

PROGRESS REPORT

Contract for: Research Services directed toward the development of a combined agent for Disease Prophylaxis and Contraception.

Contract No. AID/csd - 2822

January 15, 1973.

June 30, 1972 - December 31, 1972

REPORT SUMMARY

- A. 1. Research Services Directed Toward the Development of a Combined Agent for Disease Prophylaxis and Contraception - AID/csd - 2822
2. Principal Investigator: John C. Cutler, Director, Population Division  
Contractor: Graduate School of Public Health, University of Pittsburgh  
Mailing Address: Fifth & DeSoto Streets, Pittsburgh, PA 15213
3. Contract Period: (as amended) June 30, 1970 to June 30, 1973
4. Period covered by Report: July 1, 1972 to December 31, 1972
5. Total A.I.D. funding of contract to date: \$581,198
6. Total expenditures and obligations to date: (6/70 to 12/72) \$305,341
7. Total expenditures and obligations for reporting period: (7/72 to 12/72) \$86,467
8. Estimated expenditures for next six months (1/73 to 7/73) \$111,284
9. Budget available end of original contract period \$164,573

B. Narrative Summary of Accomplishments and Utilization

During the present reporting period, the principal accomplishments have been:

(1) Acquisition of participants for the initial human field trial at Allegheny County Health Department; (2) Visits to possible trial sites in Jamaica and Guatemala, with approval of the local government agency (Ministry of Health) and the local A.I.D. missions at each site to conduct the trial; (3) Arrangements with Magee Women's Hospital for referral of females who meet the criteria from their emergency clinic to the Pro-Con Project to increase the rate of patient acquisition (12/18/72); (4) Submission of a proposal on September 29, 1972 for an extension of time and necessary funding to complete the investigation; (5) Approval by the University of Pittsburgh Counsel of parent-guardian consent forms for minors who wish to participate in the investigation. The proposed form has been submitted to the Committee on Research Involving Human Volunteers for approval; (6) Completion of administrative and laboratory work projected in annual progress report 1971.

Principal accomplishments prior to this reporting period include: (1) Collection of base-line data; (2) Laboratory assay of products to identify most active products to field test; (3) Development of statistical models for selecting best products to test and determining degree of effectiveness needed for significant impact on rising venereal disease rates; (4) Development and approval of experimental design, field protocol, and all data forms by A.I.D., Committee on Research Involving Human Volunteers, Graduate School of Public Health, and Allegheny County Health Department; (5) Approval of I.N.D. for Conceptrol and Cooper Creme by F.D.A.; (6) Field trial with first product, Conceptrol, begun July 1, 1972.

REPORT SUMMARY

A. General Background

1. Development Toward the Development of a Combined Agent for Disease Prevention and Contraception - 1937-1942

2. Various factors such as penicillin, a high degree of public interest, the condom, and public health programs helped decrease the venereal disease rates after World War II. As the venereal disease rates declined, however, there ensued a serious decline in medical and public interest, as well as in government funding for research. As a result of this declining interest, we are again faced with rapidly rising rates of venereal disease throughout the world. The increase in venereal disease rates combined with steadily rising numbers of unwanted pregnancies presents one of the major worldwide public health problems today.

In view of the fact that both unwanted pregnancy and venereal disease are often the result of "unprotected" or casual contact, it is felt that an intravaginal pre-coital preparation offering protection to the female from venereal disease and pregnancy, as well as to the male from venereal disease would significantly complement existing contraceptive and venereal disease control techniques. Such a preparation, which could be used alone or in conjunction with other types of contraceptive agents, which would not require medical prescription or intervention, and which would be readily available regardless of age, would appeal to a large number of the sexually active and promiscuous population whose major concern is self-protection. This preparation could be promoted effectively for wide distribution and could be incorporated into existing VD and family planning programs as well as other public health programs, with a high probability of utilization.

Although prophylactic treatment is accepted in many parts of the world, little systematic evaluation of mechanical, chemical or antibiotic agents as a means of preventing venereal disease has been made in recent years. It is hypothesized that a dual-purpose intravaginal agent can be developed through research by identifying existing contraceptive products that have a dual action, and also by combining substances which are effective as local prophylactics against syphilis and gonorrhea with substances that are effective as intravaginal contraceptives.

B. Statement of Project Objectives as Stated in the Contract

This progress report, the fifth such report since the contract was awarded on July 1, 1970, covers the period from July 1, 1972 through December 31, 1972.

The objective of this project is to develop a preparation for intravaginal precoital use which will offer protection to the female from both pregnancy and venereal disease and to the male from venereal disease. Under the terms of this contract, the project proposes to accomplish its objectives by means of: (1) Laboratory screening to assess in vitro, the effectiveness of vaginal contraceptive preparations against T. pallidum, N. gonorrhoeae, C. albicans, and T. vaginalis; (2) Clinical field trials on the high risk population to assess the use effectiveness of selected preparations based on the laboratory results; (3) Widespread field trials to involve personnel and institutions of other countries, specifically, Jamaica and Guatemala, as well as of the United States to assess the application of the products in the general population.

### C. Continued Relevance of Objectives

Data from both the USA and WHO continue to show a world-wide rise in venereal disease. At the same time, in no country has there been an abrupt decline in birth rates related to family planning or population programs.

In the recent report of the National Commission on Venereal Disease to the Secretary of the Department of Health, Education, and Welfare, particular attention has been paid to the importance of cooperation between venereal disease and family planning programs with respect to prevention. Both the condom and possible chemical prophylactic-contraceptive preparations have been singled out in this regard.

In October, 1972, House Resolution 14455-Communicable Disease Control Program was passed by both Houses of Congress amending the Public Health Service Act. The resolution authorizes the Secretary of HEW to make grants for control programs relating to venereal diseases, from the \$35-40 million appropriated to him for that purpose in 1973.

Thus it would appear that the concept accepted by A.I.D. in funding this study has been fully recognized by experts and workers in the venereal disease field, as well as the federal government. With official increased interest and acceptance of this concept by the United States, the prospect of international acceptance of a combined prophylactic-contraceptive product as another tool for venereal disease programs appears to be enhanced should clinical studies validate the hypothesis.

