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REPORT ON FOURTH MEETING OF THE WHO TECHNICAL ADVISORY GROUP ON ELIMINATION OF LEPROSY

Geneva, 19 and 20 June 2002

World Health Organization

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REPORT ON FOURTH MEETING OF THE WHO TECHNICAL ADVISORY GROUP ON ELIMINATION OF LEPROSY (TAG)

1. *Background*

Over the last 20 years, MDT had been widely implemented in all endemic countries, curing more than 12 million patients, with very low relapse rates and complete absence of emergence of *M. leprae* strains resistant to MDT. Further shortening and simplification of MDT by introducing an uniform regimen would promote easier logistic support, simpler information systems, reduced training needs and thus better sustainability through integration. The third meeting of TAG (Brasilia, 29-31 January 2002 - document WHO/CDS/CPE/CEE/2002.29) had recommended:

" ... the implementation of six-months MB-MDT regimen for all leprosy patients (PB and MB) on the condition that the outcome will be closely and rigorously monitored through standardized procedures. A uniform regimen based on six MDT blister packs will be of great benefit to patients and health services. This will facilitate integration and demystify the disease. MDT has been shown to be robust in terms of treatment efficacy and safety. Relapse rates are very low (less than one per cent), resistance to MDT is virtually non-existent, and relapse cases can still be cured by MDT".

The WHO Leprosy Group, in close collaboration with TDR, would provide support to ensure close monitoring of the patients recruited in this study in different parts of the world.

A draft protocol for follow-up had been developed by Dr M. D. Gupte and shared among all TAG members and selected experts. The draft protocol had also been extensively reviewed and discussed by the WHO/TDR Steering Committee on Proof of Principle Research at its meeting in Geneva in April 2002. The Committee had strongly endorsed the proposal and agreed that the study on a uniform regimen was urgently needed to facilitate integration and improve access of treatment in many endemic countries.

The purpose of this meeting was therefore:

- to review and finalize the draft protocol;
- to agree on the next steps in the implementation process
- to suggest mechanisms for application and support;
- to develop procedures andtools for close monitoring;
- to develop procedures for data collection and analysis;
- to discuss any other issues which may arise.

2. *Introduction*

Dr Maria P. Neira, Director, Department of Control, Prevention and Eradication (CPE) welcomed all participants to this important meeting of the WHO Technical Advisory Group on Elimination of Leprosy (TAG). She particularly welcomed such a wide balance of expertise, including from both the fields of academic research and management of ongoing field-level activities. Although a great number of challenges remained to be addressed and overcome by 2005, these were now mainly operational issues and the involvement at all stages of both groups of expertise was vital for success. Integration of the treatment of leprosy into general health services was considered not only a vital element but also probably the key to sustaining achievements made so far. Simplification of treatment by introducing a uniform MDT regimen

would therefore contribute significantly to the success of integrated national programmes. She was also appreciative of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) for demonstrating its willingness to provide support to research into these operational issues.

Dr Neira reminded participants that Dr Gro Harlem Brundtland, Director-General, WHO, supported these efforts fully and was enthusiastic about the unique opportunity that currently existed to overcome the challenge that leprosy had presented for so many years. Both political and donor support were currently strong and she urged participants to advocate fully to maintain levels of awareness around the world. She wished participants a successful meeting with open, frank and transparent discussion.

Dr Marijke Becx-Bleumink, Chairperson, thanked Dr Neira for her warm words of welcome, to which she added her own appreciation of the valuable presence of all TAG members, especially the two invited experts – Professor Peter Smith and Dr (Mrs) Kiran Katoch. Participants indicated their approval of the agenda and Dr Becx invited Dr M. D. Gupte to open the proceedings by presenting the draft protocol on a uniform MDT regimen for all types of leprosy patients.

3. *Review of draft protocol for study on uniform MDT regimen for all leprosy patients*

The purpose of the protocol was to study the efficacy and effectiveness of the standard multidrug therapy regimen for multibacillary patients (MB-MDT) for six months as the uniform MDT (U-MDT) for all types of leprosy under routine field conditions. The draft protocol had been widely distributed for comment and additional input and Dr Gupte thanked participants for their valuable contributions. Subject to finalization of the protocol and preparation of a simplified version, it was now ready for implementation. TAG therefore also needed to reach consensus on an appropriate implementation strategy for the study.

4. *Next steps in implementation process and timeframe*

Dr Gupte reported that the timeframe proposed at the last meeting had been met and indicated that, subject to finalization and preparation of a simplified version during this meeting, the first intake of patients was likely to be in September 2002. The main objective was to study, under programme conditions, six months' uniform MDT for all types of leprosy cases and closely monitor treatment response in terms of acceptable cumulative level of a maximum 5% relapse rate at the end of five years.

The study would be an open design with emphasis on close monitoring of the patients during treatment and for at least five years after completion of six monthly doses of U-MDT. The study would require a total of 2500 MB and 2500 PB patients. It would be multicentric and each of the participating countries would be expected to contribute a minimum of 500 newly detected, previously untreated patients (250 MB and 250 PB) for the study.

5. *Mechanisms for application and support*

The finalized protocol together with an application form would be advertised on the Internet by WHO/TDR and distributed to all WHO Representatives and National Leprosy Elimination Programme Managers during August 2002.

The study would be conducted in areas/programmes with reasonably well-organized leprosy elimination programmes. Requirements for the participating countries would include:

- A national leprosy control programme capable of recruiting at least 500 new leprosy patients within two years (250 MB and 250 PB), although countries would be encouraged to recruit larger numbers of patients (up to 2500 MB and 2500 PB).

- Application forms from countries to participate in the study would only be considered if channelled through the appropriate national authorities, including the Ethics Committee.

- A reasonably well-equipped base hospital would be required, either within the district in which the study is being carried out or not far away, in order that patients with complications or serious side-effects could be referred/admitted.

- Adequately trained staff.

- Ability to provide follow-up to patients recruited in the study for a minimum of five years.

- Facilities for rapid communications (telephone, fax, cable and, if possible, Internet).

WHO/TDR would provide support in the development of guidelines, organization of workshops for principal investigators and their teams, identification of an international study coordinator and local independent assessors/monitors, supply of special U-MDT blister-packs, data management and provision of follow-up support. WHO/TDR would also undertake an additional study to assess the cost effectiveness of U-MDT.

TAG would provide support in reviewing applications and continuously monitor the progress with the study.

6. *Procedures and tools for close monitoring*

The study centres selected would have independent monitors appointed by WHO depending on the number of centres participating in the study from the region or country, the number of patients in the study and the geographical area. In addition to the independent monitors, the study as a whole, would have a WHO Study Coordinator to ensure that the protocol was followed uniformly in all centres. Routine reporting of side effects, reactions and relapses would be done on a quarterly basis.

7. *Data collection and analysis*

Each centre would be required to send a detailed annual progress report (including financial details), using a standard format to the WHO Leprosy Group, Geneva. The report should reach WHO by the end of December each year in order to enable review by TAG and WHO/TDR.

8. *Special session: Global case detection trends*

Global case detection trends over the last four years were reviewed by TAG. The Group expressed deep concern regarding the alarming increase in the number of new cases detected in some major endemic countries, notably India.

The trend was paradoxical as information coming from the majority of endemic countries showed clearly that after repeated leprosy elimination campaigns the detection trends showed significant decline.

TAG agreed that such paradoxical trends in some major endemic countries were mainly the result of several operational and administrative shortcomings rather than epidemiological factors.

