

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 1

1. **General instructions for submission of a request to include a pharmaceutical product in the health services “basket”:**

- 1.1 A request to include a pharmaceutical product in the national list of health services (“basket”) will include a comprehensive data file which will be submitted to the Pharmacoepidemiology and Pharmacoeconomics Department at the Pharmaceutical Administration of the Ministry of Health, according to the guidelines detailed herewith.
- 1.2 One data file will be submitted for all dosage forms, for all strengths and approved indications of the pharmaceutical product.
- 1.3 The data file will be submitted by the appointed pharmacist of the license holder of the pharmaceutical product.
- 1.4 All data and references will be in Hebrew and/or English. Official documents should be submitted in their original language. If the submission is only in English please attach a Hebrew translation of the summaries of parts II and III (see section 3.1.6 and 3.1.7).
- 1.5 Submission of the file will be submitted also on electronic media.
- 1.6 Inclusion of a pharmaceutical product in the health services basket is done on the basis of a predefined budget, according to decisions made by the public committee for the update of the basket appointed by the Minister of Health. The Pharmacoepidemiology and Pharmacoeconomics Department will consider each application and after assessment will pass its recommendations to the appropriate authorities. Therefore, a complete and detailed request does not guarantee the requested pharmaceutical product to be considered by the appropriate authorities for inclusion in the health services basket or implicates the Ministry of Health in any possible way.
However, the process of decision making is based on the data submitted in the request and hence the great importance of the request’s content.
- 1.7 These guidelines contain a number of compulsory paragraphs (designated with an asterisk). The data appearing in these paragraphs is of crucial importance in the decision making process.
- 1.8 The data submitted will be processed by the Pharmacoepidemiology and Pharmacoeconomics Department and presented to the public committee in a uniform format.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 2

2. **Structure of the data file:**

2.1 A request to include a pharmaceutical product in the national health services basket will be composed of three parts to be submitted according to section 3 of these guidelines:

Part I: Request forms and documents pertaining to details of the pharmaceutical product and a detailed summary of the data presented in parts II and III.

Part II: Clinical and epidemiological data.

Part III: Clinical-Economic evaluation.

2.2 The request will be submitted in a single binder separated by dividers.

2.3 On the back of the binder the name of the pharmaceutical product and the license holder's name, will be stated.

3. **Dossier elements:**

3.1 **Part A - General:**

3.1.1 Index

3.1.2 General description of the product (Form 1) (Appendix A).

*3.1.3 One page summary of the disease's nature and the pharmaceutical product's relative benefits in comparison to the therapeutic alternatives that are included in the basket.

*3.1.4 The product's registration certificate (including full indications).

*3.1.5 Product monograph (if there is none - Full prescribing information (Physician leaflet)).

3.1.6 Detailed summary of the data presented in part II.

3.1.7 Detailed summary of the data presented in part III.

*3.1.8 An affidavit of the product's price in Israel (Form 2) (Appendix B) - The product's price in Israel is defined as the selling price for the Sick Funds if the product is included in the basket.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 3

3.2 **Part II – Clinical and Epidemiological data:**

3.2.1 **Clinical-Pharmacological profile:**

Briefly describe the general pharmacological profile of the pharmaceutical product's therapeutic class and the specific pharmaceutical product, according to the following points:

3.2.1.1 **The pharmaceutical product:**

- Other countries in which the product is registered and the registered indications in each country (if different from the registered name in Israel)
- Recommended and commonly used treatment regimens with the product, including expected length of treatment.
- If the pharmaceutical product is indicated for use in combination with other pharmaceutical products, these combinations should be detailed, together with the required dosages.
- Summary of the adverse effects reported as part of the product's post marketing surveillance (only the summary of the last PSUR).
- Significant adverse effects, precautions / warnings and drug-drug interactions.
- Which changes have been made, if any, after receiving the marketing authorization (warnings, side effects, etc.)
- If the pharmaceutical product is being used in Israel under regulation 29 a(3), describe for which indications and how many patients are treated according to this approval.
- Detail other indications currently under research or any off label use of the pharmaceutical product, including all approved indications abroad (please state date of approval for each indication).