## D. Accomplishments To Date

### 1. Findings

Administrative - (1) On-site visits for negotiation of field trials in Jamaica and Guatemala and official clearance by local A.I.D. missions and local government agencies involved. (2) Proposal extending time and money in order to complete study as originally proposed, submitted September 29, 1972. (3) Agreement with Magee Women's Hospital to refer patients from their emergency room V.D. clinic who meet project criteria to Pro-Con Personnel for possible participation in Allegheny County Health Department field trial. (4) Continued working with legal counsel in attempt to include those under 21 years of age in the project (the sexually-active, high-risk population). (5) Developed and received approval in principle for use of parental and/or guardian consent forms to be signed by parent or guardian of under-21 subjects. Decision of Committee on Research Involving Human Volunteers, Graduate School of Public Health, is pending as well as approval for use by the Allegheny County Health Department. (6) Established contact with, and gained preliminary approval of, the New York City venereal disease control officer regarding participation in a clinical field trial. (7) Preliminary negotiations have been started with a U.S. pharmaceutical company holding patent rights to a unique intravaginal contraceptive in an effort to include their product in one of the future field trials.

Laboratory - The laboratory work was carried out as projected in our last year's progress report. Within the limits and objectives of this contract, some additional accomplishments were the studies on (a) Survival and Recovery of Neisseria gonorrhoea under different environmental conditions, (b) Chemical susceptibility of N. gonorrhoea on continuous passage in presence of contraceptive.

Field - (1) Started Allegheny County Health Department field trial and began to identify problem areas. The problems are being worked out here so that the initial trial will be successfully completed and trials at other sites will be simplified. (2) A medical procedure manual has been developed in order to assure comparability and reliability of the data from various other field trial sites. (3) Preliminary work has started on a health education manual to incorporate prophylactic information into existing VD

educational material. (4) Initial data from Allegheny County field trial, while limited, has been analyzed for characteristics of participants and trends.

Study of the initial field trial to date suggests that the use of females in the 15 to 20-year-old group would increase the number of participants in the investigation significantly. Also, it continues to appear that the use of an identified group of highly sexually-active females as subjects could give faster results in terms of product effectiveness, but not product acceptance.

## 2. Interpretation of Data and Supporting Evidence

After the required orientation period for the Pro-Con field group, the clinical trial was started at the Allegheny County Health Department, August, 1972. During August the County experienced a drop in attendance to 458 females, approximately 200 under an average for this clinic. In September, female visits returned to near normal. A week-long nationally telecasted TV series called, "The VD Blues," caused an increase in patient visits. The yield of positive cultures increased significantly in all age groups except the 21 years of age or older. In absolute numbers, more girls over 21 have visited the clinic than any other age group, however, only 56% were eligible to participate because their past infections occurred within the past 12 months. In the younger age groups with a history of a past infection, the percentage with an infection in the past 12 months increases to about 83%. Although, this age group is not eligible for participation because they are minors in Pennsylvania. The net result has been a slower patient acquisition rate than was anticipated.

Thus far eighteen girls have been interviewed. Three were not eligible because they were not on birth control. Of those remaining, twelve agreed to participate which represents an 80% acceptance rate. Six participants have dropped out but were equally divided as to test and control patients. Of the drop outs, 3 were lost to the study after the initial interview and could not be contacted by follow-up phone calls and letters. Prior to first examination 2 dropped out due to negative parental pressure and rotating work shift. After two re-examinations, 8.4% dropped out because re-examinations could not be done due to new full-time jobs, making re-examinations visits impossible.

Six of the girls remain in the study and are cooperative in keeping appointments and using products. Motivating factors to participate seem to be fear of another infection, and convenience of returning to the clinic in regard to time and location. These girls seem likely to remain in the study for the full year.

It has been observed that to date, drop outs occur before the first re-examination visit. Of thirty-five appointments given, 22 have been kept. The field trials are continuing and we are looking for other clinics in which to find participants for referral to the study to increase the number of participants.

D. 3. Research Design

Possible modifications of the research design are:

- (1) Inclusion of patients under 21 years of age in the field trials when parental and/or guardian consent forms are approved;
- (2) The possibility of variations in procedure based on local conditions at field trial sites in foreign countries;
- (3) The possibility of additional changes in regard to the requirements for use of the oral contraceptive and IUD method of preventing unwanted pregnancies. This criteria for participation does not appear to be as crucial in foreign field trial sites as it has been found to be in the Allegheny County field trial;
- (4) The possibility of using the cross-over statistical design in at least one foreign field trial site.

E. 1. Dissemination and Utilization of Research Results

Every effort has been made by the Pro-Con Group to disseminate the results of the research findings. These findings have been presented to:

- (1) American Public Health Association (Atlantic City) 1972,
- (2) Neisseria Treponema Scientific Memoranda Series,
- (3) National Commission on Venereal Disease 1972,
- (4) International Union Against the Venereal Diseases and the Treponematoses (Venice) 1972,
- (5) First and Second International Venereal Disease Symposiums (St. Louis) 1971, 1972,
- (6) Population Club (Hawaii) 1972,
- (7) American Society of Microbiology (Philadelphia) 1972,
- (8) W.H.O. Regional Office (Copenhagen) 1971,
- (9) American Public Health Association (Minneapolis) 1971,
- (10) Seminars as part of instructional programs (Allegheny County Health Department),
- (11) Lectures to American and Foreign students of Graduate School of Public Health, University of Pittsburgh and surrounding colleges,
- (12) Professional staff of local hospitals, health centers and free clinics,
- (13) Exchange of Pro-Con scientific information via Neisseria Treponema Scientific Memoranda NIAID (NIH) - 5 contributions, 1972.

In addition, results of laboratory testing have been supplied to all cooperating pharmaceutical companies concerning the antimicrobial activity of their product.

E. (1) Papers and publications developed under this contract fall into three broad categories: (1) the role of prophylaxis in the control of venereal disease; (2) description and results of laboratory studies on the development of a vaginal preparation to provide venereal disease and genital infection prophylaxis as well as contraception, (3) statistical models for predicting relative risk of contracting gonorrhoea versus syphilis, and potential impact of chemical prophylaxis on incidences of venereal diseases.

(1) Role of Prophylaxis - points discussed are: the history of prophylaxis, the success of venereal disease prophylaxis in both World Wars, discontinuance of interest in prophylaxis after World War II, importance of reconsidering prophylaxis once again in light of current epidemics, importance of providing protection against unwanted pregnancy as well as transmission of venereal disease with one product, the importance of research to evaluate effectiveness of available products, and studies involving individual motivation, practice, responsibility, and delivery of public health services.

