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MANAGEMENT OF CANCER PAIN



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*Prophylaxis - brief the
Pain management*

title:

FIELD TEST OF WHO CANCER PAIN RELIEF GUIDELINES

2

from

Cancer Unit, WHO/HQ, Geneva

WHO Collaborating Centre for Cancer Pain Relief, Milan

WHO Collaborating Centre for Cancer Biostatistics, Boston

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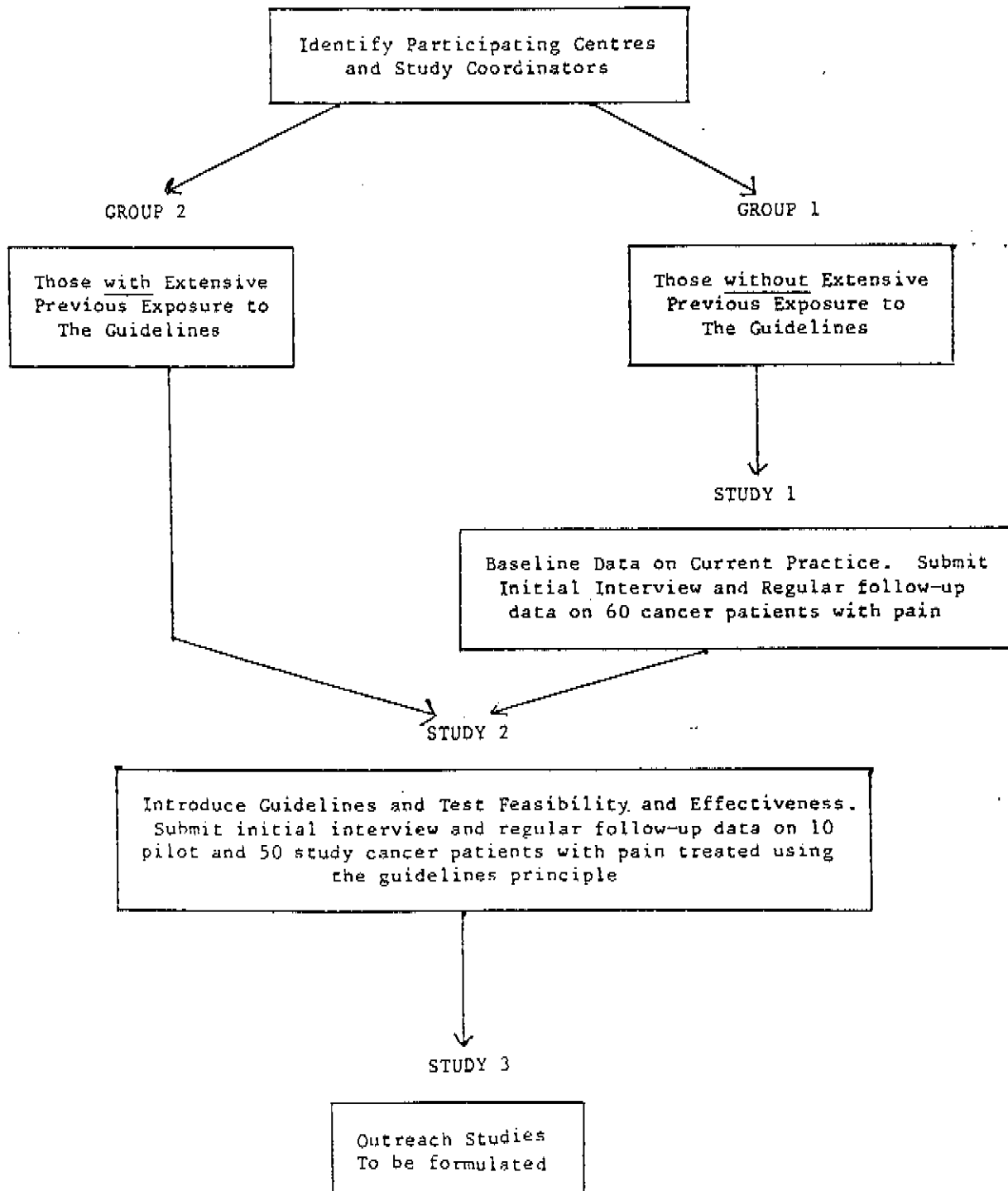
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PRELIMINARY STUDIES TO FIELD TEST WHO CANCER PAIN RELIEF GUIDELINES

OUTLINE OF APPROACH



STUDY 1 OF THE PROGRAMME TO FIELD TEST WHO CANCER PAIN RELIEF GUIDELINES

1. INTRODUCTION

In 1982 the World Health Assembly endorsed the WHO Cancer Pain Relief Programme, whose objective is to offer pain relief to cancer patients through the existing health care system. In October 1982, a WHO consultation was held in Milan with a core advisory committee of experts in pain treatment. A document entitled "WHO Draft Interim Guidelines Handbook on Relief of Cancer Pain" was prepared.

Field testing studies of the guidelines are planned to determine feasibility and effectiveness worldwide. Prior to the introduction of these guidelines in selected hospitals/clinics participating in the field testing, baseline data on current practice will be obtained. STUDY 1 is designed to accomplish this baseline data collection.

In 1984, the WHO Collaborating Centre for Cancer Pain Relief was identified in the Division of Pain Therapy at the National Cancer Institute of Milan. This centre, in conjunction with the WHO Collaborating Centre for Cancer Biostatistics Evaluation at Harvard University in Boston will coordinate the conduct of the study as the central operations office for the Field Testing.

2. STUDY OBJECTIVE

Obtain background data on the current practice of pain management in selected participating centres.

3. STUDY DESIGN

Participating centres without extensive previous exposure to the guidelines will be identified. A study coordinator for each centre will be designated to facilitate the completion and submission of the data collection forms.

Initial interview and regular follow-up data will be submitted to Milan on 60 cancer patients with pain.

4. METHODS OF APPROACH

Patient population: Patients with cancer pain are eligible for the study.

Treatment Programme: Usual practices are to be used for the treatment of pain.

Forms submission and Follow-up Schedule: The initial interview form is completed at the first visit. The patient's current self-assessment form is used to obtain the patient's assessment of the pain intensity and the degree of relief provided by the given treatment. The patient answers the four items on the form both at the initial visit and at the follow-up reports.

The follow-up reporting schedule should be weekly for the first two weeks; every four weeks thereafter, if stable; at each change in treatment; weekly for two weeks after a change; every four weeks, thereafter.

Up to four follow-up assessments can be made on each follow-up form.

Initial data and follow-up forms are submitted to Milan when completed.