3.2.1.2 **The Therapeutic class:**

- Name of the therapeutic class and its classification according to the ATC classification system.
- Major pharmacological action of pharmaceutical products in this class.
- The rationale for using pharmaceutical products in this class.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 4

3.2.1.3 **Alternative treatment options:**

What are the major treatment options (drug and non-drug) currently existing in Israel for the same indication. For each treatment option specify if it is included in the basket, or not.

For each alternative medicinal treatment option summarize according to the following points: Brief pharmacological profile; mechanism of action; rationale for use of pharmaceutical products; efficacy and major side effects.

Please emphasize the aspects that differ significantly from the proposed pharmaceutical product.

It is recommended that the data presented will be in a tabular form.

- 3.2.1.4 Summarize briefly results from relevant clinical trials pertaining to the pharmaceutical product's efficacy for the relevant indication. Preferably use comparative studies in which the proposed pharmaceutical product is compared to other treatment options used for the same indication (see explanation in paragraph 3.2.5).
- 3.2.1.5 Attach any official treatment guideline/protocol for the requested indication/s (in Israel and / or other countries) in which the proposed product is part of. Highlight the relevant part concerning the proposed product.
- 3.2.1.6 State how does the treatment with the proposed pharmaceutical product influence patient survival (percentage or in "months of living")
- 3.2.1.7 State how does the treatment with the proposed pharmaceutical product influence the patient's quality of life (if available list studies and data such as QALY)
- 3.2.1.8 Briefly summarize studies assessing the clinical outcomes of the treatment, such as indices of morbidity, mortality, quality of life, aspects of cost effectiveness and more.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 5

***3.2.1.9 Expert report:**

- 3.2.1.9.1 An expert report by at least one physician specializing in the field the pharmaceutical product is indicated for, should be submitted.
- 3.2.1.9.2 The expert report must be based on all the data presented in the request and refer to the following points:
- Efficacy and importance of the pharmaceutical product in comparison to alternative treatment for the same indication.
 - Personal experience with the pharmaceutical product.
 - Definition of the pharmaceutical product's place in therapy (for example second/third line, specific patient groups to benefit the most from the treatment, etc.)
- 3.2.1.9.3 At the end of the report the following signed statement will appear:
"I am a physician, qualified to give this expert report on behalf of the requesting party. I give this expert report in support of a request to include this pharmaceutical product in the National Health Services list, according to the National Health Insurance Law, based on the entire file presented before me and my personal experience.
- Herewith are details of my status and education:
- I hereby declare that this is my name, that is my signature and the content of my expert report is true."
- 3.2.1.9.4 Each expert report must be accompanied by a signed form of full disclosure (טופס גילוי נאות) (See appendix C)
- 3.2.1.9.5 Expert reports that do not meet with the above mentioned criteria will not be taken under consideration.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 6

3.2.2 Pharmacoepidemiological data

- *3.2.2.1 Summarize briefly the disease state to which the pharmaceutical product is indicated for (pathophysiology and clinical course) and the typical gradual treatment regimen.
- *3.2.2.2 The disease's epidemiology:
 - Prevalence: number of patients in Israel.
 - Incidence: number of new patients each year in Israel.Include, where available, incidence and prevalence data from other western world countries.
- *3.2.2.3 What is the market size (number of patients treated currently for the specific disease state) and its distribution for each of the treatment options detailed in section 3.2.1.3 (Use market surveys data, IMS, etc).
- *3.2.2.4 Cite the Israeli sales figures of the requested pharmaceutical product from the last three years.
- 3.2.2.5 By how much is the target population expected to increase within the next three years following inclusion of the proposed pharmaceutical product in the basket.
- *3.2.2.6 Is the requested pharmaceutical product included in a Sick Fund's formulary in Israel (If so, in which Sick Fund, date of inclusion in the formulary, rate of co-payment and type of insurance).
- *3.2.2.7 Is the requested pharmaceutical product included in a formulary of a public insurer in other countries (state name of country and rates of co-payment).