(2) Description and Results of Laboratory Studies - describes procedures used for testing, reports the antimicrobial effects of a number of commonly used intravaginal contraceptives and other preparations on N. gonorrhoea, T. pallidum, C. albicans, and T. vaginalis, and indicates that results are encouraging and postulates an agent simultaneously offering prophylaxis against venereal disease and contraception would be of great value to both existing family planning and venereal disease control programs.

(3) Statistical Models - describes the development of a theoretical model and uses the model to predict the possible dramatic change in the prevalence of gonorrhoea if topical venereal disease prophylaxis is incorporated into existing venereal disease programs and is used by population at risk. Also based upon joint probability of transmissibility and prevalence, the relative risk of contracting gonorrhoea versus syphilis is calculated and used in an equation to predict effectiveness of contraceptive products tested in vitro.

E. (2) Material presented to the National Commission on Venereal Disease was incorporated into the recommendations to the Secretary of H.E.W. concerning future research in venereal disease prophylaxis and public health application both in venereal disease control programs and in family planning programs which should increasingly relate to venereal disease activities.

Material presented to the First International Venereal Disease Symposium was published in V.D. Crisis, 1971. V.D. Crisis, 1972 is now in press and will include the material presented at the Second International Venereal Disease Symposium. V.D. Crisis is widely distributed as a medical service by Pfizer Laboratories Division, Pfizer, Inc., and American Social Health Association to the medical community.

Material presented at the American Society of Microbiology was released for press reporting.

Material presented at the American Public Health Association, Minneapolis, was extensively covered and reported in the press at that time.

- Cutler, J.C., Utidjian, H.M.D., Singh, B. and Arnold, R.C. Studies on Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease, Other Genital Infections, and Contraception. I. Venereal Prophylaxis, Past Experience, Present Status and Plans for Future Studies. Military Medicine (in press).
- Cutler, J.C. 1971. The Role of Prophylaxis. The International Venereal Disease Symposium. The V.D. Crisis Page 29-30.
- Cutler, J.C. 1972. The Future of Prophylaxis in V.D. Control. The International Venereal Disease Symposium. The V.D. Crisis
- Cutler, J.C. 1972. Prophylaxis in the Venereal Diseases. Medical Clinics of North America Vol. 56, No. 5, September, 1972 pp. 1211-1216. (Also available in Spanish)
- Lee, T.Y., Utidjian, H.M.D., Singh, B., Carpenter, U. and Cutler, J.C. 1972. The Potential Impact of Chemical Prophylaxis on the Incidence of Gonorrhea. Brit. J. Ven. Dis. October, 1972.
- Lee, T.Y., Utidjian, H.M.D., Singh, B., Carpenter, U. and Cutler, J.C. 1972. The Relative Risk of Contracting Gonorrhea Versus Syphilis Based Upon the Joint Probability of Transmissibility and Prevalence. HSMHA Hlth. Rep. (in press).
- Singh, B., Cutler, J.C. and Utidjian, H.M.D. 1971. Studies on Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease, Other Genital Infections and Contraception. II. In Vitro Effect of Vaginal Contraceptive and Non-contraceptive Preparations on Treponema pallidum and Neisseria gonorrhoeae. Brit. J. Ven. Dis. 48, 57-64, 1972.
- Singh, B., Cutler, J.C. and Utidjian, H.M.D. 1971. Studies on Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease, Other Genital Infections and Contraception. III. In Vitro Effect of Contraceptives and Non-contraceptive Preparations on Candida albicans and Trichomonas vaginalis. Contraception Vol. 5, No. 5, 1972.

Papers Presented in National and International Meetings

- Cutler, J.C., Singh, B., Utidjian, H.M.D. and Arnold, R.C. 1971. Studies on a Combined Venereal Disease Prophylactic-Contraceptive Agent. APHA. Official Program and Abstracts Page 109.
- Cutler, J.C. 1971. The Role of Prophylaxis. The International Venereal Disease Symposium.
- Cutler, J.C. 1972. The Future of Prophylaxis in V.D. Control. The International Venereal Disease Symposium.
- Cutler, J.C., Singh, B., Utidjian, H.M.D. 1972. Studies on the Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease and Contraception. XXVII General Assembly of the International Union Against the Venereal Diseases and the Treponematoses. Presented by Bruce Webster, M.D. - Chairman National Commission on V.D.

Singh, B. 1972. Survival and Recovery of Neisseria gonorrhoeae Under Different Environmental Conditions. APHA.

Singh, B. and Swab, G. 1972. Antimicrobial Effect of Contraceptives on Treponema pallidum, Neisseria gonorrhoeae and Candida albicans. Abstracts of the Annual Meeting of the American Society for Microbiology.

Abstracts and Scientific Communications

Singh, B. and Cutler, J.C. Effect of Intravaginal Chemical Contraceptives on Treponema pallidum. Neisseria Treponema Scientific Memoranda, Memo NT-4/1 May, 1972.

Singh, B. Antimicrobial Effect of Chemical Contraceptives on Neisseria gonorrhoeae. Neisseria Treponema Scientific Memoranda, Memo NT-5/1 May, 1972.

Singh, B., Lumpkin, H.L. and Cutler, J.C. Survival and Recovery of Neisseria gonorrhoeae Under Different Environmental Conditions. Neisseria Treponema Scientific Memoranda, Memo NT-18/1 July, 1972.

E. 2. Findings of the research project to date, in vitro results, cannot be directly applied to human response, and the preliminary results from the initial field trial do not allow for any conclusions at this time. Therefore, evidence to date has not been directly applied to the problem in the U.S.A. or L.D.C.'s. A similar study conducted by the Nevada State Health Department and private research being done by pharmaceutical companies with whom we have consulted are indications of the interest our research has stimulated toward further research to develop a pro-con product.

In Jamaica and Guatemala formal approval has been obtained to conduct field trials. Details such as the mechanism of payment and shipment of materials to foreign countries are presently being worked out.

A similar agreement has been reached with the New York City Health Department V.D. Program; further detailed planning is under way.

The proposals with different clinics call for key personnel to visit the University to observe the clinical and laboratory studies and to assist in drawing up a detailed field protocol for their individual field site.

E. 3. In line with the current recommendations that Venereal Disease information should be given to students no later than the seventh grade the VD education program would seem to be an ideal program in which to incorporate research findings of this project. Experience of the past years points out the need for prophylactic educational material for this age group. Plans for the field trial call for the development of appropriate educational material including information on prophylaxis and recognizing symptoms, as well as how and where to obtain treatment.