Statistical considerations: The submission of data on 60 cancer patients with pain will provide sufficient precision for assessing the degree of relief and duration of relief obtained by current practice. A reduction of pain by one level will be detected with 95% probability using a two-sided $\alpha = 0.05$ Wilcoxon Rank Sum Test. The results will provide a historical basis for measuring the impact of treatment guidelines which are under development.

INSTRUCTIONS FOR COMPLETING THE WHO CANCER PAIN RELIEF GUIDELINES
FIELD TESTING STUDY FORMS

The forms packet contains an Initial Interview Form, and three pages to record up to 12 follow-up reports. Patient's Current Self-Assessment of Pain Forms and additional follow-up forms are also provided.

Complete the first page of the initial interview when a patient with cancer pain is identified for the protocol. Submit a copy of the Initial Interview Form to the Collaborating Centre in Milan immediately to register the patient. Cases should be assigned numbers sequentially at each hospital. The hospital code and case number will serve to identify the patient on future forms.

- The form should be completed by an adequately instructed nurse.
- The patient's self-assessment of the level of pain and the degree of relief will be the principal items for evaluation.
- The items which should be completed at first visit are on the front page. In the other three pages up to 12 follow-ups can be registered.
- All dates are in day/month/year format.

FIRST VISIT

Report the following items:

Date of first visit (day, month, year), hospital name (with code number), patient's name and surname, sequentially determined case number for the patient, age, sex, height, weight, type of cancer classified according to organ pathology (i.e. breast, lung, colon-rectum etc.), and how many months since cancer was first diagnosed.

I PATIENT'S GENERAL CONDITION: Indicate with a check (✓) if cancer is primary, disseminated or if state is now known. Indicate also if the patient is in terminal phase (i.e. prognosis of less than three months survival). Give the UICC Performance Status Score according to the scale given on the pages of codes. State whether the patient is being treated as an inpatient or outpatient.

II DESCRIPTION OF PAIN: determine how long the patient has had cancer pain, in which part of the body the pain is localized, and what the present pain relates to. Using the Patient's Current Self-Assessment of Pain ask the patient to specify the mean intensity of pain felt in the past 48 hours (as a time-frame). Pain intensity is registered making use of three adjectives: slight, moderate and severe. The patient should then be asked the number of hours with pain per 24 hours (average), and the number of hours of sleep per 24 hours (average).

III PRESENT DRUG TREATMENT FOR PAIN: report the drug treatment for cancer pain relief which the patient is already undergoing. If no treatment is being given, check the box labelled "no drug treatment". If the patient is being treated pharmacologically, give the name of the drugs, the route (OR = oral route; IV = intravenous; IM = intramuscular; R = rectal), dose (mg), schedule and date started.

IV PAIN DRUG RELATED SIDE EFFECTS: in case the patient has already started pharmacological treatments for pain relief, report side effects, if any. If side effects occur, indicate 1 if intensity is slight; 2 if moderate; or 3 if severe, according to patient's judgement.

V OTHER PAIN RELIEVING MODALITIES: indicate the types of other treatments for pain relief undergone recently (within the past four weeks) by the patient, together with the date when treatment was started.

VI COMMENTS ON THE EFFECT OF THE CURRENT THERAPIES: give any comments which would be helpful to evaluate the current status of the patient and the effectiveness of the treatments which were tried.

FOLLOW UP REPORTING

A follow-up report is to be made:

- Weekly for the first two weeks to monitor stabilization of pain status.
- At any time the treatment is modified.
- Weekly for two weeks after any pain treatment modification to monitor the impact of the modification.
- And at a minimum of every four weeks thereafter for stable patients.

Each follow-up report refers to the period between the previous report and the current follow-up visit.

PATIENT'S CURRENT SELF-ASSESSMENT OF PAIN FORM:

At each follow-up assessment, the patient is to complete this form to provide an evaluation of pain intensity, hours of pain, hours of sleep, and evaluation of pain relief provided by the given treatment. This form may be used at a clinic visit or may be submitted (or mailed) later to the clinic coordinator (registrar). Patients may provide self-assessments without being required to return to the clinic.

FOLLOW-UP FORM

1. DATE OF FOLLOW-UP REPORT: carefully and accurately enter the date of the evaluation as day/month/year.
2. ASK THE PATIENT(using the Self-Assessment Form): how bad is the pain? Mark with a check (✓) the adjective which the patient uses to best explain the pain intensity felt. Give the number of hours per 24 hours (average) the patient had pain, and how many hours the patient slept per 24 hours (average). Using a measuring ruler (in millimetres), determine the LASA PAIN RELIEF SCORE (a number from 0 to 100 millimetres measuring from the left to the right) indicated by the placement of the mark (x) by the patient on the LASA scale.
3. PAIN DRUG TREATMENT GIVEN SINCE THE PREVIOUS REPORT: indicate the drugs given, the route of administration (OR = oral route, IV = intravenous, IM = intramuscular, R = rectal), the dose and schedule.
4. PAIN DRUG MODIFICATION: indicate the reason for any change in pharmacological treatment as due to insufficient analgesic effect, excessive side effects, or other reasons (e.g. patient's lack of confidence in the drug, too expensive, etc).
5. PAIN DRUG RELATED SIDE EFFECTS: report side effects (1 = slight, 2 = moderate, 3 = severe) due to pharmacological treatment for pain relief.
6. OTHER PAIN RELIEVING MODALITIES: indicate any other treatment for pain relief which the patient underwent since the previous follow-up report.
7. PATIENT STATUS: indicate if the patient is alive, dead, or lost to follow-up and give the date. This question needs to be completed only once on each follow-up form. An indication that the patient has died signals the conclusion of follow-up, so that no more data will be requested.
8. COMMENTS: enter any comments about the patient's pain and pain treatment course which might be helpful for evaluating the effectiveness of the treatments for this patient.

DATA SUBMISSION

Patients are to be followed until death (or until the time when final data analysis for the study will begin). The initial interview data form and the follow-up forms containing data for 12 follow-up assessments should be submitted to the Collaborating Centre in Milan as soon as they are completed. Patient's Current Self-Assessment of Pain Forms need not be submitted, as the data from these forms will be transcribed onto the follow-up forms. Additional follow-up forms, each containing four possible follow-up visit reports, should be submitted to Milan when completed.

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCORE

Score value that the patient is "capable" of performing

- 0 Normal Activity.
- 1 Symptoms but nearly fully ambulatory.
- 2 Some bed time, but needs to be in bed less than 50 per cent of the normal daytime.
- 3. Needs to be in bed greater than 50 per cent of normal daytime.
- 4. Unable to get out of bed.