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 7

3.2.3 The new treatment equilibrium:

- 3.2.3.1 As part of the treatment regimen what is the requested place of the pharmaceutical product.
- 3.2.3.2 How many patients are expected to switch from their current treatment to the proposed pharmaceutical product (based on clinical and/or economic considerations) after inclusion of the proposed pharmaceutical product in the health basket.
- *3.2.3.3 Characteristics of the specific patient population which will benefit the most from receiving treatment with the proposed pharmaceutical product.
- 3.2.3.4 After inclusion of the proposed pharmaceutical product in the health basket what is expected new market share for each treatment option (what percentage of the patients will be treated with each treatment option).
- 3.2.3.5 Is the market expected to grow after inclusion of the proposed pharmaceutical product in the health basket (will the number of treated patients increase)? If so, by how much.

3.2.4 **Pharmaceutical Products that will bear no added cost to the basket according to the dossier submitter's assessment:**

Attached to the full dossier will be a segment detailing the arguments as to why the inclusion of the proposed pharmaceutical product will bear no added cost to the health services basket. This part will be based on a comparison to therapeutic alternatives that are included in the basket.

In such a case, submission of a full dossier is necessary to ensure discussion of the requested pharmaceutical product as any other proposed product, in case there will not be an agreement as to the product not adding costs to the basket

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 8

3.2.5. Supporting clinical information:

*3.2.5.1 Attach a printout of the previous year's abstracts.

3.2.5.2 For any data / research / trial cited **it is mandatory to attach the original paper / source.**

Moreover for each trial summarize the following data elements:

3.2.5.2.1 Name of trial.

3.2.5.2.2 Location and trial date.

3.2.5.2.3 Publication citation/s.

3.2.5.2.4 Trial design, randomization and blinding procedures.

3.2.5.2.5 Inclusion and exclusion criteria.

3.2.5.2.6 Treatments to which the proposed pharmaceutical product was compared (including placebo).

3.2.5.2.7 Treatment and dosage regimens

3.2.5.2.8 Sample characteristics: demographics, sample size, disease severity and comorbidities.

3.2.5.2.9 Patient follow-up procedures: if intention to treat, were drop-outs followed ?

3.2.5.2.10 Clinical and other outcomes measured and their statistical significance.

3.2.5.2.11 Compliance behavior.

3.2.5.2.12 Concordance of the achieved outcomes in the trial's sample and the actual expected outcomes in the target population (considering differences of treatment protocol, treatment populations, comorbidities, compliance, follow-up, etc.). If such a difference exists, propose a model to link the trial's results with the expected outcomes in Israel while detailing the justification to the model's assumptions.

3.2.5.3 If meta analyses have been undertaken, these should be summarized with particular emphasis on the inclusion criteria for studies analyzed. Justify the relevance of the analysis to the target population.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 9

3.2.5.4 Where a retrospective study has been undertaken (utilizing pharmacy and medical claims databases) the study should be summarized and should include, in addition to the above information, the research question or hypothesis tested, rationale for the study design, choice of data source, techniques used to assess data quality, rationale for chosen statistical or econometric procedure and techniques used to avoid issues such as selection bias.

3.3 **Part III: Economic evaluation**

3.3.1 An economic evaluation of the proposed pharmaceutical product must be submitted (See instructions in Appendix D: Instructions for performing an economic assessment).

3.3.2 An economic evaluation conducted abroad should be adapted to Israeli settings. In such cases the request will include both evaluations.

3.3.3 The summary of the economic evaluation will be performed according to the following:

3.3.3.1 Estimated costs will be given in NIS and according to the following:

3.3.3.1.1 Cost of treatment to the patient with the proposed technology.

3.3.3.1.2 Cost of treatment to the patient with the alternative treatment.

3.3.3.1.3 Total additional cost (number of patients X additional cost per patient)

3.3.3.2 Estimated utilities will be given in QALY and according to the following:

3.3.3.2.1 Utility per patient with the proposed technology.

3.3.3.2.2 Utility per patient with the alternative treatment.

3.3.3.2.3 Additional utility per patient (the difference between the utilities)

3.3.3.3 The incremental cost per QALY (in NIS)
The additional cost per patient divided by the additional utility per patient.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 10

Appendix A

Form 1

General description of the pharmaceutical product

Name of the product: _____

Registered dosage form in Israel (including dosage forms, strength/concentration, package type and quantity/size and registration number):

1. _____
2. _____

Active ingredients (Generic names) and their quantity in dosing units:

1. _____
2. _____

Registered indications in Israel (including date of approval of each indication):

1. _____
2. _____

General:

Name of license holder:

License holder's address (in Israel and abroad): _____

Name of the appointed pharmacist: _____

Pharmacist's License number: _____

Affidavit:

To my knowledge and professional responsibility, I, the undersigned, declare herewith that all the data submitted in this request are correct.