TAG also expressed the need to encourage the national authorities to undertake urgent critically analysis of the situation.

TAG recommended the establishment of mechanisms to ensure that:

- all programmes strictly follow the definition of a "new case of leprosy" at all times;
- existing information systems are streamlined;
- every programme establishes mechanisms to validate data on case detection before its publication;
- the practice of setting targets for case detection and case discharge existing in some countries should be discontinued, instead the focus be placed on increasing programme coverage and improving cure rates;
- wherever necessary, WHO is willing to provide technical and other support to countries in improving their information systems and in validating case detection data.

Annex 1

WHO TECHNICAL ADVISORY GROUP ON ELIMINATION OF LEPROSY (TAG)
Geneva, 19 and 20 June 2002

AGENDA

Wednesday, 19 June 2002

09:00-09:15	Welcome *(Dr Neira)* Opening remarks *(Dr Becx-Bleumink – Chairperson)*
09:15-10:30	Presentation of the protocol *(Dr Gupte)* Summary of comments received *(Dr Gupte and Dr Engers)* Discussion
11:00-12:30	Implementation of the study *(Dr Gupte)* Discussion
14:00-15:30	Discussion on implementation of the study (continued)
16:00-17:30	Discussion on implementation of the study (continued)

Thursday, 20 June 2002

09:00-10:30	Guidelines for implementation: *Simplified version of protocol* Discussion
11:00-12:30	Criteria to review proposals Discussion
14:00-15:30	Discussion on operational aspects: - selection of countries - workshops for Principal Investigators (PIs) - independent monitors - data collection - guidelines for monitoring progress
16:00-17:30	Finalize next steps: - timeframe - implementation of schedule - any other issues

Annex 2

WHO TECHNICAL ADVISORY GROUP ON ELIMINATION OF LEPROSY (TAG)
Geneva, 19 and 20 June 2002

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** Invited but unable to attend

Annex 3

UNIFORM MDT REGIMEN FOR ALL LEPROSY PATIENTS

PROTOCOL
(20 August 2002)

World Health Organization
Geneva

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UNIFORM MDT REGIMEN FOR ALL LEPROSY PATIENTS

OBJECTIVES

To study efficacy and effectiveness of uniform-MDT (U-MDT) through general health services against the expected level of minimum 95% efficacy over a period of 5 years.

Specific objectives

Under programme conditions, implement 6 months' uniform MDT for all PB and MB leprosy cases and closely monitor treatment response in terms of relapse rate not exceeding the maximum acceptable cumulative level of 5% at the end of 5 years. Relapse rates are to be considered for all categories of leprosy cases, however they are to be specifically analysed separately for PB and MB subgroups. Patients will be actively followed for a minimum period of 5 years to monitor for reactions and relapses and subsequently will be encouraged to report any adverse events to the health authorities.

ADDITIONAL OBJECTIVES

Acceptability of uniform MDT by patients

Patients of leprosy in selected areas will have the option to select treatment of their choice, viz., PB or MB MDT or U-MDT. They will be provided with detailed information about the Uniform drug regimen, its advantages and limitations. Managers should aim to recruit all new leprosy cases. It is expected that refusals will constitute less than 10% of the new PB and MB cases detected during the intake period. The patients who volunteer to join uniform MDT will be required to give informed written consent. Patients will be free to leave the study , if they so wish, and opt for the routine MDT at any time. All these events will be monitored from the point of view of acceptability by the patients.

Safety

MB MDT has been in use now for several years and its adverse effects, which are minimal, are widely known. A Special Event Form and MDT Serious Adverse Drug Reaction Reporting Form for reporting these adverse effects have been developed and will be used in this study. Patients will be provided with immediate care and treatment for any adverse effects and alternative treatment, if indicated.

Compliance

Uniform MDT will be administered in the selected areas as supervised monthly doses followed by self-administration of daily doses. Patients will be informed regarding the importance of regular treatment. Information regarding compliance will be recorded based on drug administration records at the end of the 6 doses of uniform MDT. (Cost-effectiveness of uniform MDT will be considered in a separate study)

STUDY DESIGN

First component of the design is with respect to implementation of uniform MDT at the selected district level. It would involve various training workshops, standardization procedures, streamlining data management, etc.

Next, within the selected districts an open study design to provide for close monitoring of the patients will be adopted. It is possible to implement 6 months' uniform drug regimen under field conditions and accumulate data by meticulous follow-up and by providing the necessary

safeguards. There is a need for longer follow-up to generate information on relapses, and active post-treatment follow up for a period of 5 years will be done.

STUDY SITES

Study sites will be selected in response to the applications received through respective country governments by the WHO/TDR after the project protocol is circulated to various endemic countries. This study will be conducted in areas/programmes with reasonably well-organized leprosy control services. It will be preferable to include programmes, covering a complete district or similar administrative unit/area.

Requirements for the participating countries include:

1) a leprosy control programme capable of recruiting at least 500 new, previously untreated leprosy patients within 2 years' time (250 PB and 250 MB);
2) application forms should enclose clearance from the appropriate Ethics Committees;
3) a reasonably equipped base hospital, either within the district or nearby, for admission of patients, should complications or serious side effects to drugs occur;
4) adequately trained staff;
5) the programme should have ability to follow the patients recruited in the study for a minimum period of 5 years;
6) facilities for rapid communications, such as telephone/cable/fax and eventually Internet.

Countries are encouraged to recruit larger numbers of patients, up to 2500 PB and up to 2500 MB patients within 2 years.

NUMBER OF PATIENTS

This study will need a total of 5000 newly detected, previously untreated patients (2500 PB and 2500 MB). It will be a multicentric study and each participating country is expected to contribute a minimum number of 250 PB and 250 MB patients for the study. Countries are encouraged to recruit larger number of patients, up to 2500 for PB and MB categories each.

TIME FRAME

- Start preparatory activities and training workshops for prospective Principal Investigators and facilitate preparation of project proposals.
- Organise supply of drugs and other infrastructural needs by October 2002.
- Intake to start by September 2002. Intake will continue for a period of 2 years.
- TAG will closely monitor and review progress of the study at least once a year.
- First Interim analysis will be taken by WHO/TDR in 2005.
- Final analysis and publication of the results by WHO/TDR end 2009.

INCLUSION AND EXCLUSION CRITERIA

All the newly detected and previously untreated leprosy patients will be eligible for inclusion. Old patients, who are already receiving PB or MB MDT, returned defaulters and those who relapse subsequent to the earlier therapy, will not be eligible for inclusion for this study.

DRUG REGIMEN - UNIFORM MDT

Composition and pharmaceutical form: Blister packs for leprosy patients.

Each blister pack containing the drugs required for 4 weeks' treatment:

1. Rimactane® (Rifampicin)

   Adults: 2 capsules of 300 mg

   Children (10-14 years): 1 capsule of 300 mg and 1 capsule of 150 mg

2. Lamprene® (Clofazimine)

   Adults: 3 capsules of 100 mg and 27 capsules of 50 mg

   Children (10-14 years): 3 capsules of 50 mg and 13 capsules of 50 mg

3. Dapsone

   Adults: 28 tablets of 100 mg

   Children (10-14 years): 28 tablets of 50 mg

Dosage and administration:

Patients must be given instruction in how to take their medication correctly and told to report any untoward signs and symptoms promptly. Patients should keep medicines in a secure area out of reach of small children. The 4-weeks' treatment should be administered 6 times.