LASA INSTRUCTION EXAMPLE

PATIENT'S CURRENT SELF-ASSESSMENT OF PAIN

Patient's Name: _____ Date: _____

- a. How bad is the pain?
(past 48 hours)
- | | | |
|----------|--------------------------|--------|
| none | <input type="checkbox"/> | |
| slight | <input type="checkbox"/> | Please |
| moderate | <input type="checkbox"/> | check |
| severe | <input type="checkbox"/> | one |

b. How many hours do you have pain per 24 hours (average)? _____ hours

c. How many hours do you sleep per 24 hours (average)? _____ hours

d. Overall, how do you evaluate the relief of pain provided by the given treatment?

Please put a mark (x) on the scale below to show how you feel.

No	/		/	Complete
Relief	0		100	Pain
At All				Relief

Example:

No	/	x	/	Complete
Relief	0		100	Pain
At All		72		Relief

Score: (72) millimetres written into follow-up form

WHO PAIN RELIEF GUIDELINES FIELD TESTING STUDY 1

PATIENT NAME _____

FOLLOW-UP EVALUATION DATA

HOSPITAL _____

CASE NUMBER |_____|

1. DATE OF FOLLOW-UP REPORT

d m y	d m y	d m y	d m y
-----------	-----------	-----------	-----------

2. ASK THE PATIENT: (Use self-assessment form)

a. How bad is the pain (past 48 hours)?

check one	check one	check one	check one
<input type="checkbox"/> none	<input type="checkbox"/> none	<input type="checkbox"/> none	<input type="checkbox"/> none
<input type="checkbox"/> slight	<input type="checkbox"/> slight	<input type="checkbox"/> slight	<input type="checkbox"/> slight
<input type="checkbox"/> moderate	<input type="checkbox"/> moderate	<input type="checkbox"/> moderate	<input type="checkbox"/> moderate
<input type="checkbox"/> severe	<input type="checkbox"/> severe	<input type="checkbox"/> severe	<input type="checkbox"/> severe

b. How many hours of pain per 24 hours (average)?

____ ____ hours	____ ____ hours	____ ____ hours	____ ____ hours
------------------	------------------	------------------	------------------

c. How many hours of sleep per 24 hours (average)?

____ ____ hours	____ ____ hours	____ ____ hours	____ ____ hours
------------------	------------------	------------------	------------------

d. LASA Pain Relief Score (0=none; 100=complete)

____ ____ millimetres	____ ____ millimetres	____ ____ millimetres	____ ____ millimetre
------------------------	------------------------	------------------------	-----------------------

3. PAIN DRUG TREATMENT GIVEN SINCE THE PREVIOUS REPORT

(give generic name, route [OR, IV, IM, R], dose and schedule

- Non-narcotics
- Weak narcotics
- Strong narcotics
- Anticonvulsants
- Psychotropics
- Antihistamines
- Antidepressants
- Steroids
- Others

yes name/route/dose	yes name/route/dose	yes name/route/dose	yes name/route/dose
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. PAIN DRUG MODIFICATION

If pain drug is being modified, check reason(s):
No analgesia
Side effects
Other (specify)

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. PAIN DRUG RELATED SIDE EFFECTS. Give intensity

(0 = none; 1 = slight; 2 = moderate; 3 = severe)

- Nausea
- Vomiting
- Drowsiness
- Bleeding
- Gastralgia
- Restlessness
- Sweating
- Drymouth
- Tremor
- Vertigo
- Others (specify)
- " "

intensity	intensity	intensity	intensity
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. OTHER PAIN RELIEVING MODALITIES (if yes, specify date and type)

- Radiation
- Chemotherapy
- Surgery
- Traditional methods
- Others (specify)

yes date type	yes date type	yes date type	yes date type
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. PATIENT STATUS

Alive	Yes <input type="checkbox"/>	Date last seen	____ ____	____ ____	____ ____
Dead	Yes <input type="checkbox"/>	Date of death	____ ____	____ ____	____ ____
Lost to follow-up	Yes <input type="checkbox"/>	Date lost to follow-up	____ ____	____ ____	____ ____

8. COMMENTS

STUDY 2 OF THE PROGRAMME TO FIELD TEST THE WHO DRAFT
INTERIM GUIDELINES HANDBOOK ON RELIEF OF CANCER PAIN

Paper prepared by Dr Richard Gelber, World Health Organization Collaborating Centre
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1. INTRODUCTION

It is estimated that over half of all cancer patients suffer needlessly from pain. Studies conducted in the United Kingdom and United States, where high levels of expertise are available, indicate that fully 25% of patients die with pain. The problem of inadequate control of cancer pain is even greater in the developing countries, where basic analgesic drugs are not available to 60-80% of the population.

Even when the means to control cancer pain are available, they are often not effectively utilized. Administration at adequate doses is avoided even in suffering patients for fear of drug addiction and toxicity. A lack of understanding of the basic principles and methods already available to relieve pain contributes to the problem.

The World Health Organization (WHO) Cancer Control Programme has identified three major targets: to prevent cancer; to cure patients detected early; and to promote a good quality of life and death with dignity for the 65% of patients who cannot be cured.

In 1982 the WHO Executive Board, Advisory Committee on Medical Research and World Health Assembly endorsed the WHO Cancer Pain Relief Programme, whose objective is to offer pain relief to cancer patients through the existing health care system. In October 1982, a WHO consultation was held in Milan with a core advisory committee of experts in pain treatment. A document entitled "WHO Draft Interim Guidelines Handbook On Relief of Cancer Pain" was prepared. The principle objective of the present study is to field test these guidelines. Feasibility, compliance and effectiveness are the main endpoints for the evaluation.

In 1984, the WHO Collaborating Centre for Cancer Pain Relief was identified in the Division of Pain Therapy at the National Cancer Institute of Milan. This centre, in conjunction with the WHO Collaborating Centre for Cancer Biostatistics Evaluation at Harvard University in Boston, will coordinate the conduct of this study as the central operations office for the Field Testing.

2. SUMMARY OF THE GUIDELINES

The guidelines being tested are those described in the document dated 7 December 1983 and entitled "WHO Draft Interim Guidelines Handbook on Relief of Cancer Pain". These guidelines propose a therapeutic strategy for the effective use of drugs to treat cancer pain. After the assessment of the exact nature of the patient's pain, when specific pain relieving procedures (surgical or chemo-radio-hormono therapies) are not indicated or not available, treatment should be started at once with the pain relief drug or drugs carefully selected. Drugs have to be administered at adequate doses at fixed times, by oral route whenever possible. The drugs used for relieving cancer pain can be classified into four groups as shown in Table 1. The specific indications for use, recommended doses, and potential side effects are given in detail in the guidelines document.