Name of the appointed
Pharmacist

Stamp and signature of the appointed
pharmacist

Date

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 11

Appendix B

Form 2

Affidavit of the product's price

ISRAEL

Institutional Price – the selling price to the Sick Funds if the product will be included in the basket

Dosage forms					
Strength					
Package type and quantity					
Price per package (for institutions)*					
Number of estimated patients					

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 12

Global:

Current institutional price in The Netherlands, France, Belgium, Germany, Great Britain, Spain, Portugal, Hungary and Poland (Fill the form separately for each country):

Country					
Dosage forms					
Strength					
Package type and quantity					
Price per package (for institutions)*					
Number of estimated patients					

Name of the license holder
or a corporate manager who
is the license holder

Stamp and signature of the license
holder or the corporate manager who
is the license holder

Date

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 13

Appendix C

Recommendation for the health services basket – Full disclosure form

תאריך: ____/____/____

הואיל ובכוונתי לתת חוות דעתי המקצועית ביחס לתכשיר _____ מתוצרת חברת _____, לשם הבאתה בפני הועדה הציבורית להרחבת סל שירותי הבריאות, המייעצת לשר הבריאות בכל הקשור להכללת טכנולוגיות חדשות בסל שירותי הבריאות שלפי חוק ביטוח בריאות ממלכתי, הריני מצהיר כלהלן:

1. הריני לאשר כי איני עובד בחברה _____, אינני יועץ לה, תמורת תשלום, במישרין או בעקיפין, אינני ממלא תפקיד או נושא משרה במוסדותיה, או קשור אליה בקשר אחר המונע ממני לתת חוות דעתי בצורה אובייקטיבית ו/או בצורה המעלה חשש לניגוד עניינים. אינני קשור לחברה בכל קשר אחר ולא הייתי קשור עמה, באחת או יותר מהזיקות המפורטות, גם בעבר, אם בזיקה לתכשיר הנדון, ואם בזיקה לתכשיר אחר.

מאשר לא מאשר

2. הריני להודיע כי מתקיימת אצלי זיקה אחת או יותר מן הזיקות המפורטות לסעיף 1 לעיל והן מפורטות להלן:

- השתתפתי במחקר קליני במימון החברה ביחס לתכשיר הנדון, או מחקר אחר ביחס לתכשיר הנדון: כן / לא
- השתתפתי במחקר קליני אחר במימון החברה (מחקר שטרם הסתיים בתקופת שלוש השנים, שקדמה לחתימה על טופס זה) – כן / לא, (אם כן: פרט מועד תחילת המחקר וסימונו _____)
- הרציתי בכנס במימון החברה בשלוש השנים שקדמו לחתימת טופס זה, כן / לא
- נסעתי על חשבון החברה לכנס מקצועי, בשלוש השנים שקדמו לחתימת טופס זה: כן / לא
- שימשתי כיועץ של החברה, בשלוש השנים שקדמו לחתימת טופס זה: כן / לא
- עבדתי בחברה, בשלוש השנים שקדמו לחתימת טופס זה: כן / לא
- אחר (פרט) _____

3. הריני לאשר כי לא ידוע לי על זיקת תחרות בין גורם או גורמים אחרים עימם אני מצוי באחת או יותר מהזיקות המפורטות לעיל, לבין החברה, ביחס לתכשיר הנדון או לשאלת הכללתו בסל שירותי הבריאות, המונעת ממני ליתן חוות דעתי זאת, מחשש לניגוד עניינים כאמור.