Preliminary work in this area has begun, and can be carried out under current provisions of the contract. It is expected that the experience of the Allegheny County Venereal Disease Clinic and the American Social Health Association will be helpful in this endeavor, as well as assisting with incorporation of the developed programs into existing school programs and existing venereal disease educational materials.

Experience of the past reporting period has also made us aware that little is known concerning women's attitudes and preferences concerning creams, jellies, foams, suppositories and foaming tablets as intravaginal contraceptives. Pending development of different delivery systems for these products by pharmaceutical companies, the proposed trials could be conducted using different dosage forms to evaluate the acceptance factors of different systems. Also, an opportunity has arisen which might well make it possible to include a unique intravaginal contraceptive product in field trials. Negotiations have been started with the pharmaceutical company in the U.S. that holds the patent rights to C-Film, a product developed in Hungary. If details can be worked out, C-Film would be tested in one of the field trials.

E. 4. Trials in other countries are being planned for implementation after preliminary results are known from Allegheny County Health Department trial. Jamaica and Guatemala are countries which have been contacted. A proposal for a time extension and necessary funding for these clinical field trials has been submitted to A.I.D. for approval. Essentially, the same experimental design will be used in all localities with minor modifications for adaptation to local conditions. After short-term consultation by University personnel, the field trial will be planned and executed by professional personnel of the country hired for this purpose, using medical procedure manuals developed during the initial field trial at the Allegheny County Health Department. Results of the field trials elsewhere will be reported to the Graduate School of Public Health where they will be analyzed.

F.

The most significant problem related to the initial field trial has been the slower-than-projected acquisition of participants. This problem is caused by unclear laws in the Commonwealth of Pennsylvania governing the age at which a female can give effective consent to participate as a subject in research and investigation. The opinion of the Legal Counsel of the University of Pittsburgh is that females under the age of 21 must have parental or guardian consent to participate in this project. This condition has greatly reduced the population from which possible participants can be selected. While the possibility exists that parental consent forms which have been approved in principle as complying with H.E.W. guidelines might also be approved for use in the field trial in Allegheny County, it is felt that this would give only limited access to the sexually active, high risk 15 to 20-year-old age group. Therefore, arrangements have recently been completed for referral of females who meet the criteria to the Pro-Con Project from a large private hospital V.D. clinic to enlarge the population of possible participants. Laws governing the rights of minors vary in different states and abroad, and selection of future trial sites has been made with this identified problem in mind.

Expenditures for the remaining six months of the original contract reflect revisions made in past proposed budgets. These revisions have been made pending approval of the proposal for a time extension submitted during this reporting period. Specifically, budgeting for Local Hire of Foreign Nationals, Subcontract, and Participants, has been lowered. In addition, an additional laboratory technician and medical aide that were budgeted for have been removed pending approval of the proposal for a time extension.

G. Work Plan and Budget Forecast for Coming Six Months

Unanticipated delays in beginning and conducting the initial field trial in Allegheny County described in past reports, have for the most part, been overcome. Plans for increasing the number of participants for this trial will be put into effect during the remaining six months of the original contract. A proposal for a time extension has been submitted to complete the remaining trials necessary for this study. It is proposed that field trials will be conducted in Jamaica, Guatemala, possibly some African nations and New York City with the most active products identified through in vitro testing that are available in acceptable packaging. Necessary negotiations with the countries involved prior to beginning these trials will be completed during the reporting period. Continuing laboratory testing of new products which appear on the market or which are approved by F.D.A. for testing, and selected existing products for conformation of results and effects on additional diseases such as Chancroid will be carried out.

All field trials will be carried out using the field procedure manual developed during the initial field trial (attachment). Modifications in the field trial protocol will be made to conform with the prevailing conditions at each trial site.

Negotiations with pharmaceutical companies who hold the rights to the most promising compounds will be continued to encourage the development of unit-dose packaging for field trials in cases where suitable packaging has not been developed. All measurable results from these trials will be disseminated as widely as possible to the scientific community by means of articles in appropriate journals, presentations at scientific meetings and ultimately, representatives of the companies who hold the rights to the products tested.

Expenditures and Obligations To Date

June, 1970 - December, 1972

Salaries and Wages		\$141,511
Fringe (13.1)		18,537
Local Hire of Foreign Nationals		0
Consultants		1,238
Travel and Transportation		5,828
Other Direct Costs		1,550
Telephone	900	
Postage	75	
Participants	475	
Publications	100	
Subcontract		0
Equipment, Material and Supplies <sup>1</sup>		37,652
Expendable	25,643	
Non-expendable	12,009	
TOTAL DIRECT		<u>206,316</u>
Indirect		99,025
GRAND TOTAL		<u><u>\$305,341</u></u>

1/ Includes Repair and Maintenance

Proposed Planned Expenditures

January 1, 1973 - June 30, 1973

Salaries and Wages		\$ 49,578
On Campus	35,388	
Off Campus	14,190	
Fringe (13.1)		6,495
Local Hire Foreign Nationals <sup>1</sup>		2,200
Consultants		2,000
Travel and Transportation		3,000
Other Direct Costs		4,325
Telephone	200	
Postage	125	
Participants <sup>2</sup>	3,500.	
Publications	500	
Subcontract <sup>3</sup>		4,000
Equipment, Material, Supplies <sup>4</sup>		7,500
Expendable	5,000	
Non-expendable	2,500	
TOTAL DIRECT		<u>79,098</u>
Indirect		32,186
On Campus (70.3)	24,878	
Off Campus (51.5)	7,308	
GRAND TOTAL		<u><u>\$111,284</u></u>

1/ One month salaries Jamaica and Guatemala

2/ One month participants foreign trial sites and U.S. site

3/ One month other U.S. trial

4/ Includes maintenance and repairs

## I. Primary Objective and Scope

The primary objective of the Pro-Con Project Field Trials is to evaluate in humans the effectiveness of intravaginal contraceptive products that have demonstrated in vitro against gonococcus and T. pallidum and in the rabbit against T. pallidum a high degree of antimicrobial activity against organisms causing venereal disease infection, particularly, the gonococcus.

## II. Source of Cases

These trials can be carried out in any county health department venereal disease clinic, free clinic, planned parenthood, or hospital clinic where there is a sufficiently large number of female patients whose sexual practices place them at risk of acquiring venereal infection.