The sequence of administration of these drugs will follow the course and increase in severity of pain with time, starting from nonnarcotic drugs, which represent the first step. When the recommended analgesic dosage and frequency fail to relieve pain, the medication should be strengthened by a drug of the weak narcotic group. If the weak narcotic and the nonnarcotic proves ineffective, a strong narcotic should be used. Especially in patients with bone pain, requiring additional analgesia, aspirin or other antirheumatics may be added to the narcotics. Adjuvant drugs should be used together with narcotic and nonnarcotic drugs in case of specific indications. The analgesic ladder, which illustrates the basic principle of treatment as defined by the guidelines, is shown in Figure 1.

THE COMPLETE GUIDELINES DOCUMENT MUST BE CONSULTED PRIOR TO INITIATION OF PAIN TREATMENT TO OBTAIN DETAILS OF THE APPROPRIATE REGIMENS TO FOLLOW.

The following seven points are indicated in the Summary of the Guidelines (page 25):

1. Cancer pain can and must be treated.
2. First, take a full history and examination and exclude acute conditions that require urgent treatment.
3. Drugs will usually provide good relief provided you use the right drug(s), the right dose(s), and the right frequency of dosage. The drugs must be given regularly by the clock and not on demand ("p.r.n.").
4. Start the patient on a nonnarcotic drug and adjust the dose to optimum level (see Guidelines Table III). If necessary, use an adjuvant drug in addition (Guidelines p. 20).
5. If or when this treatment no longer relieves the pain, administer a weak narcotic drug (Guidelines p. 10) in addition to the nonnarcotic and together with an adjuvant if necessary.
6. When this no longer relieves the pain, start the patient on strong narcotic therapy together, if necessary, with adjuvant drugs and other analgesics (Guidelines p. 20).
7. The patient must be supervised as often as possible to ensure that treatment continues to match the pain and to exclude side effects and toxic effects.

Table 1

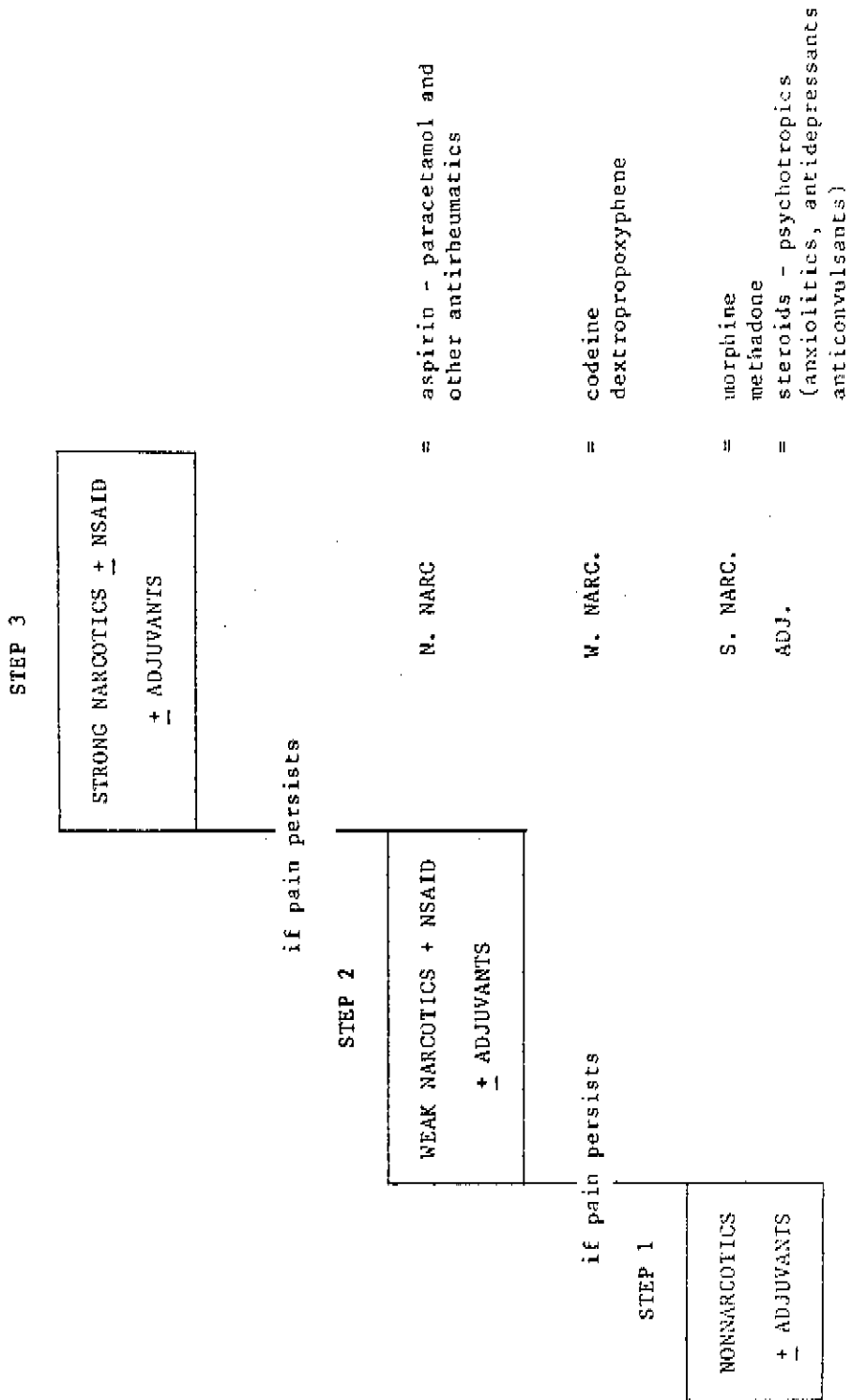
A BASIC DRUG LIST

<u>Category</u>	<u>Parent drug</u>	<u>Alternatives</u>
1. Nonnarcotic	aspirin and other antirheumatics	paracetamol (acetaminophen)
2. Weak narcotic	codeine	dextropropoxyphene
3. Strong narcotic	morphine	methadone pethidine (meperidine) buprenorphine standardized opium hydromorphone levorphanol
4. Adjuvant		
a. Anticonvulsants	carbamazepine	phenytoin
b. Psychotropics	chlorpromazine haloperidol diazepam	prochlorperazine
c. Antihistamines	hydroxyzine	
d. Antidepressants	amitryptiline	
e. Steroids	prednisolone	dexamethadone medroxyprogesterone

3.