מאשר לא מאשר

4. קשר עם חברה מסחרית, הנובע כל כולו מתפקידי כעובד מדינה או כעובד קופה, אינו בגדר זיקה מן הזיקות מפורטות בסעיף 1, אלא אם כן – לעניין עובד קופה – הקופה הינה בעלת מניות בחברה ו/או העובד ממלא בה תפקיד או מישרה, בשכר או שלא בשכר, אף אם מילוי התפקיד או המשרה הם מטעם הקופה, או מתוקף תפקידו של העובד בה.

5. ידוע לי כי הטופס שמילאתי, על הפרטים הנכללים בו, הוא מידע שעל משרד הבריאות לגלותו לכל דורש לפי חוק חופש המידע (תשנ"ח-1998).

חתימה: _____

שם: _____

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 14

Appendix D

Instructions for performing an economic assessment

The economic evaluation of medical technologies includes comparative analysis between alternatives in terms of costs and outcomes, and seeks to provide an objective and systematic method to improve the prioritizing process among decision-makers.

The assessment of the submitted material and the economic evaluation are conducted by a multi-disciplinary team of experts. The team examines whether the request fulfills the criteria for assessment and demands additional information, as needed.

The economic evaluation form provides a unified format to enable comparison between all medical technologies considered for inclusion in the Israeli National List of Health Services (INLHS)

The principles of the Israeli model upon which the guidelines are based are:

- The perspective adopted on benefits is of the health care system
- The perspective adopted on costs is that of the supplier (Ministry of Health, Health Management Organizations)
- The preferred comparators are standard-of-care technologies included in the INLHS
- The methods of economic evaluation should be Cost-Utility analysis
- Outcomes will be expressed in QALYs
- The costs are the direct medical costs for the supplier and consumer
- Time horizon for costs and outcomes will be defined for each comparison separately in such a way as to reflect the course of the disease and the effects of the interventions
- Sensitivity analyses should be performed as needed
- Discounts will be made according to the time horizon, and the discount percentage will be 3%

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 15

Guidelines for completion of the economic evaluation form for health technologies:

The guidelines refer to all information in the economic evaluation form. The guidelines describe the necessary data and provide examples as needed.

The request form is a stand-alone document, and all data must be presented and submitted according to instructions provided in these guidelines.

General guidelines:

1. The applicant is responsible for providing current, relevant and unbiased information, supported by acceptable and accessible scientific sources, in order to allow the reviewers to perform the necessary analyses and make recommendation accordingly.
2. All parts of the form must be completed according to the type of technology. If certain parts cannot be completed, the applicant must provide detailed justification.
3. Additional documents, must be relevant and justified, but do not replace the formal form.
4. All data must be supported by documentation.
5. Data sources must be scientifically accepted and available for assessment and should be submitted as attached documents.
6. Decision trees or other models relevant to the analysis should be included

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 16

The economic evaluation report is composed of 5 sections:

1. Title: contains general data, including the name or description of the technology, the name of the manufacturer or company, details of the person conducting the economic evaluation and of a contact person.
2. General description of the submitted technology: the purpose of this section is to provide general details of the submitted technology, the health condition and indication for use, clinical guidelines' references, treatment regimen, and target population
3. Description of comparator and comparative effectiveness: this part should describe the comparator used in the economic evaluation (name and whether it is included in the INLHS), the sources for effectiveness comparisons (complete references and characteristics of studies) and the endpoints compared.
4. Comparison of costs: this section should present the data used for calculation of cost for the submitted technology and comparator (including references for pricing) as well as any other costs added or saved due to increase or decrease use of other technologies or services.
5. Results of the economic evaluation: this section should contain a clear and concise summary of the main assumptions and parameters upon which the economic evaluation is based and the model used (if any). The results should include the costs of the submitted technology and comparator and the incremental cost (including discounting), the benefits (in QALYs) of the submitted technology and comparator and the incremental benefit (including discounting) and the incremental cost-effectiveness ratio (additional cost per additional QALY). Sensitivity analyses should be also included.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 17

Section 1- Title

The opening page of the request form includes:

- Proprietary (trade) name of the technology, proper name or description of the technology and the name of the manufacturer or company.
- Name, title and e-mail of the applicant.
- Contact person, including name, title, address, phone number, fax and e-mail. The contact person need not be the applicant, but should be able to provide official responses to queries.
- The name and contact details of the person conducting the economic evaluation

Section 2- general description of the submitted technology:

This section includes the following data (if a data is considered not-relevant, it should be noted and explained).