## III. Procedure for Identifying Possible Participants

Any female patient of the clinic will be accepted as a possible participant for the trial if she has:

- A. Reached the age of consent as defined by law,
- B. Had two or more previous venereal infections within the past 12 months,
- C. Taken precautions against unplanned pregnancy by either taking oral contraceptives, having an IUD inserted, or has been surgically sterilized,
- D. Demonstrated a reasonable degree of reliability and responsiveness.

## IV. Clinic Atmosphere

- A. Courtesy to Participants
  1. All participants are to be addressed by all members of the field team as Mrs., Miss, or Ms., as the case may be,
  2. Participants will remain in the comfortable waiting area until called for individually for their examination,
- B. Courtesy to Project Personnel
  1. During clinic sessions, project personnel should be addressed as Dr., Mr., Mrs., Ms., or Miss, as the case may be.

## V. Confidentiality and Release of Information

No information will be furnished to any person or institution outside of the Graduate School of Public Health without a signed release by the patient. In compliance with A.I.D. policy, all provisions found necessary for safeguarding information that could be traced to, or identified with the subjects in the trial will be coded. Each participant will be identified by a code number. This number along with the participant's name, address and telephone number will be recorded on a Master Code Card (Attachment) in the

clinic and will not leave that site. All other forms will be identified only by code number. These data forms have been carefully designed to limit personal information acquired to that absolutely essential to the research project. All Master Code Cards and other identifying data will be destroyed at the termination of the study.

#### VI. Field Protocol for Trial

- A. The field efficacy trial of an intravaginal, precoital prophylactic agent as preventive treatment against venereal disease will employ a completely randomized control design without a placebo. Clinic patients selected for possible participation in the field trial will be those adult females:
1. Who present themselves to the clinic with medically established gonorrhoea after the field trial has begun.
  2. Who have had one or more venereal disease infections prior to the index infection, ascertained by clinic records or confirmed medical history.
  3. Who are currently using oral contraceptives, the I.U.D., or have undergone surgical sterilization procedures.
  4. Who have been judged by the clinic staff to be suitable subjects with reference to:
    - a. Level of past cooperation and judgment as revealed by treatment and follow-up attendance at the clinic.
- B. Those patients who meet the criteria described will be initially contacted by the treating clinician to determine whether they would be willing to talk with pro-con personnel about their possible participation in the field trial.
- C. Once selected, these patients will be interviewed by a member of the research team and their voluntary cooperation in the field trial solicited.
1. The purpose of the trial will be thoroughly explained (Attachment A). The selected patients will be informed that:
    - a. The investigational drug has been proven safe to use by the F.D.A. and is currently available on the market. We are testing the drug for its usefulness in the preventive treatment of venereal disease.
    - b. The investigational drug has practically no inherent risk of serious side effects.
    - c. The investigational drug has shown a high degree of effectiveness against venereal disease organisms in the laboratory tests.
    - d. The investigational drug is expected to be effective as preventive treatment against future venereal disease re-infection.
    - e. The patient must sign an "informed consent" form (Attachment B) before being allowed to participate in the field trial. A summary statement describing the study and its risks which is the basis for the discussion with the prospective subject will be on the reverse side of the "informed consent" form. Each patient who agrees to participate in the trial will be required to initial this summary statement after the discussion with the project staff member.

- D. Each patient who agrees to participate will come on trial immediately after successful termination of antibiotic treatment for her most recent attack of venereal disease. Since random assignment to test or control group occurs after the patient has agreed to participate, all patients will be given information about:
1. The intravaginal preparation and applicator to be used.
  2. The proper use of the preparation.
  3. The free supply of the preparation they will be given if assigned to the test group. The investigational drug that is supplied to the test group will be adequately labeled CAUTION: NEW DRUG -- LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE to fulfill the requirements of F.D.A.
- E. Observation will be carried out for one year to see whether there is a significant reduction in the rate of re-infection of the test group as compared to the control group. To accomplish this statistical comparison, the following will be done:
1. Twice-a-month routine examination of all female patients in the study regardless of whether they have venereal disease symptoms or not. These examinations will include:
    - a. Clinical examination of the genitalia for venereal disease and local skin reactions to the preparation.
    - b. Cultures and examination for gonococcus, trichomonas and candidiasis infection.
    - c. Dark field microscopy of any suspicious lesions.
    - d. Prompt treatment for those patients who contract a venereal disease infection while on trial.
    - e. History of use of preparation and sexual activity pattern.
    - f. Serology for syphilis monthly.
    - g. Search for problems encountered.
    - h. Re-instruction or re-reinforcement of instructions.
    - i. Issue further supplies for their own personal use.
    - j. Regular screening which will be medically beneficial in detecting vaginal infection particularly asymptomatic gonorrhoea.
- F. Each patient who agrees to participate will receive \$5.00 plus \$1.25 for transportation per re-examination visit.
- G. The Hypothesis: Use of a topical venereal disease prophylaxis will significantly reduce the venereal disease re-infection rate of the test group, in contrast to the control group who will not be receiving this prophylactic measure.
- H. To insure confidentiality of the information derived from the study, review of medical records will be conducted by the treating physician, and information vital to the study will be kept on coded cards. This coding will be done at the site of the trial and the names of the subjects will not leave the location. All Master Code Cards and identifying data will be destroyed at the termination of the study.

VII. Responsibilities of Physician in Pro-Con Field Trials

- A. Carries responsibility for general management of clinic.
- B. Functions by:
  - 1. Supervising staff assigned to clinic, i.e., nurse, educator, aide, etc.
  - 2. Reviewing records to insure proper medical care,
  - 3. Examining patients for reaction to clinic environment and drug therapy,
  - 4. Initial complete medical examination of each patient - fills in form,
  - 5. Obtaining cultures,
  - 6. Making appropriate referral of selected patients,
  - 7. Discussing patients needs and problems with other members of the field team,
  - 8. Developing and maintaining an education program for patients and team members,
  - 9. Diagnosing and prescribing treatment when needed,
  - 10. Outlining "Problem Oriented Progress Note" for patients problems as they occur.