Figure 1

ANALGESIC LADDER IN CANCER PAIN RELIEF



4. STUDY DESIGN

The Guidelines Field Testing Protocol Study 2 will consist of three phases.

Phase I involves identifying the participating centres and study coordinators who will be responsible for local testing of the guidelines. These centre coordinators will complete the questionnaire described in Phase II, and submit it to the Collaborating Centre in Milan. The centre coordinator will also instruct local staff in the use of the guidelines document and will be responsible for monitoring patients and completing data forms for Phase III of the field testing trial.

In Phase II, a Participating Centre Questionnaire will be completed by the study coordinator for each participating centre. This questionnaire will request information about the availability of drugs for pain relief, the use of non-pharmacological methods for pain treatment, and the personnel resources, facilities, and continuing care networks which are available. Information about specific drugs to be used at each of the three steps of the ladder will also be obtained. This information is required to determine current feasibility for using the WHO Guidelines worldwide.

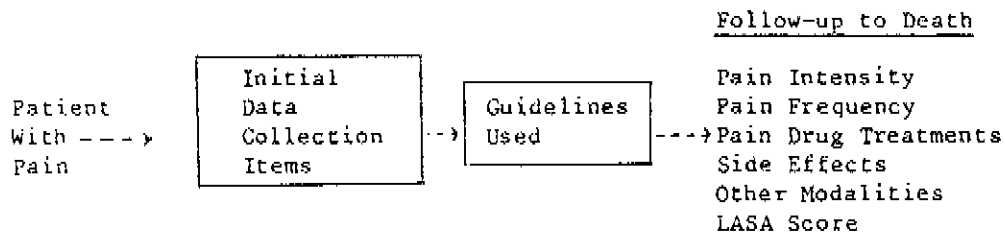
The evaluation of endpoints in Phase II will provide a description of the clinical settings which make up the sample of centres participating in the Guidelines Testing. It is required to obtain data on the feasibility for each clinic to apply the full guidelines procedures.

Not all clinics participating in the guidelines testing must have access to all of the drugs required for each level of the analgesic ladder. In some clinics where access to narcotic agents is limited, the ladder may only be feasible to apply up to step two. By evaluating results of Phase III according to the ability of the individual clinics to completely apply the guidelines we will obtain information about the possible role played by guidelines feasibility.

In Phase III, the guidelines will be applied for the treatment of pain in approximately 60 patients per participating centre. Initial baseline data on the status of the disease and the severity of the pain will be collected for each patient. The guidelines will be applied with monitoring of pain drug treatment and compliance with the analgesic ladder approach. Pain intensity, pain frequency, treatments, side effects, and use of other modalities will be recorded on follow-up forms. A LASA (linear analogue self-assessment) will also be used to obtain the patient's evaluation of the extent of relief achieved. The objectives for Phase III are to determine the level of compliance in delivery of guideline treatment and to determine the effectiveness for reducing pain intensity and frequency without side effects.

5. STUDY SCHEMA

- Phase I - Identify participating centres and study coordinators.
- Phase II - Centre questionnaires submitted by participating centres.
- Phase III - Treat 60 patients on the guidelines approach to determine a) compliance, and b) effectiveness for reducing pain intensity without side effects. The first 10 patients from each centre will be considered pilot patients for the analysis.



Follow-up Report Schedule: Weekly for the first two weeks until stabilization of the drug regimen, thereafter, at each change in the pain drug treatment, weekly for two weeks after the change, and once every four weeks if stable.

6. STUDY OBJECTIVES

- 6.1 To determine the feasibility of using the WHO Guidelines in selected participating clinics.
- 6.2 To test the compliance with the WHO Guidelines approach in selected clinics.
- 6.3 To test the effectiveness of the WHO Guidelines in individual patients based on measurement of pain reduction with minimal side effects.

7. METHODS OF APPROACH (PHASE III)

Patients with cancer pain are to be identified and an initial interview form is to be completed. Following a complete history and physical to assess the causes of the pain, treatment for the pain is started according to the analgesic ladder. Follow-up forms are submitted to report on the level of pain and treatment modifications over time. Specific criteria for patient population, starting the ladder, forms submission and follow-up schedule, evaluation, and statistical considerations are presented below.

- 7.1 Patient Population - Patients with cancer pain are eligible for the study. Patients who received prior drug treatment for pain are eligible for the study and will begin the analgesic ladder at a step which depends on the prior treatment received.
- 7.2 Treatment Programme - When appropriate, the initial study treatment should be at Step 1 for at least three days regardless of the initial severity of the pain. Step 1 when delivered according to the guidelines, may be effective even for severe pain. The initial entry step is described in the following table:

TABLE FOR DETERMINING INITIAL LADDER TREATMENT

<u>Prior Drug Treatment Status</u>		<u>Initial Ladder Treatment</u>
No prior drug treatment for pain	→	Start on Guidelines Step 1 for at least three days
Received prior drug treatment for pain but this prior treatment was not given according to the guidelines (e.g. only occasionally, not by the clock, at inadequate doses)	→	Start on Guidelines Step 1 for at least three days
Received prior drug treatment for pain which satisfies the requirements for Guidelines Step 1	→	Start on Guidelines Step 2 for at least three days
Received prior drug treatment for pain which satisfies the requirements for Guidelines Step 2 or 3 (i.e. regular administration of weak or strong narcotics)	→	Start on Guidelines Step 2 or 3 as appropriate

As described in the guidelines document, if pain persists or recurs, modification of the treatment, including stepping up the ladder, is to be made.

