previously.

- Structuring and broadening the possible savings that could be made by using the new drug (NOTE: this question would refer to any costs, different to medication costs, which would be avoided). (C18)

Conclusions

- Introduction of a synoptic table containing conclusions drawn from the request, regarding efficacy, effectiveness, safety and cost. (C19)

Classification of requests

- Introduction of a new category for submission classification that foresees reviewing the drug after an initial period of use.

Appendix V. Participants in the experts' panel

Name	Position / Job titles
Mariano D. Aguayo Canela	Head of Internal Medicine Unit at Virgen Macarena University Hospital in Seville.
Joan Bautista Altimiras Ruiz	Head of Pharmacy and President of the Pharmacy and Therapeutics Institutional Commission at Parc Taulí Hospital Sabadell.
Mª Dolores Bejarano Rojas	Head of the Pharmaceutical Supplies Department. Central Services at the Andalusian Health Service. Seville.
José Cabeza Barrera	Head of Pharmacy. Clinical Hospital San Cecilio. Granada.
José Ramón del Prado Llergo	Head of Pharmacy. Reina Sofía University Hospital. Cordoba.
Salvador Peiró	Professor at the Health Sciences School in Valencia.
Francesc Puigventos Latorre	Responsible for the GENESIS Group. Secretary of the Pharmacy Commission at Son Dureta University Hospital, Palma Mallorca
Teresa Requena Cartula	Specialist Physician, Hospital Pharmacy Unit, La Paz University Hospital. Ministry for Health and Consumer Affairs, Madrid.
José Manuel Varela Aguilar	Specialist Physician, Internal Medicine Unit at Virgen del Rocío University Hospital in Seville. Group for Rational Use of Drugs (RUD) at the Andalusian Health Service's Central Services.

Appendix VI. Summarised assessment form 2nd Round

CHAPTER 1: CHANGES TO THE PROCEDURE

EXTENDING COVERAGE	Score											
Include a recommendation for implementation of GINF in Commissions on Infections and Anti-biotherapy if they are involved in selection of antibacterial drugs.	0	0	0	0	0	0	1	2	6			
	1	2	3	4	5	6	7	8	9	*9*	*A*	*A*
Include a recommendation for implementation of GINF in the Nutrition Commission so that they use the Guide when selecting artificial nutrition products	0	0	2	0	1	2	3	1	0			
	1	2	3	4	5	6	7	8	9	*6*	*U*	*D*
Include a recommendation for implementation of GINF in other hospital commissions if they take part in decision-making on introduction of drugs or healthcare products.	0	0	0	0	0	0	2	5	2			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*

REQUEST CIRCUIT	Score											
Recommend that each hospital establish an appropriate circuit for GINF request and assessment, and that it be made explicit to all clinicians.	0 1	0 2	0 3	0 4	0 5	0 6	0 7	2 8	7 9	*9*	*A*	*A*
Recommend that deadlines be established for each of the stages in the request and assessment circuit and that the Pharmacy and Therapeutics Commission remain committed to compliance with the deadlines.	0 1	0 2	0 3	0 4	0 5	0 6	2 7	3 8	4 9	*8*	*A*	*A*
Recommend that GINF which have not been completed totally, or which have gaps, be rejected: (THREE OPTIONS) (Note: this would alter option A-1 in final classification)												
Option A. At least one of the sections has not been completed.	2 1	3 2	4 3	0 4	0 5	0 6	0 7	0 8	0 9	*2*	*A*	*I*
Option B. More than three sections have not been completed.	1 1	4 2	1 3	0 4	0 5	1 6	1 7	1 8	0 9	*2*	*U*	*I*
Option C. One of the following sections, under version 2.0, have not been completed: 1, 2, 3, 4, 6, 9 & 15	0 1	0 2	1 3	0 4	2 5	0 6	2 7	2 8	1 9	*7*	*U*	*A*
Option D. Same as Option C provided that assistance has not been requested from the Pharmacy and Therapeutics Commission, and that articles are not attached to the request.	0 1	0 2	0 3	1 4	1 5	0 6	2 7	2 8	3 9	*8*	*A*	*A*
Option E. Same as Option C but not including the technical sheet.	0 1	1 2	1 3	0 4	0 5	1 6	1 7	3 8	2 9	*8*	*U*	*A*

Recommend that the petitioner defend his/her GINF request by delivering a brief oral presentation to the Pharmacy and Therapeutics Commission.	0	0	0	0	2	2	2	0	3			
	1	2	3	4	5	6	7	8	9	*7*	*U*	*A*
If there is unequivocal evidence that the GINF has been completed by a Pharmaceutical /Lab, recommend automatic rejection of the request.	0	2	4	1	1	1	1	0	0			
	1	2	3	4	5	6	7	8	9	*3*	*U*	*I*
Recommend that it is mandatory to accompany GINF with an assessment report stating the position of the Hospital's Managing Director or Head of Finance, when the drug in question may have considerable budgetary impacts.	0	3	4	1	0	1	0	1	0			
	1	2	3	4	5	6	7	8	9	*3*	*A*	*I*