VIII. Responsibilities of Nurse in Pro-Con Field Trials

- A. Coordinates member of field team.
  - 1. Helps agency determine eligibility of prospective participant for field trials,
  - 2. Assist M.D. in re-examination of participants,
  - 3. Routes patients to educator for interview, payment, etc.
  - 4. Consults with other staff involved in the trial regarding needs of the individual patients such as referrals to other clinics or private M.D. for additional medical care,
  - 5. Maintains an open channel of communication between field staff and regular Pro-Con staff regarding problems and/or needs occurring during the trial.
- B. Serves Pro-Con Field Trials as follows:
  - 1. Brings files to clinic,
  - 2. Instructs participant regarding field trial medical procedures,
  - 3. Obtains specimens and cultures for laboratory test,
  - 4. Notifies physician of positive laboratory tests, obtains RX orders; new patients,
  - 5. Carries out treatment as directed by physician and completes record.
- C. Assist in observing participants for reaction to environment and drug therapy and recording same.
  - 1. Maintains current medical record, problem-oriented progress notes.
- D. Reviews participants files before and after clinic sessions to be sure all the proper data is collected and recorded and medical care given as required.
- E. Return all medical records and file.
- F. Carrys out responsibility for general management in absence of physician.

## IX. Routine Medical Re-examination Procedures

- A. Obtain subjective data from patient (attach)
  1. How she feels,
  2. Recent treatment, medication, reactions,
  3. Search for physical signs of disease.
  
- B. Perform medical re-examination.
  1. Serological test for syphilis (monthly)
    - a. Prep skin with 70% alcohol,
    - b. Obtain blood sample in labeled tube,
    - c. Secure request slip (attachment) with rubber band to vacutube
  2. Examine external genitalia.
    - a. Palpate lower abdomen for tenderness,
    - b. Palpate groin area for adenopathy,
    - c. Observe vulva for any lesion,
    - d. Separate all folds of labia for lesions,
    - e. Observe vulva, labia and inner thighs for rashes.
  3. Obtain culture for GC.
    - a. Urethral
      - (1) Separate labia,
      - (2) Insert sterile cotton-tipped swab into entrance of urethra and rotate gently for several seconds to absorb organisms on swab,
      - (3) Roll swab directly on first half of Thayer-Martin media plate in a large "Z" pattern to provide adequate exposure of swab to plate for transfer of organisms.
    - b. Cervical
      - (1) Samples will be taken from cervical area using a clean speculum,
      - (2) Speculum may be moistened with water, but no other lubricant will be used,
      - (3) Procedure for obtaining culture,
      - (4) Remove mucous with a cotton ball held in a ring forceps or with a cotton-tipped swab, if cervix is covered with excessive mucous,
      - (5) Insert sterile cotton-tipped swab and move the swab from side-to-side allowing several seconds for absorption of organisms to the swab,
      - (6) Roll swab directly on Thayer-Martin (TM) medium plate in a large "Z" pattern to provide adequate exposure of swab to plate for transfer of organisms.
      - (7) Label each plate so as to properly identify the participant and the portion of the plate inoculated with cervical and urethral specimen,
      - (8) Place culture plates upside-down in an air-tight candle jar. Place a moistened paper towel or gauze within the jar to supply maximum humidity. Light a short, thick, smokeless candle fixed to a glass microscopic slide or small candle holder beaker and place it in the jar. Put the lid or cap on the jar making a proper air-tight seal.
    - c. Rectal
      - (1) Insert sterile cotton-tipped swab slightly into rectal and rotate gently for several seconds allowing for absorption of organisms to the swab,

- (2) Do not obtain any feces on swab,
  - (3) Roll swab directly on a separate Thayer-Martin medium plate in a large "Z" pattern to provide adequate exposure to swab to plate for transfer of organisms. Place the plate upside-down in the candle jar as described above.
- d. Culture for Moniliasis (May be done during GC culture from cervix) Specimen is taken with a separate cotton-tipped swab. Cervical area and vaginal vaults are the best places for specimen. Roll swab directly on the Sabouraud Agar plate in a large "Z" pattern to provide adequate exposure of swab to plate for transfer of microorganisms. Turn plate upside-down and label for proper identification. Keep the plates at room temperature until the end of the day.
- e. Culture for Trichomonas (May be done during cervical culture for GC) Specimen is taken with a separate cotton-tipped swab from cervical area and vaginal vaults as described above. Inoculate specimen into the STS medium. Only remove the cap from the test tube when ready to inoculate medium. Insert the cotton swab into the medium. Break the extra end of the stick in such a way that the cotton swab remains inside the medium. The cap is then replaced and tightened. Label the tube and keep the inoculated tubes at the room temperature.
- f. Additional examinations
- (1) Monthly Serology
  - (2) Darkfield microscopy of any suspicious external or internal lesions

(a) Procedure

Adjustment of the Microscope for dark field (DF) examinations:

- 1) Check if microscope has proper condenser and objective.
- 2) Using a piece of paper placed across the mirror surface, adjust the illuminator for sharp focus.
- 3) Lower the substage slightly and place 1-2 drops of immersion oil on the top of the condenser.
- 4) Place slide on the fixed stage and raise substage so that the oil on the condenser should make contact with the underside of the slide and completely cover the top of the condenser.
- 5) Focus the illuminated specimen with 10X objective. The light should be centered in the field by means of the centering screws located on the base of the condenser. Intense light and fine adjustment to compensate thickness of the specimen is obtained by moving the condenser up or down.
- 6) Bring the 40X high, dry objective into place above the slide by rotating the objective turret.
- 7) Focusing with the fine adjustment, search the specimen for spiral spirochete (*T. pallidum*) with characteristic morphology and motion. A careful and exhaustive search should be made before rendering a negative report.

Treponema pallidum is a thin, tightly wound rigid spiral organism exhibiting little flexion and does not move rapidly from place to place.

- (3) Pap smear (if not had one within a year)
- (4) Pregnancy test (if menstruation is more than two weeks late)
  - (a) Use 2 minute Pregnancy Dot Test (or similar test)
- g. Treatment of positive cultures
  - (1) Gonorrhoea
    - (a) Patient notified and brought in for treatment at earliest possible time
    - (b) Follow approved treatment schedule
  - (2) Other genital infections
    - (a) Inform patient of culture results
    - (b) Check subjective complaints
    - (c) Treat if necessary
  - (3) Positive serology
    - (a) Patient notified (Report to County immediately - they treat)
  - (4) Refer to educator.

#### X. Laboratory Procedures for Pro-Con

##### A. Gonorrhoea - T.M. plates

1. Plates streaked by "Z" method,
2. Transported from field to lab in candle jar at room temperature,
3. Incubated for 24 hours at 37°C in CO<sub>2</sub> atmosphere (40% CO<sub>2</sub>)  
If negative after 24 hours, incubate another 24 hours,
4. Examined for GC colony morphology
  - a. Greyish-white to clear
  - b. Small
  - c. Round
5. Oxidase test,
6. Gram stain,
7. Microscopic examination,
8. Sugar fermentation test,
9. Record results.