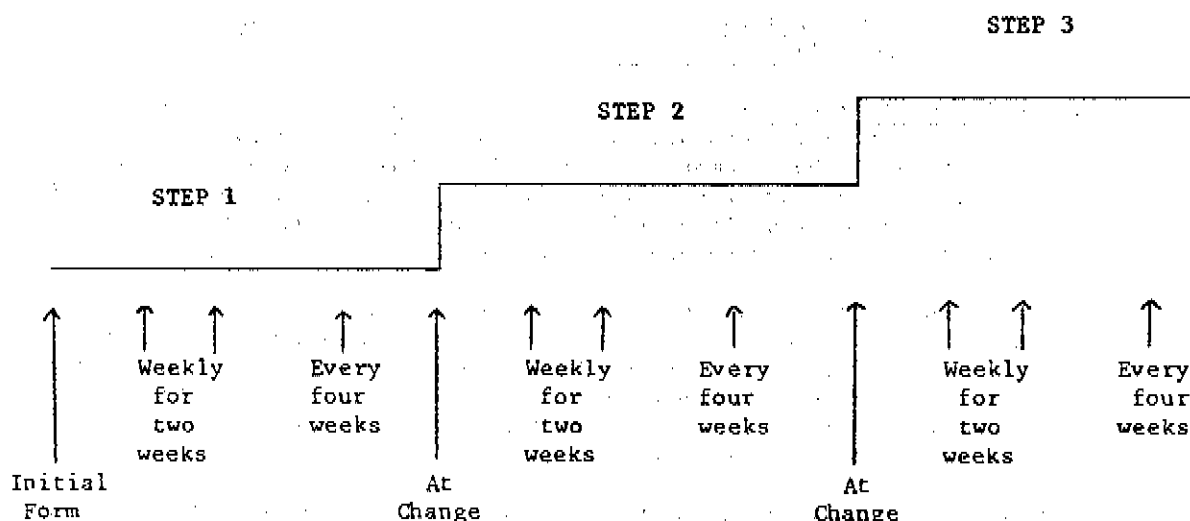
7.3 Forms Submission and Follow-up Schedule

A) The initial interview form is to be completed at the time of the first patient interview prior to beginning guidelines treatment. The purpose is to establish baseline data on the patient and his/her pain status at the time of starting the guidelines. A copy of this form is to be sent to the WHO Collaborating Centre in Milan as soon as it is completed to officially register the patient in the study.

B) Follow-up data are recorded on follow-up forms according to the schedule:

- Weekly assessments for the first two weeks to monitor stabilization of the initial ladder regimen.
- Every four weeks thereafter as a minimum contact if stable.
- At the time of change in the pain drug treatment.
- Weekly for two weeks after each change to monitor effect, and
- Every four weeks thereafter.

The diagram below illustrates the typical follow-up schedule:



Up to four follow-up reports can be made on each follow-up form. When each form is completed, a copy is to be sent to the WHO Collaborating Centre in Milan.

The critical evaluation of the effectiveness of the guidelines will be based upon the patient's self-assessment of pain and the degree of pain relief provided by the given treatment. A Patient's Current Self-Assessment of Pain Form is completed by the patient at each follow-up report. The results from this self-assessment are then recorded on the follow-up form.

Application of the guidelines and follow-up of the patients continues until death (or until the time of the final analysis of the results).

7.4 Other Pain Relief Modalities - The use of non-pharmacologic pain relief modalities is discouraged during the period of testing of the guidelines. If, however, the use of other modalities is felt to be in the best interest of the patient (i.e. radiation for bone pain) then these non-pharmacological treatments must be recorded on the Follow-up form. If traditional remedies (herbs, spells, etc.) are also being used, these should be noted but will not be grounds for disqualifying a patient. All patients are to be followed until death; those who receive non-guidelines pain treatment will have the influence of these interventions accounted for in the analysis, but are to continue to have guidelines treatment applied as appropriate.

- 7.5 Evaluation - The evaluation of analgesic effectiveness will be based on the patient's self report of pain intensity according to the four-point scale of none, slight, moderate, severe. The patient will be asked to specify the number of hours of pain, and the number of hours of sleep experienced (per 24 hours average). These simplified measures were adopted so that the field testing could be accomplished in a wide diversity of clinical settings. Reduction in the pain intensity report without intolerable side effects is the objective of the programme.

The experience of pain is subjective, and attempts to objectively quantify pain intensity may not adequately reflect the patient's overall impression about the effectiveness of the treatment. How the patient feels about the experience may be the most appropriate way to evaluate the programme. A linear analogue self-assessment (LASA) will be given to the patient to record how he/she evaluates the relief of pain provided by the given treatment [from "of no value" to "complete relief" on a 100 millimetre scale]. Each ladder step will be evaluated by LASA reports, and correlations between the LASA score and "objective" reports of pain intensity and hours will be obtained.

The duration of effect at each step of the ladder will be evaluated. Furthermore, the compliance with respect to providing stronger relief in response to loss of analgesic effect at the previous level will be ascertained. Thus, it is critical that all modifications of pain treatment and the reasons for these modifications be recorded on the follow-up form.

- 7.6 Statistical Considerations - The objectives of the present study are limited to those described earlier: feasibility, compliance, and effectiveness within individual patients. No attempt is being made in this protocol to compare the guidelines with current practice, or to determine if introducing the guidelines has an impact on the general quality of life for cancer patients with pain. The latter questions will be addressed by other protocols which are being planned.

Because the questions of interest in this protocol are not comparative in nature, we will use the concept of acceptable standard error estimates for evaluating extent of compliance to guidelines as a percent of the total cases entered. We would like to evaluate n patients per centre so that the standard error of the compliance estimate is no more than .06. If compliance is around 80%, then $n=50$ patients will satisfy this objective.

In terms of pain relief, 50 evaluable patients per centre will be sufficient to determine if patients on the guidelines experience a noticeable decrease in pain of one score or more. Indeed, a shift of one score or more can be detected with 95% probability using a two-sided $\alpha = .05$ Wilcoxon Rank Sum Test based on 50 patients

A pilot study of 10 patients will be carried out in each centre. The Collaborating Centre will contact each participant after this pilot phase to clarify guidelines compliance and data collection issues which arise. Thus, a total of 60 patients entered per centre are recommended for study.

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INSTRUCTIONS FOR COMPLETING THE WHO CANCER PAIN RELIEF GUIDELINES FIELD TESTING STUDY FORMS

The forms packet contains an Initial Interview Form, and three pages to record up to 12 follow-up reports. Patient's Current Self-Assessment of Pain Forms and additional follow-up forms are also provided.

Complete the first page of the initial interview when a patient with cancer pain is identified for the protocol. Submit a copy of the Initial Interview Form to the Collaborating Centre in Milan immediately to register the patient. Cases should be assigned numbers sequentially at each hospital. The hospital code and case number will serve to identify the patient on future forms.

- The form should be completed by an adequately instructed nurse.
- The patient's self-assessment of the level of pain and the degree of relief will be the principal items for evaluation.
- The items which should be completed at first visit are on the front page. In the other three pages up to 12 follow-ups can be registered.
- All dates are in day/month/year format.

FIRST VISIT

Report the following items:

Date of first visit (day, month, year), hospital name (with code number), patient's name and surname, sequentially determined case number for the patient, age, sex, height, weight, type of cancer classified according to organ pathology (i.e. breast, lung, colon-rectum etc.), and how many months since cancer was first diagnosed.