Condition - primary disease or condition.

Requested indication - the indication requested for inclusion, including place in the therapeutic sequence.

References for clinical guidelines - acceptable references include guidelines of professional associations, national institutes and scientific publications. References must be provided.

Context of use - full hospitalization, day hospitalization, outpatient clinic, primary care clinic, home use

Therapeutic regimen - description of treatment regimen, including duration of treatment.

Target population age - indicate the average age of the intended target population.

Contraindication, precautions and warnings - if exists.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 18

Section 3- Description of comparator and comparative effectiveness.

Description of comparator

Comparators are other technologies used for exactly the same indication.

Comparisons with standard-of-care comparators included in the INLHS are preferred. If no such comparison is made, the applicant must supply an appropriate explanation. If more than one technology exists, the applicant may choose with which to compare.

Comparators not in the INLHS are acceptable if there are no alternative in the INLHS, or in addition to one.

If there are no comparators (either in the INLHS or not), the technology will be compared to "do nothing", based on data regarding the costs and outcomes of not intervening.

Description and explanation regarding characteristics of sources for outcome comparison:

Clinical trials or studies, where the primary endpoint is the direct clinical outcome used for comparison, are preferred. If no such trials or studies exist, clinical trials in which the secondary end points are the outcome used for comparison are acceptable.

The end-point variable may be a direct clinical outcome (e.g. mortality, survival, incidence of disease, functional performance, quality of life etc.) or a surrogate measure (e.g. change in blood pressure, hemoglobin A1C, FEV1, etc.). When a surrogate measure is used, the relation with direct clinical outcomes must be established.

The outcome presented should be accompanied by confidence interval, unless it is not specified in the cited trial. For any comparison the statistical significance level must be given.

When there are several studies comparing the two technologies, it is preferable to use for the comparison the most recent ones and/or the ones with the largest study population or is most appropriate for the Israeli population and setting.

If the study was designed to assess differences in safety, safety should be regarded as the primary endpoint.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 19

The comparison between the technologies must be based on accepted scientific sources and be appropriate to the submitted indications and outcomes compared.

Study description should be provided according to type of the study/trial used in the comparison, as follow:

For clinical (interventional) trials, the following data should be presented (Table 1a):

- **Allocation**
- **Blinding**
- **Control**
- **Assignment**
- **Study Population**- includes definition of the disease/condition and inclusion and exclusion criteria.
- **Primary outcome measure**
- **Secondary outcome measures**- include only those with statistically significant differences.
- **Length of follow-up**
- **Comparative safety**- only if there were statistically significant safety differences in the adverse events profile between the two technologies.

For non-clinical-trials studies, the following data should be presented (Table 1b):

- **Study Design**
- **Study Population**
- **Outcome measures**
- **Length of follow-up**
- **Comparative safety**- only if there were statistically significant safety differences in the adverse events profile between the two technologies.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 20

Comparison of outcomes:

The clinical outcomes compared will be based only on the references described in the earlier part of the section (see Table 1). The comparison between the technologies' outcomes (submitted vs. comparator) will be presented by means of a table detailing the endpoints used to assess the benefit and the benefit in numerical value with confidence intervals.

These results will serve as a basis for the calculations of QALYs used in the model in section 5.

Table 1

a. Example of presentation of characteristics of a cited clinical trial

Allocation:	randomized controlled trial
Blinding:	double blind
Control:	active
Assignment :	parallel
Study population:	Colorectal cancer patients with bone and/or liver metastases, between the ages 45-85, with no CNS metastases and with no significant coronary heart disease.
Primary outcome measures :	Overall survival
Secondary outcome measures :	Tumor response rate Progression-free survival
Length of follow-up :	2 years
Comparative safety :	No significant differences

b. Example of presentation of characteristics of a cited non-clinical trial

Study type:	Prospective cohort study
Study population :	Colorectal cancer patients with bone and/or liver metastases, between the ages 45-85, with no CNS metastases and with no significant coronary heart disease.
Outcome measures :	Overall survival
Length of follow-up :	2 years
Comparative safety :	No significant differences

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 21

Section 4: Cost comparison between technologies.