##### B. Candida-Sabouraud plates

1. Plates streaked by "Z" method,
2. Transported from field to lab at room temperature,
3. Incubated at 37°C for 48 hours, check every 24 hours for growth. If no growth after six days then discard specimen,
4. Examine plate for cell morphology
  - a. White
  - b. Large
  - c. Odor (yeast smell)
5. Gram stain,
6. Microscopic examination,
7. Record results.

##### C. Trichomonas - STS media (10ml/tube)

1. Add 0.5 cc horse serum and 0.5 antibiotic mixture to media on day of use,
2. Break off exposed cotton-tipped swab into media,

3. Transport from field to lab at room temperature,
4. Lids tight for partial CO<sub>2</sub> atmosphere,
5. Incubate at 37°C for 24 hours,
6. Invert tube several times,
7. Prepare wet slide,
8. Examine microscopically 10-15 fields on 3 slides,
9. Record results.

D. Serologic test for syphilis

1. Transport blood from field to laboratory,
2. Spin blood and remove serum,
3. lcc of serum is sent to Allegheny County Health Department laboratory for VDRL,
4. Rest of serum is saved by project to have further studies done.

XI. Responsibilities of the Educator in the Pro-Con Field Trials

- A. Greet and fully explain the purpose of the pro-con field trial to each possible participant (Attachment).
- B. Fully explain to each possible participant what she will be asked to do, the benefits and risks involved in participating in the trial (Attachment).
- C. Obtain the participant's signature on "Informed Consent" form and initials on written summary of the trial (Attachment)
  1. Assign code number - 0 = control, 1 = first product, 2 = second test product + patient clinic number,
  2. Make a re-examination appointment - date and time,
  3. Give participant supply of product (15 units),
  4. Pay the participant \$6.25.
- D. Complete participants' records after first clinic session
  1. Complete Master Code Card (Attachment),
  2. Complete first portion of pre-trial history form (Attachment),
  3. File Master Code Card at the Clinic,
  4. Return remaining forms to trial file cabinet.
- E. Make preparations for first re-examination visit
  1. Fill in serology slip (monthly),
  2. Label culture dishes and test tubes with patient code number and culture site,
  3. Pull file for all participants to be seen that session.
- F. Set up clinic for each session.
- G. Interview and/or re-instruct each participant on each visit after medical exam.
- H. Follow-up on appointments not kept.

## XII. Interview and Re-instruction Procedures

### A. First Interview

1. Completely inform patient and get consent (Attachments),
2. Obtain pre-trial form information (Attachments),
3. Fill out master code form (Attachments),
4. Make appointment for re-examination,
5. Give the patient supply of product if in test group,
6. Pay participant,
7. Place master code card and records in appropriate file.

### B. Second Interview (first re-examination)

1. Complete pre-trial form if not done at first interview,
2. Have participant complete sex activity form for past two weeks,
3. Question participant on attitude about the trial - using product?
4. Solicit questions from participant,
5. Re-inforce instructions if needed,
6. Make appointment for next re-examination,
7. Give participant supply of product,
8. Pay participant,
9. Place records in appropriate file.

### C. Third Interview (second re-examination)

1. Have participant complete sex activity form for past two weeks,
2. Question participant on attitude toward trial - using product?
3. Question participant on attitude toward product of test group (Attachment),
4. Solicit questions,
5. Re-inforce instructions if needed,
6. Make appointment for next re-examination,
7. Replenish supply of test product if in test group,
8. Pay participant,
9. Return records to file.

### D. Future Interview

1. Conducted in the same manner every two weeks
  - a. Question on attitude toward product monthly,
  - b. Continually work toward a friendly, professional relation to elevate high degree of cooperation throughout the trial.

## XIII. Responsibility of Aide in Pro-Con Field Trials

### A. Sets up clinic for technical operation for each clinic session.

1. Cleans and prepares equipment in examination rooms,
2. Assists in routing patients through the clinic,
3. Properly labels all plates and tubes for laboratory,
4. Places cultures in candle jars,
5. Cleans rooms after clinic sessions.

### B. Assists other members of team by:

1. Calling patients for examination or interview room,
2. Prepares patient for examining by clinician,

3. Stays with physician during physical examination,
4. Participates in observing patient for reactions to clinic environment and drug therapy,
5. Notifies team members of social, economic and health problems revealed by the patient,
6. Discusses patient's needs and problems with other members of the team.