I PATIENT'S GENERAL CONDITION: indicate with a check (✓) if cancer is primary, disseminated or if state is now known. Indicate also if the patient is in terminal phase (i.e. prognosis of less than three months survival). Give the ECOG Performance Status Score according to the scale given on the pages of codes. State whether the patient is being treated as an inpatient or outpatient.

II DESCRIPTION OF PAIN: determine how long the patient has had cancer pain, in which part of the body the pain is localized, and what the present pain relates to. Using the Patient's Current Self-Assessment of Pain ask the patient to specify the mean intensity of pain felt in the past 48 hours (as a time-frame). Pain intensity is registered making use of three adjectives: slight, moderate and severe. The patient should then be asked the number of hours with pain per 24 hours (average), and the number of hours of sleep per 24 hours (average).

III PRESENT DRUG TREATMENT FOR PAIN: report the drug treatment for cancer pain relief which the patient is already undergoing. If no treatment is being given, check the box labelled "no drug treatment". If the patient is being treated pharmacologically, give the name of the drugs, the route (OR = oral route, IV = intravenous, IM = intramuscular, R = rectal), dose (mg), schedule and date started.

IV PAIN DRUG RELATED SIDE EFFECTS: in case the patient has already started pharmacological treatments for pain relief, report side effects, if any. If side effects occur, indicate 1 if intensity is slight; 2 if moderate; or 3 if severe, according to patient's judgement.

V OTHER PAIN RELIEVING MODALITIES: indicate the types of other treatments for pain relief undergone recently (within the past four weeks) by the patient, together with the date when treatment was started.

VI INITIAL GUIDELINES TREATMENT: indicate by a check (✓) which of the four categories to define the initial treatment step apply for this patient. (Note that patients receiving regular administration of weak or strong narcotics are not eligible for this field testing study, and that other patients should start treatment on Step 1 or Step 2 regardless of reported pain intensity.)

FOLLOW UP REPORTING

A follow-up report is to be made:

- Weekly for the first two weeks to monitor stabilization of pain status.
- At any time the pain drug treatment is modified.
- Weekly for two weeks after any pain drug treatment modification to monitor the impact of the modification.
- And at a minimum of every four weeks thereafter for stable patients.

Each follow-up report refers to the period between the previous report and the current follow-up visit.

PATIENT'S CURRENT SELF-ASSESSMENT OF PAIN FORM:

At each follow-up assessment, the patient is to complete this form to provide an evaluation of pain intensity, hours of pain, hours of sleep, and evaluation of pain relief provided by the given treatment. This form may be used at a clinic visit or may be submitted (or mailed) later to the clinic coordinator (registrar). Patients may provide self-assessments without being required to return to the clinic.

FOLLOW-UP FORM

1. DATE OF FOLLOW-UP REPORT: carefully and accurately enter the date of the evaluation as day/month/year.
2. ASK THE PATIENT(using the Self-Assessment Form): how bad is the pain? Mark with a check (✓) the adjective which the patient uses to best explain the pain intensity felt. Give the number of hours per 24 hours (average) the patient had pain, and how many hours the patient slept per 24 hours (average). Using a measuring ruler (in millimetres), determine the LASA PAIN RELIEF SCORE (a number from 0 to 100 millimetres measuring from the left to the right) indicated by the placement of the mark (x) by the patient on the LASA scale.
3. PAIN DRUG TREATMENT GIVEN SINCE THE PREVIOUS REPORT: indicate the drugs given, the route of administration (OR = oral route, IV = intravenous, IM = intramuscular, R = rectal), the dose and schedule.
4. PAIN DRUG MODIFICATION: indicate the reason for any change in pharmacological treatment as due to insufficient analgesic effect, excessive side effects, or other reasons (e.g. patient's lack of confidence in the drug, too expensive, etc).
5. PAIN DRUG RELATED SIDE EFFECTS: report side effects (1 = slight, 2 = moderate, 3 = severe) due to pharmacological treatment for pain relief.
6. OTHER PAIN RELIEVING MODALITIES: indicate any other treatment for pain relief which the patient underwent since the previous follow-up report.
7. PATIENT STATUS: indicate if the patient is alive, dead, or lost to follow-up and give the date. This question needs to be completed only once on each follow-up form. An indication that the patient has died signals the conclusion of follow-up, so that no more data will be requested.

3. COMMENTS: enter any comments about the patient's pain and pain treatment course which might be helpful for evaluating the compliance and effectiveness of the guidelines for this patient.

DATA SUBMISSION

Patients are to be followed until death (or until the time when final data analysis for the study will begin). The initial interview data form and the follow-up forms containing data for 12 follow-up assessments should be submitted to the Collaborating Centre in Milan as soon as they are completed. Patient's Current Self-Assessment of Pain Forms need not be submitted, as the data from these forms will be transcribed onto the follow-up forms. Additional follow-up forms, each containing four possible follow-up visit reports, should be submitted to Milan when completed.

PILOT STUDY

The first 10 patients entered from each participating centre will be reviewed as a pilot study. Patient Self-Assessment Forms should be submitted to Milan for these patients to ensure the effectiveness of the methodology. Data for these patients should be submitted more frequently to facilitate rapid review and feedback from the Collaborating Centre in Milan.

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCORE

Score value that the patient is "capable" of performing

- 0 Normal Activity.
- 1 Symptoms but nearly fully ambulatory.
- 2 Some bed time, but needs to be in bed less than 50 per cent of the normal daytime.
- 3 Needs to be in bed greater than 50 per cent of normal daytime.
- 4 Unable to get out of bed.

WHO PAIN RELIEF GUIDELINES FIELD TESTING STUDY 2
INITIAL INTERVIEW FORM

DATE
d d m m y y
 HOSPITAL
 PATIENT NAME CASE NUMBER
 AGE (Years) SEX HEIGHT (cms) WEIGHT (kg)
 TYPE OF CANCER HOW MANY MONTHS SINCE CANCER WAS DIAGNOSED? months

I PATIENT'S GENERAL CONDITION

STATE OF CANCER	Check	ECOG PERFORMANCE STATUS	HOSPITALIZATION STATUS	Check
1. Primary only	<input type="checkbox"/>	Terminal patient	1. In-patient	<input type="checkbox"/>
2. Disseminated	<input type="checkbox"/>	(check if yes)	2. Out-patient	<input type="checkbox"/>
3. Not known	<input type="checkbox"/>		3. Home care only	<input type="checkbox"/>

II DESCRIPTION OF PAIN

How long has the patient had the pain? months
 Where is the pain?
 Pain relates to (check each that applies):
 bone nerve compression soft-tissue extension Other: specif
 visceral involvement raised intracranial pressure muscle spasm

ASK THE PATIENT (PATIENT'S CURRENT SELF ASSESSMENT FORM):

a. How bad is the pain? (past 48 hours) none slight moderate severe
 check one
 b. How many hours of pain per 24 hours (average)? hours
 c. How many hours of sleep per 24 hours (average)? hours

III PRESENT DRUG TREATMENT FOR PAIN - What drug is the patient taking for pain?