General principles for cost calculation:

- Cost is presented in current New Israeli Shekels (NIS) values.
- The cost is the direct and indirect medical cost
- The dosing, schedule and duration of treatment are based on standard clinical guidelines.
- If use of the new technology requires or spares spending on other medical technologies, these costs should be included in the calculation.

In calculation of costs, the costs of each of the two technologies (submitted and comparator) should be presented, including, as needed, the numbers of units per package and/or per year. The source of pricing of the technologies should be clearly specified.

If the use of the new technology will require the use of additional medical technologies, or, alternatively, will spare the use of other medical technologies, this information (costs) should be included in the calculation.

These additional costs include, but are not limited to:

- **Drugs**
- **Medical devices/ equipment**
- **Tests-** laboratory test and imaging, both as pre-evaluation and as follow-up.
- **Clinical examinations-** include examinations by both primary care physicians and specialists, as pre-evaluation and as follow-up.
- **Hospitalization**
- **Medical/ surgical procedures**

If there is a need for a one-time expenditure, such as infrastructure or training, this cost should be presented, but it would not be included in the economic evaluation.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 22

Section 5: Results of economic evaluation.

How to calculate quality adjusted life years (QALYs):

The concept behind QALYs is based on the fact that the outcome of an intervention must affect at least one out of two components, the quantity of life and the quality of life. QALYs is an arithmetic product to assess the clinical benefit of an intervention by multiplying the value of the health-related quality of life (HRQoL) - utility by the length of time (in years) in a particular health state - survival. Utilities are cardinal values describing the individual's preferences for different health states.

All outcomes compared should be translated into QALYs. This can be done by calculating the effect of the clinical outcomes of the studies on HRQoL and survival.

This translation may be based on medical literature or on professional opinion.

The following site may be useful for determination of utilities:

<https://research.tufts-nemc.org/cear/default.aspx>

It is recommended to use values from populations similar to that of Israel.

The utilities should be age and gender-adjusted according to table 2.

The economic evaluation:

This section should describe the model used for the economic evaluation, and its main results. **The model itself (as a computerized file such as Excel, TreeAge etc.) should be sent directly by E-mail to Tova.nahmani@moh.health.gov.il.**

This description should include the model assumptions, HRQoL weights (utilities), time horizons etc. If the model has a time horizon of over 1 year, a 3% annual discounting should be used for both costs and benefits.

If a model prepared for another country is used, adjustment should be made, and specified, to ensure appropriateness to Israel. These adjustments apply to differences in treatment management as well as the different pricing of drugs and services. Simple currency conversion at exchange rates is not considered sufficient adjustment.

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 23

Both costs, relevant costs from section 4 and costs used in the model should be itemized.

The results should include the following:

- Cost per patient treated with the submitted technology
- Cost per patient treated with the comparator
- Difference in costs
- Benefit per patient treated with the submitted technology in QALYs
- Benefit per patient treated with the comparator in QALYs
- Difference in benefits in QALYs
- Incremental cost-utility ratio

Sensitivity analyses

Sensitivity analyses examine the effects of the different parameters on the results of the economic evaluation. Sensitivity analyses should be performed for both the costs and benefits, and the parameters examined specified. The range of values used in the sensitivity analyses may be based on the results of studies (reported confidence intervals) or on clinical judgment. Parameters found to have significant effects must be specified clearly, along with their implications on the meaning of the results of the economic evaluation.

Table 2: age adjustments for utilities.