Adults:

600 mg rifampicin every four weeks + 300 mg clofazimine every four weeks +

50 mg once a day + 100 mg dapsone once a day

Children (10-14 years):

450 mg rifampicin every four weeks + 150 mg clofazimine every four weeks +

50 mg clofazimine once every other day + 50 mg dapsone once a day

Children (< 10 years):

The dosage should be adjusted to body weight: 10-20 mg/kg rifampicin +

1-2 mg/kg clofazimine + 1-2 mg/kg dapsone.

Detailed prescribing information is given in Appendix 2.

ETHICAL CONSIDERATIONS

Approval of authorities: Before the WHO/TDR Committee reviews the study application, approval of the competent governmental and institutional authorities must be obtained, including approval by institutional/national ethical committees.

Consent of the patients: The general conduct of the study will be guided by ethical and scientific standards for carrying out biomedical research in human subjects by following international guidelines, including the Declaration of Helsinki - Ethical Principles for Medical Research involving Human Subjects, October 2000 (www.wma.net); International Ethical Guidelines for Biomedical Research Involving Human Subjects, July 2002 (www.cioms.ch/guidelines), prepared by the Council for International Organizations of Medical Sciences (CIOMS); CIOMS International Guidelines for Ethical Review of Epidemiological Studies, 1991, and the current versions of WHO and ICH Guidelines for Good Clinical Practice (GCP).

In any research involving human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He/she should be informed that he or she is at liberty to abstain from his/her consent at any time. The doctor should then obtain the subject's freely given, informed consent, in writing (Appendix 7).

In addition, national and institutional requirements with respect to patient consent must also be met. Each participating treatment centre must furnish evidence of compliance with these requirements.

CONDUCT OF THE TRIAL

At the intake: The Principal Investigator will ensure that every new patient is carefully assessed for suitability for inclusion in the study according to the inclusion and exclusion criteria laid down in the protocol. A detailed clinical examination will be done. Wherever indicated, other tests necessary to rule out any systemic pathology will be done. Each patient will be informed about the nature of his/her disease, the duration and rhythm of the treatment and the importance of the compliance for drug consumption. Patients will also be informed about important special events, such as reactions, neuritis, appearance of new skin patches, and side effects, and advised to report such events to the treatment facility as quickly as possible.

If the patient is willing to participate in the study, the Principal Investigator (PI) should obtain the subject's informed consent in writing in the prescribed form (Appendix 7). In case of a child, consent of one of the parents or the legal guardian will be obtained. Patients who are not willing to join the study will be given the standard WHO-PB or MB-MDT. The PI will maintain the confidentiality.

Patients who refuse to participate in the study: Records will have to be maintained for those patients who opt out of this study, clearly documenting the reasons for refusals.

During treatment: Patients included in the trial will be given the monthly-supervised dose in the presence of the PI or his/her nominee. Home- visits can be organized without violating ethical norms by the health auxiliaries to ensure regularity of treatment. This visit should be used to examine patients for any evidence of side effects, reactions or any other complications and where necessary to provide missed U-MDT dose to absentees. At each clinic visit for the supervised dose of treatment, patients will be interviewed and carefully examined for side effects, reversal reactions, and neuritis. The findings, if any, will be recorded in the special event forms or the adverse drug reaction reporting forms as per the requirement. Besides these events, any other incidents resulting in removal/dropping of a patient from the trial, for example migration/death/refusal will also require completion of a special event form.

If any patient fails to attend a monthly clinic, he/she should be contacted within 24 hours, if possible, to find out the reason for absence. It is possible that some patients may default because of side effects or complications.

Regularity of treatment: A patient who completes the regimen within 9 months will be considered a regular patient. Others who take longer to complete the prescribed number of doses in the regimen will be considered as irregular patients. Please note that no patient will be dropped from the trial on the grounds of irregularity.

At the end of treatment: A detailed clinical examination will be performed at the end of the treatment.

Follow-up after completion of treatment: Each patient will be clearly informed regarding the symptoms and signs of reaction, relapse, and neuritis and to report such events immediately to the centre. Patients will be actively followed up for evidence of relapse once every year, up to 5 years. Patients will be encouraged to report these events voluntarily beyond the 5 years.

Annual follow up of the patients is the responsibility of the participating centres and all efforts must be made to minimise the number of drop-outs to follow up. Since in the field situation there is a possibility of delays, some special campaigns for periodic assessments can be considered.

INFORMATION SYSTEM

Each centre will use the standard reporting form to facilitate uniform reporting to the coordinating centre. Following are the various forms to be used in the study (Appendix 1):

Form I	- Intake
Form 2	- At the end of treatment
Forms 3-7	- Annual follow-up forms
Form 8	- Special event form
Form 9	- MDT serious adverse drug reaction reporting form (Appendix 4).

In addition, each centre may use the existing data collection system at their centre. Two sets of reporting forms will be issued for each patient. Original forms will be retained at the study centre and the duplicate copies will be sent to the Leprosy Unit, WHO (the coordinating centre). All forms will be sent in once in every three months i.e., during the first week of January, April, July and October. In addition, a progress report and budget renewal request, in the prescribed format will be sent every year so as to reach the Leprosy Unit, WHO, Geneva, by the end of December (for TAG to review in its January meeting). WHO will provide the appropriate forms to all study sites.

EXAMINATION PROCEDURES

These will include:

1) collection of information on patient identification and medical history at the time of intake and obtaining of informed consent;
2) initial and periodic clinical examinations and recording of the findings on standard forms at intake, treatment completion, and annually for a period of up to 5 years;

3) monitoring for side effects, complications, reactions, neuritis, and relapses and their reporting during the study period;
4) Information on loss of patients for follow-up on account of refusal, migrations and death.

FREQUENCY OF EXAMINATIONS DURING TREATMENT

Patients will be clinically examined at every visit to the health centre. Monitoring of side effects will be carried out through questioning of the patient by the physician and, where indicated, through haematological and other investigations. The physician or the paramedical worker will ask the patient the question, "How do you feel today?" and, in the event of the patient having a specific complaint, he/she will be further investigated. The patient's response and physical findings should be recorded, along with an indication as to whether the side effect is likely to be attributed to any of the drugs used in the trial. The treatment of drug side effects will be carried out promptly and patients hospitalised as necessary. In addition, occurrences of reaction, neuritis, and relapse will be monitored during treatment and follow up periods. Services, available to the patients should be of good quality, to ensure patient compliance and also to ensure availability of information on all the special events of interest to the project.

SUSPENSION / STOPPING OF TREATMENT

Drug administration may be stopped or temporarily suspended at the discretion of the Principal Investigator, in the following situations:

1) occurrence of severe intercurrent illness;
2) adverse drug reactions;
3) patient's refusal to continue treatment;
4) severe complications requiring cessation of treatment;
5) any other situation considered necessary by the Principal Investigator.

The PI will be responsible for management of the situation including further management of leprosy, in consultation with the Independent Monitor.

MONITORING DURING TREATMENT

In order to standardize this procedure, this activity should include the following steps:

1) Aall patients included in the study should be informed at the first visit about the rhythm and duration of treatment.
2) Patients must be informed about the importance of compliance for treatment.
3) A written appointment card with date and time of the next visit should be given to the patient, also in the local language.
4) If the patient fails to keep an appointment, a home-visit should be made within the next 24 hours, to ascertain the reason for absence and to motivate the patient to come for treatment and utilise the opportunity for supervised administration of U-MDT.
5) The reason for absence should be recorded.