CHAPTER 2: CHANGES TO THE OVERALL STRUCTURE OF THE GUIDE

MODIFICATIONS TO THE GINF	Score											
Harmonising the main sections of the GINF request Guide and the assessment report released by the GENESIS Group (Group for Assessment of Innovation, Standardisation and Research in Drug Selection), so that questions are worded in the same way and to ensure that the requester's responses can be directly transferred to the GENESIS format.	1	0	1	0	0	0	4	3	0			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*
Simplify the grammar of some of the sentences in the Guide, without deleting sections or changing the meaning of the sentences. Please INDICATE WHICH SECTIONS SHOULD BE MODIFIED. Please REFRAIN FROM PROPOSING PRECISE WORDING.	0	0	0	0	1	1	4	3	0			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*
Production of a specific GINF Guide for assessment of anti-neoplastic drugs given the stark difference between these and other drugs.	1	0	7	0	0	0	1	0	0			
	1	2	3	4	5	6	7	8	9	*3*	*A*	*I*

CREATION OF OTHER PRODUCTS	Score											
Producing an explanatory guide (as an annex) describing more precisely how to complete the various sections, underlining the importance of the most relevant sections for assessment, providing basic EBM concepts (efficacy, effectiveness, ITT, NNT…) and the necessary tools for calculations to be made	0	0	0	0	1	1	2	2	3			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*
Production of a specific GINF Guide for assessment of anti-neoplastic drugs given the stark difference between these and other drugs.	0	0	0	0	1	0	1	3	4			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*
Producing a Manual for GINF Implementation, that includes the best possible evidence on how to conduct the implementation process in a hospital.	0	0	0	0	1	1	7	0	0			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*
Preparing training materials, to be made available to GINF users, for dissemination of GINF methodology – e.g. ppt sessions, examples of GINF models, cases and workshop material.	0	0	0	0	1	1	4	2	1			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*
Preparing material to assess the quality of the GINF request process, to be made available to users, on the basis of the experience gained by the Virgen del Rocio University Hospital with prior assessments.	0	0	0	0	0	0	7	2	0			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*
Preparing material to assess the satisfaction of petitioners in a given hospital, also to be made available to GINF users.	0	0	0	0	1	1	6	0	1			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*

Setting-up a web page with all the above mentioned products, along with relevant bibliography and other products which may emerge as a result of daily practice.	0	0	0	0	1	1	6	0	1			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*

CHAPTER 3: CHANGES TO SPECIFIC SECTION IN THE CURRENT GUIDE

Section to be modified: Information on the requester and on the drug

Introduction of a brief questionnaire regarding any potential conflict of interests affecting petitioners	0	0	0	0	0	1	2	0	6			
	1	2	3	4	5	6	7	8	9	*9*	*A*	*A*
Enquire about which sections have been completed with external assistance.	0	0	0	0	0	1	3	3	2			
	1	2	3	4	5	6	7	8	9	*9*	*A*	*A*
Questionnaire regarding precise sections completed by the Pharmaceutical Industry.	1	0	0	0	0	0	1	1	5			
	1	2	3	4	5	6	7	8	9	*9*	*A*	*A*
Introduction of a new section requesting a brief summary on the epidemiology of the disease for which the new drug is requested, placing special emphasis on treatment aspects of the disease, and any issues of special relevance regarding the switch to or introduction of the new drug	0	0	0	0	0	0	1	7	1			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*