Check	Category	Generic name	route	dose	*schedule	date started
<input type="checkbox"/>	No drug treatment					
<input type="checkbox"/>	Non-narcotics					
<input type="checkbox"/>	Weak narcotics					
<input type="checkbox"/>	Strong narcotics					
<input type="checkbox"/>	Anticonvulsants					
<input type="checkbox"/>	Psychotropics					
<input type="checkbox"/>	Antihistamines					
<input type="checkbox"/>	Antidepressants					
<input type="checkbox"/>	Steroids					
<input type="checkbox"/>	Other					

* Schedule: Specify whether only occasionally (3 or less times per week), or frequently; as needed, or regularly by the clock.

IV PAIN DRUG RELATED SIDE EFFECTS (If present, give intensity: 0 = none; 1 = slight; 2 = moderate; 3 = severe)

<input type="checkbox"/> Nausea	<input type="checkbox"/> Bleeding	<input type="checkbox"/> Sweating	<input type="checkbox"/> Vertigo
<input type="checkbox"/> Vomiting	<input type="checkbox"/> Gastralgia	<input type="checkbox"/> Drymouth	<input type="checkbox"/> Others (specify)
<input type="checkbox"/> Drowsiness	<input type="checkbox"/> Restlessness	<input type="checkbox"/> Tremor	

V OTHER PAIN RELIEVING MODALITIES (If yes, specify date and type)

Check	date (dd/mm/yy)	type
<input type="checkbox"/>		Radiation
<input type="checkbox"/>		Surgery
<input type="checkbox"/>		Chemotherapy
<input type="checkbox"/>		Traditional Methods
<input type="checkbox"/>		Others (specify)

VI INITIAL GUIDELINES TESTING - Indicate the initial guidelines step for this patient (check one which applies)

<input type="checkbox"/> No prior drug treatment for pain	→	Start on Guidelines Step 1 for at least 3 days
<input type="checkbox"/> Receiving prior drug treatment for pain, but this prior treatment was not given according to Guidelines (e.g. only occasionally... (3 or less times per week))	→	Start on Guidelines Step 1 for at least 3 days
<input type="checkbox"/> Received prior drug treatment for pain which satisfied the requirements for Guidelines Step 1	→	Start on Guidelines Step 2 for at least 3 days
<input type="checkbox"/> Received prior drug treatment for pain which satisfied the requirements for Guidelines Step 2 or 3 (i.e. regular administration of weak or strong narcotics)	→	Start of Guidelines Step 2 or 3 as indicated

WHO PAIN RELIEF GUIDELINES FIELD TESTING STUDY 2

PATIENT NAME _____

FOLLOW-UP EVALUATION DATA

HOSPITAL _____

CASE NUMBER _____

1. DATE OF FOLLOW-UP REPORT

d	m	y	d	m	y	d	m	y	d	m	y
---	---	---	---	---	---	---	---	---	---	---	---

2. ASK THE PATIENT: (Use self-assessment form)

a. How bad is the pain (past 48 hours)?

check one			check one			check one			check one		
<input type="checkbox"/>	none		<input type="checkbox"/>	none		<input type="checkbox"/>	none		<input type="checkbox"/>	none	
<input type="checkbox"/>	slight		<input type="checkbox"/>	slight		<input type="checkbox"/>	slight		<input type="checkbox"/>	slight	
<input type="checkbox"/>	moderate		<input type="checkbox"/>	moderate		<input type="checkbox"/>	moderate		<input type="checkbox"/>	moderate	
<input type="checkbox"/>	severe		<input type="checkbox"/>	severe		<input type="checkbox"/>	severe		<input type="checkbox"/>	severe	

b. How many hours of pain per 24 hours (average)?

_____	hours	_____	hours	_____	hours	_____	hours
-------	-------	-------	-------	-------	-------	-------	-------

c. How many hours of sleep per 24 hours (average)?

_____	hours	_____	hours	_____	hours	_____	hours
-------	-------	-------	-------	-------	-------	-------	-------

d. LASA Pain Relief Score (0=none; 100=complete)

_____	millimetres	_____	millimetres	_____	millimetres	_____	millimetre
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3. PAIN DRUG TREATMENT GIVEN SINCE THE PREVIOUS REPORT

(give generic name, route [OR, IV, IM, R], dose and schedule)

- Step 1: Non-narcotics
- Step 2: Weak narcotics
- Step 3: Strong narcotics
- Anticonvulsants
- Psychotropics
- Antihistamines
- ADJ Antidepressants
- Steroids
- Others

yes name/route/dose	yes name/route/dose	yes name/route/dose	yes name/route/dose
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. PAIN DRUG MODIFICATION

If pain drug is being modified, check reason(s):
 No analgesia
 Side effects
 Other (specify)

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. PAIN DRUG RELATED SIDE EFFECTS. Give intensity

(0 = none; 1 = slight; 2 = moderate; 3 = severe)

- Nausea
- Vomiting
- Drowsiness
- Bleeding
- Gastralgia
- Restlessness
- Sweating
- Drymouth
- Tremor
- Vertigo
- Others (specify)
- " "

intensity	intensity	intensity	intensity
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. OTHER PAIN RELIEVING MODALITIES (If yes, specify date and type)

- Radiation
- Chemotherapy
- Surgery
- Traditional methods
- Others (specify)

yes	date	type	yes	date	type	yes	date	type	yes	date	type
<input type="checkbox"/>			<input type="checkbox"/>			<input type="checkbox"/>			<input type="checkbox"/>		
<input type="checkbox"/>			<input type="checkbox"/>			<input type="checkbox"/>			<input type="checkbox"/>		
<input type="checkbox"/>			<input type="checkbox"/>			<input type="checkbox"/>			<input type="checkbox"/>		
<input type="checkbox"/>			<input type="checkbox"/>			<input type="checkbox"/>			<input type="checkbox"/>		

7. PATIENT STATUS

- Alive
- Dead
- Lost to follow-up

Yes
 Yes
 Yes

Date last seen _____
 Date of death _____
 Date lost to follow-up _____

_____	_____	_____	_____	_____	_____
d	d	y	m	m	y

8. COMMENTS

— — —