END POINT OF TREATMENT

The treatment will be stopped after completion of 6 doses of uniform MDT, for all patients.

FOLLOW-UP AFTER COMPLETION OF TREATMENT

All patients will be clearly informed regarding the symptoms and signs of relapse, reactions, and neuritis and encouraged to report such events immediately. Patients will be examined for clinical changes and evidence of relapse every year up to 5 years after the completion of treatment and will be encouraged to report to the health facility during the subsequent periods.

MANAGEMENT OF SPECIAL EVENTS

Management of serious drug side-effects/toxicity: In the event of serious side-effects/ toxicity, suspected to be associated with the drugs used in the study, the PI will stop all anti-leprosy treatment and hospitalise the patient for the management of the event (Appendix 3).
The Principal Investigator must take full responsibility for such decisions in the best interest of his/her patient.

Management of reaction and neuritis: The management of reactions will be performed according to the standards set by the participating centres (Appendix 5).

Management of relapse: The possibility of relapse after completion of treatment should be suspected if new lesion(s) appear. The initial clinical findings should be compared with the findings at the follow-up examinations to establish the presence of true new lesion(s). The PI should seriously consider the possibility of reactions. The independent monitor is to be informed about the event (for the role of independent monitor, see Appendix 6). If the independent monitor is not available for immediate confirmation, decision on re-treatment is to be made by the P.I. alone based on his/her findings.

Patients with confirmed relapse will be administered one more course of the uniform MDT and will be reassessed and kept under follow up. All events of relapses are to be reported to the coordinating centre at the earliest using the Special Event forms. The independent monitor will still examine the patient and/or records subsequently for confirmation of diagnosis of relapse. If he/she confirms suspicion of relapse, the findings and conclusions of the independent monitor, will also be recorded and reported to the coordinating centre.

OUTCOME INDICATORS

Efficacy and Effectiveness of the regimen will be assessed in terms of at least 95% success at the end of 5 years of follow up. Success will be measured in terms of absence (not occurrence) of relapse. A cumulative confirmed relapse rate of not more than 5% during the follow up period of 5 years from the date of completion of uniform MDT is considered acceptable. The efficacy and effectiveness will be assessed for all patients and for PB and MB patients separately.

Acceptability will be assessed in terms of number and proportion of patients opting for the uniform MDT. Reasons for refusal will be documented.

Safety will be assessed in terms of drug related episodes.

Compliance will be assessed in terms of patients completing 6 doses of U-MDT. This will be based on the patients' records.

MONITORING THE STUDY

The trial centres will have an independent monitor appointed by WHO depending on the number of centres participating in the trial from the region or the country, the number of patients in the

study, and the geographical area. In addition to the independent monitor, the trial as a whole will have a WHO trial coordinator to ensure that the trial protocol is followed uniformly in all centres. Routine reporting of side effects, reactions and relapses will be done on a quarterly basis.

Each centre will be required to send a detailed annual progress report (including budget details), using a standard format, to the Leprosy Unit, WHO, Geneva. The report should reach WHO by the end of December each year to enable review by the TAG/WHO/TDR.

MDT SUPPLIES

Novartis donates all MDT supplies to WHO free of cost for distribution to all leprosy patients all over the world. They will supply special packages of 6 months uniform MDT in blister packs for both adults and children through WHO. This package will contain information on uniform MDT for health workers and patients in 4 languages (English, French, Hindi, and Portuguese).

DATA MANAGEMENT

For this multicentric trial, creation of database, updating the database and periodical analysis of data collected from various participating centres, will be undertaken at the Leprosy Unit, WHO. WHO will provide to all the PIs necessary software for data management, updating of database, and periodical analysis will be undertaken by the PIs. Coordinated analysis will be undertaken by the Leprosy Unit, WHO/TDR.

PUBLICATIONS

As the success of the study will depend upon close collaboration among many individuals working in different organizations, the analysis of the data as well as the authorship of publications resulting from the trial will be collective, and the data analysis and publications will be coordinated through the Leprosy Unit WHO. After the final report is published, PIs will be encouraged to publish any special aspects of their studies in consultation with WHO/TDR. PIs may present the reports of the study from their centres at national levels in consultation with the WHO trial coordinator.

APPENDIX 1

SAMPLE STANDARD REPORTING FORMS

UNIFORM MDT REGIMEN FOR ALL LEPROSY PATIENTS
FORM 1 – INTAKE FORM

1. Country code : ---
2. Centre code : ---
3. Patient Identification Number : --- --- --- --- ---
4. Regimen : ---
   (Child – 1, Adult – 2)
5. Name : --- --- --- --- --- --- --- --- --- --- ---
6. Age : --- ---
   (Years completed)
7. Sex : __
   (Male – 1, Female – 2)
8. Date of examination and intake : ---/---/--- --- --- ---
9. Number of skin patches : ---
   (1 patch – 1, 2-5 patches – 2, 6 or more – 3, diffuse infiltration – 4)
10. Number of nerve lesions : ---
11. Presence of Grade-2 disability : ---
    (Yes – 1, No – 0)
12. Evidence of reaction : ---
    (Mild – 1, Severe –2, No – 0)
13. Neuritis : ---
    (Mild – 1, Severe –2, No – 0)
14. Previous leprosy treatment : ---
    (Yes – 1, No – 0)
15. Informed Consent : ---
    (Patient – 1, Legal guardian – 2)

UNIFORM MDT REGIMEN FOR ALL LEPROSY PATIENTS
FORM 2 – AT THE END OF SIX MONTH TREATMENT

1. Country code : ---

2. Centre code : ---

3. Patient Identification Number: --- --- --- --- ---

4. Regimen : ---
(Child – 1, Adult – 2)

5. Name : -- ---- --- --- --- --- --- --- ---

6. Age : --- --- 7. Sex : __
(Years completed) **(Male – 1, Female – 2)**

8. Date of completion of 6 doses of U-MDT :---/---/--- -- -- ---

9. Date of examination : ---/---/--- --- --- ---

10. Special event reported during past 6 months : ---
(Yes – 1, No – 0) If Yes, specify

10.1. Appearance of New lesion(s): --- 10.2. Reactions : ---
(Yes – 1, No – 0) **(Mild – 1, Severe –2, No – 0)**

10.3 Neuritis :--
(Yes – 1, No – 0)

10.4. Adverse Drug Reactions :---- 10.5 If yes, specify: ----------
(Yes – 1, No – 0)

10.6. Discontinuation : ---
(Not discontinued – 0, Refusal – 2, Migration – 3, Death – 4, Others - 5)

10.6.1. If others, specify reason : ----------

10.7. Date of special event : ---/---/---------

(Note: Kindly fill and attach special event form – form 8, if special event is 'yes')