Section to be modified: Efficacy, Effectiveness and Safety

Introduction of new information in the summary tables containing information on the clinical trials backing the request												
Type of study	0 1	0 2	0 3	0 4	3 5	0 6	0 7	2 8	4 9	*8*	*U*	*A*
Nº. of patients	0 1	0 2	0 3	0 4	3 5	0 6	0 7	2 8	4 9	*8*	*U*	*A*
ITT Analysis	0 1	0 2	0 3	1 4	2 5	1 6	1 7	2 8	2 9	*7*	*U*	*A*
Study duration	0 1	0 2	0 3	0 4	2 5	1 6	1 7	1 8	4 9	*8*	*U*	*A*
Inclusion/exclusion criteria	0 1	0 2	1 3	1 4	2 5	1 6	3 7	0 8	1 9	*6*	*U*	*D*
Patients' base-line characteristics	0 1	0 2	0 3	1 4	2 5	1 6	2 7	2 8	1 9	*7*	*U*	*A*
For each clinical trial, include a quality assessment with closed items, and YES or NO options.	1 1	0 2	0 3	0 4	0 5	0 6	1 7	6 8	2 9	*8*	*A*	*A*
Are the standard treatments used in the clinical trials relevant?	1 1	0 2	2 3	1 4	1 5	1 6	1 7	1 8	1 9	*5*	*D*	*D*
Are the variables used relevant?	1 1	0 2	2 3	2 4	0 5	0 6	1 7	3 8	0 9	*4*	*D*	*D*
Are the intermediate variables relevant?	1 1	0 2	3 3	1 4	0 5	1 6	1 7	2 8	0 9	*4*	*D*	*D*
Introduction of a new line in the table summarising evidence for each clinical trial, in which the petitioner should provide a **brief assessment on safety**	0 1	0 2	0 3	0 4	1 5	1 6	2 7	3 8	2 9	*8*	*A*	*A*
Introduction of a new line in the table summarising evidence for each clinical trial, in which the petitioner should provide a **brief assessment on safety**	0 1	1 2	0 3	0 4	0 5	0 6	3 7	2 8	3 9	*8*	*A*	*A*

Request Clinical Practice Guidelines published by official organisations, which include usage of the assessed drug for the indication requested here.	0	0	0	0	0	1	3	3	2			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*
Introduction of a new question on patients with special characteristics who may benefit more especially from the requested treatment.	0	0	0	0	0	1	0	4	4			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*
Criteria, diagnostic or additional tests that may be required for the recruitment/follow-up of proposed patient sub-groups.	0	0	0	0	0	2	1	2	4			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*
Brief description of the therapeutic ranking of the new drug, should it be introduced. Line of treatment, prior treatments, and rescue treatments.	0	0	0	0	0	0	1	2	6			
	1	2	3	4	5	6	7	8	9	*9*	*A*	*A*

Section to be modified: Economic assessment

Include a new question regarding the degree of replacement of a previously used drug by the new drug (Patients switch).	0	0	0	0	0	1	4	2	2			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*
Prevalence of the disease / disease staging for which the new drug is requested in the hospital (NOTE: this and the preceding questions, would replace the current question regarding number of foreseeable patients).	1	0	0	0	0	0	5	2	1			
	1	2	3	4	5	6	7	8	9	*7*		*A*

Incidence (No. of new cases/year) of the disease/disease staging for which the new drug is requested in the hospital (NOTE: this and the preceding questions, would replace the current question regarding number of foreseeable patients).	1	0	0	0	0	0	2	4	2			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*
Include a new question on use of new concomitant treatments not applied previously.	0	0	0	1	1	0	1	2	4			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*
Include a new question on the lesser use of concomitant treatments used previously (NOTE: this question refers to avoided medication costs)	0	0	1	0	0	1	3	0	4			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*
Structuring and extending the possible savings that could be made by introducing the new drug (NOTE: this question refers to avoided costs, other than medication costs)	0	0	1	0	0	1	4	2	1			
	1	2	3	4	5	6	7	8	9	*7*	*A*	*A*

Section to be modified: Conclusions

Introduction of a synoptic table containing the conclusions of the request in terms of efficacy, effectiveness, safety and cost	0	0	3	0	1	2	2	1	0			
	1	2	3	4	5	6	7	8	9	*6*	*D*	*D*

Section to be modified: Classification of requests

Introduction of a synoptic table containing the conclusions of the submission in terms of efficacy, effectiveness, safety and cost.	0	0	0	0	0	0	2	4	3			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*

Section to be modified: Others

Introduction of a new question regarding the impact of the new drug in terms of health assistance delivery at primary care level.	0	0	1	0	0	0	0	5	3			
	1	2	3	4	5	6	7	8	9	*8*	*A*	*A*
Same as above, but also addressing impact on Health Service indicators.	0	2	2	1	2	0	0	1	1			
	1	2	3	4	5	6	7	8	9	*4*	*U*	*D*
Include the current OFF-LABEL concept in the GINF Guide.	0	1	1	0	1	1	3	1	1			
	1	2	3	4	5	6	7	8	9	*7*	*U*	*A*

[1] The last box in blue, far right of the score scale, contains the median calculated for each scenario.

[2] The first box with a letter, next to the median, contains letters A, D or U, depending on whether that particular scenario obtained Agreement, Disagreement or was classed as Undetermined by the group of experts.

[3] The next box, with letters in red, contains letters A, D or I if that particular scenario was classed as Appropriate, Uncertain or Inappropriate, respectively.

[4] The area in yellow shows the summary of votes from all panel experts for that given scenario.

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