AGE	Factor - male	Factor - female	Factor - both	AGE	Factor - male	Factor - female	Factor - both
0	0.9930	0.9935	0.99325	50	0.8350	0.8216	0.828264
1	0.9918	0.9928	0.992334	51	0.8306	0.8165	0.823549
2	0.9907	0.9922	0.991417	52	0.8268	0.8162	0.82149
3	0.9892	0.9915	0.990501	53	0.8224	0.8109	0.816618
4	0.9883	0.9908	0.989584	54	0.8179	0.8056	0.811745
5	0.9872	0.9902	0.988668	55	0.8118	0.7986	0.805198
6	0.9860	0.9895	0.987752	56	0.8073	0.7933	0.800302
7	0.9848	0.9888	0.986835	57	0.8035	0.7838	0.793604
8	0.9837	0.9882	0.985919	58	0.7992	0.7788	0.789000
9	0.9825	0.9875	0.985002	59	0.7949	0.7739	0.784395
10	0.9813	0.9868	0.984086	60	0.7890	0.7675	0.778292

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

Date: January 2010

Guideline no. 53 version no: 8

Page 24

AGE	Factor - male	Factor - female	Factor - both	AGE	Factor - male	Factor - female	Factor - both
11	0.9802	0.9862	0.98317	61	0.7849	0.7628	0.773806
12	0.9790	0.9855	0.982253	62	0.7800	0.7595	0.76972
13	0.9778	0.9849	0.981337	63	0.7759	0.7546	0.765235
14	0.9767	0.9842	0.98042	64	0.7718	0.7497	0.760751
15	0.9755	0.9835	0.979504	65	0.7657	0.7428	0.754237
16	0.9743	0.9829	0.978588	66	0.7616	0.7377	0.749636
17	0.9732	0.9822	0.977671	67	0.7562	0.7327	0.744436
18	0.9720	0.9815	0.976755	68	0.7525	0.7281	0.740299
19	0.9708	0.9809	0.975838	69	0.7489	0.7235	0.736162
20	0.9696	0.9802	0.974922	70	0.7426	0.7165	0.729537
21	0.9653	0.9751	0.970182	71	0.7388	0.7113	0.725038
22	0.9741	0.9760	0.975041	72	0.7356	0.7063	0.72099
23	0.9693	0.9706	0.969981	73	0.7317	0.7021	0.716899
24	0.9645	0.9653	0.96492	74	0.7280	0.6980	0.712958
25	0.9608	0.9598	0.960297	75	0.7227	0.6899	0.706303
26	0.9560	0.9544	0.955219	76	0.7182	0.6858	0.701987
27	0.9546	0.9578	0.956169	77	0.7160	0.6824	0.699211
28	0.9496	0.9521	0.950874	78	0.7121	0.6797	0.69586
29	0.9447	0.9465	0.945579	79	0.7090	0.6763	0.692661
30	0.9391	0.9405	0.939796	80	0.7049	0.6696	0.687211
31	0.9342	0.9349	0.934524	81	0.7026	0.6599	0.68126
32	0.9262	0.9219	0.924046	82	0.7003	0.6679	0.684122
33	0.9214	0.9166	0.918978	83	0.6965	0.6621	0.6793
34	0.9166	0.9113	0.913911	84	0.6925	0.6577	0.675095
35	0.9116	0.9051	0.908338	85	0.6886	0.6497	0.669184
36	0.9068	0.8998	0.903295	86	0.6850	0.6456	0.665316
37	0.9050	0.8998	0.902389	87	0.6810	0.6401	0.66056
38	0.9001	0.8942	0.89714	88	0.6777	0.6351	0.656398
39	0.8951	0.8887	0.891916	89	0.6772	0.6381	0.657663
40	0.8883	0.8817	0.885018	90	0.6650	0.6204	0.642708
41	0.8835	0.8763	0.87989	91	0.6628	0.6171	0.639945
42	0.8783	0.8692	0.873776	92	0.6603	0.6133	0.636797
43	0.8735	0.8639	0.868695	93	0.6569	0.6090	0.632945
44	0.8687	0.8585	0.863614	94	0.6516	0.6033	0.627472
45	0.8617	0.8521	0.856905	95	0.6483	0.5998	0.624039
46	0.8569	0.8468	0.851847	96	0.6442	0.5926	0.61839
47	0.8504	0.8382	0.844342	97	0.6397	0.5878	0.61375
48	0.8459	0.8331	0.839506	98	0.6362	0.5834	0.609783
49	0.8414	0.8280	0.83467	99	0.6316	0.5775	0.60454