11. Clinical Status

11.1 Skin : ----
(Same – 1, Improved – 2, Worsened – 0)

11.2 Nerve : ----
(Same – 1, Improved – 2, Worsened – 0)

UNIFORM MDT REGIMEN FOR ALL LEPROSY PATIENTS
FORMS 3-7– ANNUAL REPORTING FORMS

1. Country code : --- 2. Centre code : ---

3. Patient Identification Number: --- --- --- --- ---

4. Regimen : ---
(Child – 1, Adult – 2)

5. Name : -- ---- --- --- --- --- --- --- ---

6. Age : --- --- 7. Sex : __
(Years completed) **(Male – 1, Female – 2)**

8. Date of examination : ---/---/--- --- --- ---

9. Year of follow-up (circle appropriate) : 1 / 2 / 3 / 4 / 5

10. Special event reported during past 6 months : ---
(Yes – 1, No – 0) **If Yes, specify**

10.1. Appearance of New lesion(s): --- 10.2. Reactions: ---
(Mild – 1, Severe –2, No – 0) **(Yes – 1, No – 0)**

10.3 Neuritis --
(Mild –1, Severe –2, No – 0)

10.4. Discontinuation of follow up : ---
(Not discontinued – 0, Refusal – 2, Migration – 3, Death – 4, Others - 5)

10.3.1. If others, specify reason : ----------

10.5. Date of special event : ---/---/---------

(Note: Kindly fill and attach special event form – form 8, if special event is 'yes')

11. Clinical Status

11.1 Skin : ----
(Same – 1, Improved – 2, Worsened – 0)

11.2 Nerve : ----
(Same – 1, Improved – 2, Worsened – 0)

UNIFORM MDT REGIMEN FOR ALL LEPROSY PATIENTS
FORM 8 – SPECIAL EVENT FORM

1. Country code : --- 2. Centre code : ---

3. Patient Identification Number: --- --- --- --- ---

4. Regimen : ---
(Child – 1, Adult – 2)

5. Name : -- ---- --- --- --- --- --- --- ---

6. Age : --- --- 7. Sex : __
(Years completed) **(Male – 1, Female – 2)**

8. Date of examination : ---/---/--- --- --- ---

9. Special event reported after the last examination : ---
(Yes – 1, No – 0) If Yes, continue

9.1. Appearance of New lesion(s): --- 9.2. Reactions : ---
(Mild – 1, Severe –2, No – 0) **(Yes – 1, No – 0)**

9.3. Neuritis : --- 9.4. Adverse Drug Reactions :----
(Mild – 1, Severe –2, No – 0) **(Yes – 1, No – 0)**

9.4.1. If yes, specify: ----------

9.5. Discontinuation : ---
(Not discontinued – 0, Refusal – 2, Migration – 3, Death – 4, Others - 5)

If others, specify reason : ----------

9.6 Relapse :---
(Yes –1, No –0)

9.6.1 Date of special event : ---/---/---------

10. Hospitalized : ---
(Yes – 1, No – 0)

11. Treatment given for the special event (Specify) : ---

12 If relapse confirmed, re-treatment given :---
(Yes – 1, No – 0)

12.1 Date for commencing re-treatment :--/--/----

13 Continuation of MDT : ----
(at treatment phase)
(Continued – 1, Suspended – No: of weeks, Not applicable – 0)

14. Outcome : ---

(Fully recovered – 1, Partially recovered – 2, Not applicable – 0)
FORM 8 – SPECIAL EVENT FORM (contd.)

Please attach a detailed account of investigations, management and the final outcome of any suspected relapse or serious drug-side effects

Date: ---/---/--------- Medical Officer: ----------

16. Independent Monitor's Report : -----
(Required – 1, Not Required – 0)

17. Independent monitor conclusion :

APPENDIX 2

PRESCRIBING INFORMATION

Free of charge
Supplied by World Health Organization (WHO)
Donated by Novartis

Uniform MDT
Treatment of leprosy with multidrug therapy* (MDT)

Rimactane® (Rifampicin)
Adults: 2 capsules of 300 mg
Children (10-14 years): 1 capsule of 300 mg and 1 capsule of 150 mg
Lamprene® (Clofazimine)
Adults: 3 capsules of 100 mg and 27 capsules of 50 mg
Children (10-14 years): 3 capsules of 50 mg and 13 capsules of 50 mg
Dapsone
Adults: 28 tablets of 100 mg
Children (10-14 years): 28 tablets of 50 mg

DOSAGE AND ADMINISTRATION

Patients must be given instruction in how to take their medication correctly and told to report any untoward signs and symptoms promptly.

Each blister pack contains treatment for 4 weeks. The 4-weeks' treatment should be administered 6 times.

ADULTS BLISTER PACK

600 mg rifampicin every four weeks + 300 mg clofazimine every four weeks +
50 mg clofazimine once a day + 100 mg dapsone once a day

Children blister pack (10-14 years)

450 mg rifampicin every four weeks + 150 mg clofazimine every four weeks +
50 mg clofazimine once every other day + 50 mg dapsone once a day

Children (< 10 years)

The dosage should be adjusted to body weight: 10-20 mg/kg rifampicin +
1-2 mg/kg clofazimine + 1-2 mg/kg dapsone.

TREATMENT WITH MDT UNDER SPECIAL CIRCUMSTANCES

Lepra reactions
MDT should not be interrupted during a lepra reaction. Moreover, MDT reduces the frequency and the severity of lepra reactions.

Treatment of patients with concomitant tuberculosis
If the patient has both tuberculosis and leprosy, it is necessary to treat both infections at the same time. Appropriate antituberculosis therapy should be given in addition to MDT. Rifampicin is common to both regimens and must be given at the dosage required for tuberculosis.

Treatment of patients with concomitant HIV infection
The management of a leprosy patient infected with HIV is the same as that of any other patient. Information available so far indicates that the response of such patients to MDT is similar to that of any other leprosy patient and management, including treatment of reactions, does not require modifications.

Patients who do not tolerate dapsone
If dapsone cannot be given, patients can be treated by the standard combination of rifampicin and clofazimine. Dapsone should be removed from the blister packs before handing it to the patient.

CONTRAINDICATIONS

Hypersensitivity to rifampicin (and/or other rifamycins), clofazimine, dapsone (and/or its derivatives) or any of the excipients.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

None of the drugs described below should be used alone for the treatment of leprosy. All the drugs must be used in combination to prevent the emergence of drug resistance.

RIFAMPICIN

The "flu syndrome" (fever, shivering and, possibly, headache, dizziness and musculoskeletal pain) is chiefly encountered during intermittent therapy and may be a prelude to serious complications such as thrombocytopenia, purpura, haemolytic anaemia, dyspnoea and asthma-like attacks, shock, and renal failure. Where the "flu syndrome" assumes a relatively severe form, and, if the aforementioned serious complications occur, the medication must be withdrawn.

Corticosteroids may prove useful in attenuating possible immunopathological reactions.
In patients with chronic liver disease, as well as in chronic alcoholics and undernourished patients, the therapeutic benefits of rifampicin must be weighed against the possible risks. In the presence of severely impaired liver function or jaundice the dosage may have to be reduced.
Owing to its enzyme-inducing effect, rifampicin must be employed with extreme caution in patients with porphyria, because activation of delta-aminolaevulinic acid synthetase may lead to an acute manifestation of the porphyria. During prolonged treatment blood counts and liver function tests should be performed periodically, and at baseline if possible.

Patients should be informed that rifampicin may cause reddish discoloration of body fluids, and occasionally other body secretions, e.g. urine, sputum, lacrimal fluid, faeces, saliva, sweat. It may permanently discolour soft contact lenses.

Antacids, opiates, anticholinergic drugs and ketoconazole reduce the bioavailability of rifampicin. To avoid this interaction, rifampicin must be administered a few hours before these preparations. Owing to its enzyme-inducing effect, rifampicin accelerates the metabolism of many concomitantly administered drugs, e.g. oral anticoagulants, oral antidiabetics, digitalis preparations, antiarrhythmics, methadone, hydantoins, nortriptyline, benzodiazepines,

corticosteroids, oral contraceptives, theophyllines, chloramphenicol, azole antifungal agents, cyclosporin A, azathioprine, beta-blockers, calcium-channel blockers, enalapril, cimetidine.

CLOFAZIMINE

After prolonged administration in high doses, clofazimine may accumulate in tissue, e.g. the wall of the small bowel, and precipitate. Enteropathy may develop if crystals are deposited in the lamina propria of the jejunal mucosa and the mesenteric lymph nodes, sometimes leading to intestinal obstruction. If gastrointestinal symptoms develop during treatment, the dosage should be reduced or the interval between doses prolonged. Symptoms may slowly regress on withdrawal of the drug. In the event of persistent diarrhoea or vomiting, the patient should be hospitalized.

If possible, leprosy patients suffering repeatedly from abdominal pain and diarrhoea, as well as those with liver or kidney damage, should not be treated with clofazimine. If treatment is necessary, these patients should be kept under medical supervision. Daily doses of > 100 mg clofazimine should be given for as short a time as possible (< 3 months) and only under close medical supervision.

Patients should be warned that clofazimine may cause discoloration of the conjunctiva, lacrimal fluid, sweat, sputum, urine, faeces, nasal secretions, semen and breast milk and reddish to brownish-black discoloration of the skin. They should be informed that discoloration of the skin, although reversible, may take several months to disappear after the end of clofazimine therapy.

DAPSONE

Dapsone should be given with caution to patients with glucose-6-phosphate dehydrogenase deficiency, methaemoglobin reductase deficiency or haemoglobin M, or if the patient is exposed to other agents or conditions capable of producing haemolysis (e.g. certain infections, diabetic ketosis).

When feasible, baseline and subsequent monitoring of liver function is recommended. If abnormal, dapsone should be discontinued until the source of the abnormality is established.
The patient should be warned to report the presence of clinical signs such as fever, pallor, purpura or jaundice. Complete blood counts should be carried out frequently in patients receiving dapsone. If a significant reduction in leucocytes, platelets or haemopoiesis is noted, dapsone should be discontinued and the patient monitored intensively.

Severe anaemia should be treated prior to the initiation of therapy with dapsone, and haemoglobin monitored.

Dapsone may be poorly tolerated by patients with severe cardiopulmonary disease.

PREGNANCY AND LACTATION

Leprosy is exacerbated during pregnancy and WHO therefore recommends that MDT be continued unchanged during pregnancy. A small quantity of the antileprosy drugs is excreted in breast milk but there have been no reports of adverse effects as a result of this, with the exception of mild discoloration of the infant caused by clofazimine.

UNDESIRABLE EFFECTS

The most frequent and/or most severe undesirable effects are:

RIFAMPICIN

Increase in liver enzymes, hepatitis, jaundice; leucopenia, eosinophilia, thrombocytopenia; 'flu-syndrome' with or without complications; gastric intolerance, erosive gastritis, pseudomembranous colitis; skin rashes, exfoliative dermatitis, Lyell's syndrome and pemphigoid reactions; dizziness, visual disturbances; muscle weakness.

CLOFAZIMINE

Reversible skin discoloration, skin rash, photosensitivity reactions; gastrointestinal disturbances, including eosinophilic enteropathy; conjunctival discoloration, vision disturbances; hyperglycaemia.

DAPSONE

Haemolysis, methaemoglobinaemia, blood dyscrasias; hepatitis; headache, vertigo, tinnitus, peripheral neuropathy; cutaneous hypersensitivity reactions; nausea, vomiting.

OVERDOSE - SIGNS AND SYMPTOMS

RIFAMPICIN

Reddish-brown or orange discoloration of the skin, sputum, lacrimal fluid, sweat and/or faeces ("red man syndrome"); nausea, vomiting, abdominal pain; enlargement of the liver, jaundice, elevated liver enzyme levels; possibly acute pulmonary oedema, lethargy, clouding of consciousness, convulsions.

Treatment
Gastric lavage together with administration of an activated charcoal suspension via the stomach tube; general supportive measures to maintain vital functions; forced diuresis; haemodialysis; in the presence of severe liver damage, bile drainage if necessary.

CLOFAZIMINE

No specific data are available on the treatment of overdose with clofazimine. In cases of acute overdose the stomach should be emptied by inducing vomiting or performing gastric lavage, and symptomatic treatment should be given as required.

DAPSONE

Signs and symptoms
Nausea, vomiting and/or hyperexcitability can appear a few minutes up to 24 hours after ingestion of an overdose. Methaemoglobin-induced depression, convulsions and severe cyanosis require prompt treatment.

Treatment
In normal and methaemoglobin-reductase-deficient patients, methylene blue, 1-2 mg/kg body weight, given slowly i.v. is the treatment of choice. The effect is complete in 30 minutes, but may have to be repeated if methaemoglobin reaccumulates. For non-emergencies, if treatment is needed, methylene blue may be given orally in doses of 50 mg capsules every 4-6 hours till cyanosis is relieved.

The administration of activated charcoal (20 gm four times daily) substantially increases the elimation of dapsone and its acetylated metabolite. Haemodialysis may also be useful.

EXCIPIENTS

Rimactane*® *(Rifampicin)

Calcium stearate, lactose, iron oxide red, titanium dioxide, gelatin. The 300 mg capsules also contain iron oxide yellow and black.

Lamprene*® *(Clofazimine)

Butylated hydroxytoluene; sodium salt of ethyl hydroxybenzoate; sodium salt of propyl hydroxybenzoate; p-methoxy acetophenone; propylene glycol; rapeseed oil; soybean lecithin; hydrogenated soybean oil; partially hydrogenated vegetable oils; beeswax; gelatin; glycerol; citric acid; ethylvanillin; black iron oxide, red iron oxide.

DAPSONE

Potato starch BP, silica colloidal anhydrous BP, magnesium stearate BP, croscarmellose sodium NF, povidone BP. The 100 mg tablets also contain methyl hydroxybenzoate BP, hydroxy propyl methylcellulose BP, macrogol 400 and polysorbate 80. The 50 mg tablets also contain lactose BP and sunset yellow S-ph.

STORAGE

Protect from light, moisture and heat.
The preparation should not be used after the date marked "EXPIRY" on the pack.
Medicines should be kept out of the reach of children.

APPENDIX 3

MONITORING OF DRUG SIDE-EFFECTS AND TOXICITY

Patients will be interviewed and clinically examined at every visit during the 6 months of U-MDT administration. Monitoring of side effects will be carried out through questioning of the patients by the investigator or by an experienced paramedical worker. In the event of the patient having a specific complaint, he/she will be further investigated, where indicated, through haematological and other investigation. In case of serious side effect, patient's response and physical findings should be recorded in the Special Events form.

All the three known antileprosy drugs, rifampicin, clofazimine and dapsone, being used in the study have been proved to be safe and well tolerated in the leprosy control programmes all over the world. However, the investigator must ensure that the combination is safe for his/her patients. Some important drug side effects, which should be kept in mind while questioning the patient during every monthly examination, include:

i) Gastrointestinal - manifesting as severe nausea, vomiting and diarrhoea (Commonly associated with Clofazimine);
ii) Dermatitis manifesting as exfoliative dermatitis, photodermatitis or hypersensitivity reactions (Commonly associated with Dapsone);
iii) Hepatitis - manifesting as jaundice (Commonly associated with Rifampicin, and Dapsone);
iv) Central nervous system - manifesting as dizziness, vertigo, behavioural changes, psychosis (Commonly associated with Dapsone).

In addition, the investigator should be alert to the occurrence of any other side effects that have not been listed. In the event of a serious side-effects, strongly suspected to be associated with the drugs used in the trial, the Principal Investigator will stop all antileprosy treatment and hospitalise the patient for the management of the event.

GENERAL GUIDELINES FOR THE MANAGEMENT OF SERIOUS SIDE EFFECTS

For example:

If a patient reports with severe dermatitis during the second month, the physician may suspect hypersensitivity reaction to one of the drugs used in the trial. All antileprosy treatment will be stopped and the patient will be hospitalised for investigations and management of this event.

The patient's condition may improve within a few weeks. The results of the investigations may indicate the nature and cause of the dermatitis (such as allergic, bacterial, fungal, chemical or drug induced).

At this stage, the investigator must decide if the antileprosy drugs were responsible for dermatitis or not. If the investigator is reasonably certain that one of the antileprosy drugs caused this condition, then the patient **will be put on alternative therapy**.

The Principal Investigator, if necessary, in consultation with the independent monitor, will decide further management of patients removed from the trial.

The Principal Investigator must take full responsibility for all such decisions in the best interest of his/her patient.

APPENDIX 4

Adverse Drug Reaction Form

MDT SERIOUS ADVERSE DRUG REACTION REPORTING FORM

This form should be sent to WHO/CDS/LEP (fax 00 41 22 791 48 50, Email daumeried@who.int)

A. PATIENT INFORMATION

Patient identifier(initials)
Location identifier (country, district, health centre)

Age or date of birth (dd-mm-yy)

Sex
female
male

Weight

B. SERIOUS ADVERSE REACTION

Seriousness criterion

Life-threatening	
Hospitalization	
Disability	
Change of regimen	
Other	

Onset Date of the event

Date of the report

Describe the event*

Suspected drug causing adverse reaction: Rifampicin / Dapsone / Clofazimine

OUTCOME

Full recovery	
Adverse drug reaction continues	
Sequelae	
Death	
Unknown	

Relevant laboratory data*

Other relevant history, including preexisting medical conditions*

C. SUSPECT MDT BLISTER PACK

Batch number and expiry date
MB / PB

Medications prescribed (other than MDT) dur

Management of adverse drug reaction*

D. INITIAL REPORTER

Name

Title

Address

Telephone

Telefax

Final remarks (diagnosis, outcome, follow up)

* Note: If necessary, please attach copies of details of medical management, laboratory reports etc.

APPENDIX 5

MANAGEMENT OF REACTIONS AND NEURITIS

Mild reactions:

These consist of swelling and redness of skin lesions with or without the appearance of new lesions, painful reddish nodules, and/or slight nerve tenderness without pain or loss of function.

i) The patient should continue to receive antileprosy treatment as usual.
ii) Analgesics, either aspirin (acetylsalicylic acid) or paracetamol, may be given, as required.
iii) If there is nerve tenderness, the affected limb should be rested.
iv) The patient should be seen at least every two weeks, and asked to return if the reactionbecomes severe.

Severe reactions:

Reactions are graded severe, if there is oedema of face, hands and/or feet, if lesions ulcerate and/or if there is nerve pain and tenderness or loss of nerve function with or without fever and malaise, or if a mild reaction has lasted for more than six weeks without subsiding. The patient must be referred immediately to a hospital or referral centre.

The patient should continue to receive antileprosy treatment unchanged.

Eyes should be examined regularly for the appearance of iridocyclitis.

In the hospital (or referral centre), the correct treatment is to commence immunosuppression as rapidly as possible: The most effective drugs are corticosteroids, prednisolone being the most commonly used. It should be continued for the duration of the reaction. Therefore:

a) Rest painful nerve(s), splinting the affected limb(s), if necessary.

b) Give prednisolone. Patients will vary in their requirements, dosage being related both to the severity of the reaction and to the individual's body weight (usually not more than 1 mg/Kg body weight).

A suggested average course is:

Weeks 1 and 2:	prednisolone 40 mg daily
Weeks 3 and 4:	prednisolone 30 mg daily
Weeks 5 and 6:	prednisolone 20 mg daily
Weeks 7 and 8:	prednisolone 15 mg daily
Weeks 9 and 10:	prednisolone 10 mg daily
Weeks 11 and 12:	prednisolone 5 mg daily

c) If analgesics are required, aspirin or paracetamol may be given.

APPENDIX 6

ROLE OF THE INDEPENDENT MONITOR

OBJECTIVE

To ensure close monitoring of all patients included in the study.

To provide expert opinion in case of special events (such as serious side-effects, reactions, neuritis, relapse or others as appropriate).

The role of the independent monitor is basically to ensure that, all special events are properly recorded, managed and reported. However, it must be emphasized that the conduct of the study and all decisions related to the patients is the responsibility of the Principal Investigator alone.

SELECTION

Independent trial monitors will be selected and recruited by the WHO.

QUALIFICATIONS

i. Adequate knowledge of clinical leprosy
ii. Experience in field studies.
iii. Preferably from the same country/region.

VISITS

Regular visits to ensure close monitoring of all the patients and when requested by the Principal Investigator and/or by the LEP / TAG / TDR

APPENDIX 7

PATIENT CONSENT FORM

Centre Code:

Patient Identification Number: Patient's Name:

Regimen: Adult / Child

The World Health Organization and TDR, through the Leprosy Elimination Programme, wish to implement 6 months uniform MDT regimen, which can be given under programme conditions. The regimen consists of drugs, which are already in use in leprosy. We believe that the combinations of these drugs will be as effective and safe as the current WHO recommended MDT.

You are being requested to take part by accepting the drug regimen, which will last for 6 months. During this time, you will be questioned and examined by your doctor several times, and a few tests will be made on you if and when necessary. The purpose of these tests is to make certain that the treatment is effective and to detect unwanted effects of the regimen. Your doctor can stop or change the treatment if he/she believes that the regimen is causing unwanted effects. Even after completion of treatment, we will periodically call you for examinations to ensure that the treatment had been effective and there is no evidence of relapse.

If you take part in this trial, you may be exposed to some possible unwanted effects of the combinations of drugs but we believe that the danger is minimal and the chance of benefit to you is much greater. If you decide not to take part, you will still be able to have the usual treatment here. If you agree to take part now and later change your mind, you will be free to withdraw from the study and you will still be able to receive the usual treatment.

You will be free to ask your doctor questions about the treatment offered to you and the tests at any time. If you agree to take part in this trial, as shown by signing your name below, you will be responsible for keeping your appointments, following your doctor's instructions, taking your medication regularly and reporting to your doctor immediately if something appears to be going wrong. We will be responsible for making certain that your treatment is effective and for detecting unwanted effects of the treatment as early as possible.

Subject signature: Signature of witness:

Signature of person giving explanation: Date:

APPENDIX 8

DEFINITIONS

MB leprosy patient: All patients of leprosy with more than 5 skin patches

PB leprosy patient: All patients of leprosy with 1 to 5 skin patches

U-MDT: Uniform MDT is a combination of dapsone, clofazimine and rifampicin prescribed in the same standard dosages as for MB leprosy cases but the number of doses is limited to only six blister packs.

Relapse: An individual, who after completion of six doses of uniform MDT regimen, develops one or more new skin patches consistent with leprosy, without evidence of reactions, is considered to have relapsed.

Treatment completion: Any patient who has taken six doses of U-MDT will be considered to have completed treatment.

Regularity of treatment : A patient, who completes the 6-dose regimen in 9 months, will be considered as a regular patient. Others, who take longer than 9 months to complete the prescribed regimen, will be considered as irregular patients.

Defaulter: A patient who remains absent for treatment for 12 or more consecutive months.

Reactions: Reactions are acute exacerbation of disease manifesting as: a) existing skin lesions becoming reddish and swollen, b) appearance of reddish, painful nodules, c) painful, tender and swollen peripheral nerves, including signs of nerve damage such as loss of sensation and muscle weakness. These may or may not be accompanied by constitutional symptoms such as fever and malaise.

Neuritis: The involvement of peripheral nerves manifesting as definite new areas of loss of sensation and/or new muscle weakness with or without accompanied tenderness or pain in the affected nerves. In the absence of definite signs of new areas of sensory loss or muscle weakness, demonstration of nerve thickening or tenderness alone is likely to be subjective and therefore, should not be considered as signs of neuritis.

WHO/CDS/CPE/CEE (Leprosy Group) and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

CALL FOR PROPOSALS:

Uniform MDT (U-MDT) regimen for all types of leprosy

Introduction

WHO's Strategic Plan 2000-2005 – *The Final Push Towards the Elimination of Leprosy* – emphasizes the need to rapidly increase coverage with multidrug therapy (MDT) and to encourage communities and local health services to accept responsibility for sustaining case detection and management facilities after elimination has been reached. A limited number of new cases will inevitably continue to occur in the foreseeable future. A key element to overcoming this challenge before and beyond 2005, will be to further simplify treatment and to demonstrate its effectiveness. Accumulated scientific data over the past three decades demonstrates that this possibility now exists.

The face of leprosy has changed for the better. What we see now are mostly skin patches and a much lower proportion of grade-2 disabilities. Patients are willing to report for diagnosis and treatment, which is easily available free of cost. This is now the time to make treatment regimens much more simple, patient-friendly and easy for implementation by the general health services. WHO therefore proposes a uniform MDT regimen for all types of leprosy patients – which is essentially the six months' MDT for multibacillary (MB) leprosy. MB MDT has been in use for over two decades and has proven to be safe and effective. Side effects and toxicity from the three drugs constituting the treatment are rare.

Justification

- From the operational point of view, the duration of MDT for MB leprosy is still considered very long, which seriously affects successful treatment of patients living in difficult-to-access areas or belonging to special population groups.
- Duration of treatment depends upon the amount of time necessary to reduce substantially the size of the viable bacterial population to achieve (a) minimization of relapses and (b) complete elimination of rifampicin-resistant mutants. Rifampicin is by far the most powerful bactericidal drug against
- *M. leprae* and more than 99.999% of viable organisms are killed by three monthly doses of rifampicin. Thus, the elimination of drug-susceptible organisms is almost entirely due to the bactericidal effect of the initial few doses of rifampicin.
- The major role of the dapsone-clofazimine component in MDT is to ensure the elimination of any rifampicin-resistant mutants from the bacterial population. Results from both nude mouse experiments and clinical trials have demonstrated that three months' treatment with dapsone-clofazimine combination killed more than 99.999% of viable *M. leprae*. This suggests that any rifampicin-resistant mutants in an untreated lepromatous patient are likely to be eliminated with three months' treatment with the dapsone-clofazimine component of the MDT regimen.
- MDT has proved to be both extremely efficient and safe with very low relapse rates (less than 1%) and the same MDT regimen can still be used for relapsed cases, as resistance to MDT is virtually non-existent.
- Patients suffering from PB leprosy are already being treated with six months' PB-MDT. It can be expected that the addition of clofazimine will substantially improve the treatment. Thus the questions of interest to PB leprosy are how much better than the existing regimen would the new regimen be, and how would it affect compliance.
- In February 2002, the WHO Technical Advisory Group on Elimination of Leprosy (TAG) reviewed in detail the present scenario concerning duration of treatment for leprosy. In view of accumulated scientific evidence, TAG was convinced that the duration of MB MDT could be reduced further and that the six-months' MB MDT regimen could be implemented for all types of patients (PB and MB) on the condition that the outcome be closely monitored through standardized procedures. TAG considered that a uniform regimen would be of great benefit to patients and would facilitate integration of treatment into the general health services.

OUTLINE OF THE PROTOCOL

Purpose: To study the efficacy and effectiveness of the standard multidrug therapy regimen for multibacillary patients (MB-MDT) for six months as the Uniform MDT (U-MDT) regimen for all types of leprosy under routine field conditions.

Main objective: To implement six-months' U-MDT under programme conditions for all types of leprosy patients and to closely monitor response in terms of an acceptable cumulative level of 5% maximum relapse rate at the end of five years.

Study design: The study will be an open design with emphasis on close monitoring of patients during treatment and for at least five years after completion of six monthly doses of U-MDT.

Number of patients: The study will require a total of 2500 MB and 2500 PB patients. It will be multicentric and each participating country will be expected to contribute a *minimum* of 500 newly detected, previously untreated patients (250 PB and 250 MB).

Study sites: The study will be carried out in areas/programmes that have reasonably well organized leprosy control services. Requirements for the participating countries will be:

- A leprosy control programme capable of recruiting at least 500 new leprosy patients within two years (250 PB and 250 MB).
- Countries will be encouraged, however, to recruit larger numbers of patients (up to 2500 PB and 2500 MB) within two years.
- Application forms should enclose clearance from appropriate national authorities and ethics committees.
- The study site will need to be within easy access of a reasonably equipped base hospital in case complications or serious side effects should occur.
- Staff should be adequately trained.
- The programme should have the ability to provide follow-up to patients for a minimum of five years.
- Facilities should exist for rapid communication (telephone, cable, fax and, preferably, Internet).

Ethical considerations: Before applications are reviewed, the approval of the appropriate national and/or institutional authorities must be sought, as well as that of the national ethical committees. In addition, national/institutional guidelines with respect to informed patient consent must be met. All applications must include evidence of compliance with these requirements.

Monitoring: Independent monitors will be appointed by WHO, the numbers of which will depend on the number of centres/districts participating, the number of patients in the study and the geographical area. In addition, WHO will appoint an overall Study Co-ordinator to ensure that the protocol and procedures are respected in all study sites. Routine reporting of side effects, reactions and relapses will be done on a quarterly basis.

Reporting: Each study site will be required to submit to Leprosy Unit, WHO a detailed annual progress report (including budget details), using a standard format. The report should reach WHO by the end of December each year to enable review by TAG/WHO/TDR.

Proposal application forms and copies of the protocol can be obtained from:

CDS/CPE/CEE (Leprosy Group), World Health Organization, 1211 Geneva 27, Switzerland
(Tel. +41 22 791 3919, Fax. +41 22 791 4850, E-mail. daumeried@who.int)
or TDR Communications (Fax. 41 22 791 4854, E-mail. tdrnews@who.int)
or from the either of the following Websites http://www.who.int/lep or http://www.who.int/tdr

Proposal applications must be received no later than ***30 September 2002***

Please send an advance copy of your proposal application by E-mail, Fax or other fast method. The original should be signed by the appropriate responsible officer and sent by mail.