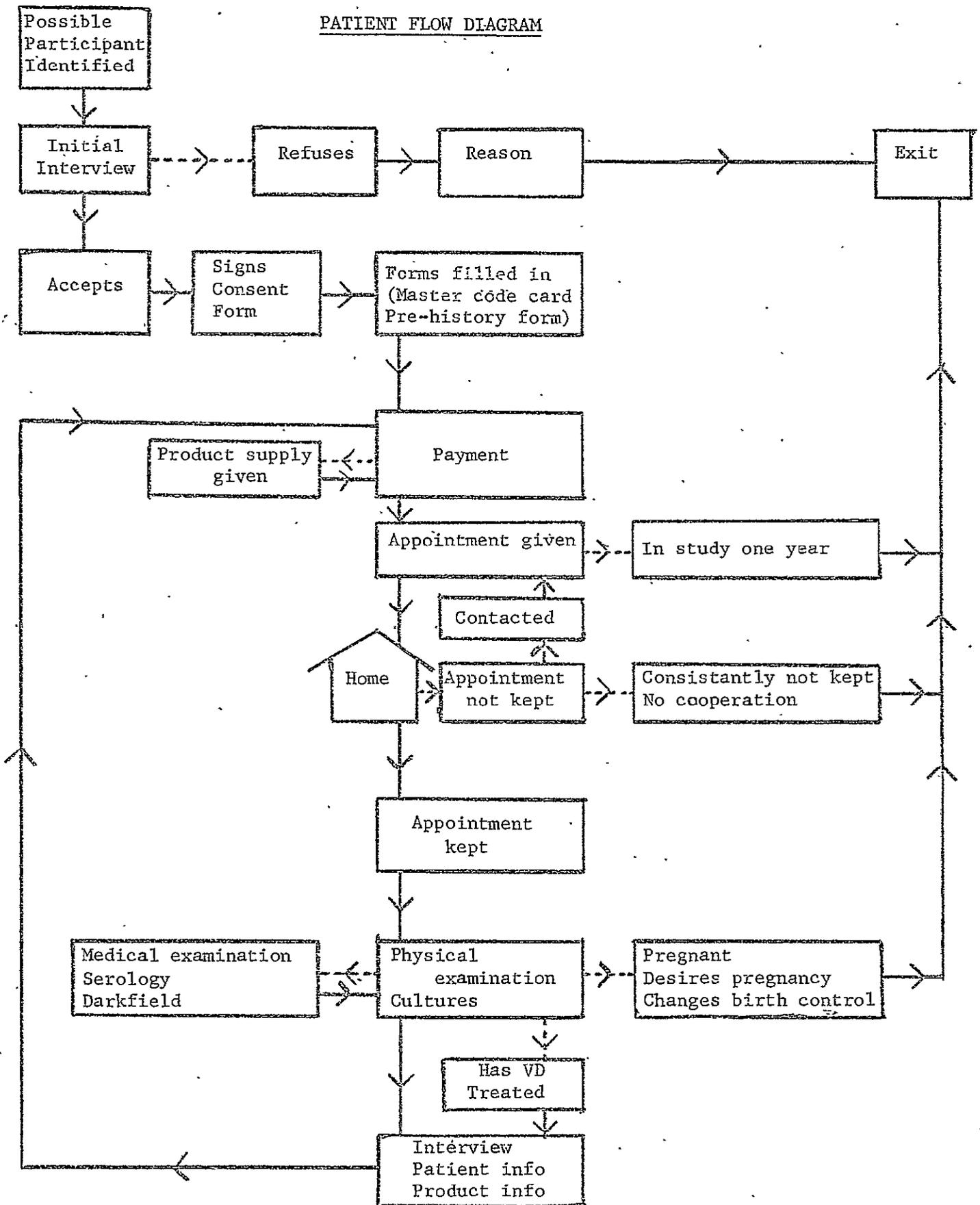
#### XIV. Specimen and Serology

Once a month, blood specimen (about 7-10cc) will be obtained from the participants. The tubes containing blood will be properly identified.

##### A. Supplies needed for field trial

1. Thayer-Martin selective medium plates,
2. Sabouraud Agar plates,
3. Simplified Trypticase Serum (STS) base medium,
4. Candle jar complete set with candle,
5. Cotton swab applicators,
6. Glass slides and cover slips,
7. Vacutainer tubes, holder and needles,
8. Tourniquet,
9. Speculum (disposable),
10. Gloves,
11. Band-aids,
12. Paper supplies (drapes, paper pads, rolled paper sheets for examining table),
13. Marking pencils and lab slips.

PATIENT FLOW DIAGRAM



PRO-CON. PROJECT FIELD TRIAL RECOMMENDED TREATMENT SCHEDULE

DIAGNOSIS	TREATMENT	FOLLOW-UP
Gonorrhoea in the Female (and Epidemiologic Rx of female contacts to GC)	Probenicid 1 gm orally 30 minutes prior to penicillin injection. 4.8 million units of Aqueous Procaine Penicillin G, I.M. (2.4 million units each buttock)	STS, Smear & Culture STAT Repeat Smear & Culture 1 week. STS in 1 month.
Gonorrhoea patients or Contacts with Allergy or Sensitivity to Penicillin (Male or Female) or Gonorrhoea patients who are treatment failures of a schedule utilizing Aqueous Procaine Penicillin.	1st Choice - Vibramycin, 100 mgm, bid X 5 days. (except during pregnancy give Erythromycin) 2nd Choice - Trobicin, 4 gm I.M. (2 gm each buttock) 3rd Choice - Tetracycline 500 mgm, po, qid X 5 days. (except during pregnancy give Erythromycin) 4th Choice - Erythromycin, 500 mgm, po, qid X 5 days.	STS every month X 2. Repeat Smear & Culture in 10 days
Primary Syphilis (S-10)	Benzathine Penicillin G. Total dose - 4.8 million units. 2.4 million units I.M. stat (1.2 million units each buttock) then 2.4 million units at 7 day interval.	STS every 6 weeks X 2, then 6 months, then 1 year.
Syphilis with Penicillin Sensitivity.	1st Choice - Tetracycline 500 mgm, po, qid X 20 days (total 40 grams) (except during pregnancy use Erythromycin) (Same dosage) 2nd Choice - Erythromycin 500 mgm, po, qid X 20 days (total 40 grams) Late Syphilis - may have to double above dosage, according to status of patient.	Same as for appropriate stage.
Epidemiological Rx of Contacts of Primary, Secondary and Early-Latent Syphilis	Benzathine Penicillin G. 2.4 million units one dose (complete physical must be done on all contacts) Alternate antibiotic; Tetracycline 500 mgm qid X 5 (except during pregnancy use Erythromycin, 500 mgm, po, qid X 5 days)	STS Stat STS every month X 2.
Chancroid	Tetracycline 500 mgm qid X 14 days or Sulfadiazine 1.0 gm qid X 7 days Further treatment depends on clinical activity	STS & Darkfield STAT (to rule out syphilis)
Lymphogranuloma Venereum	(Same as for Chancroid)	(Same as for Chancroid)
Granuloma Inguinale	(Same as for Chancroid)	(Same as for Chancroid)

MASTER CODE CARD

NAME \_\_\_\_\_ Code No.

ADDRESS \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

TELEPHONE NO. \_\_\_\_\_

DATE OF ENTRY INTO STUDY \_\_\_\_\_

Pre-Trial History Form I

Code No.       Column 1-6

1. Date of Birth \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_  
 Month Day Year
2. Age \_\_\_\_\_  9-10
3. Marital Status: S 1 M 2 D 3 Sep. 4 Other 5  11
4. Contraceptive practice(s) (Before the participation in study)  
 IUD 1 ORAL PILL 2 STERILIZATION 3 OTHER 4  12
5. Race: W 1 B 2 Other 3  13
6. Educational level completed:  
 7th grade or under 1 8th to 9th grade 2  
 10th to 12th grade 3 College freshman to sophomore 4  
 Junior to senior 5 Graduate School 6  14
7. Number of sexual partners (per two weeks):  
 One 1 Two 2 Three 3 4-9 4 More than 10 5  15
8. Sex of partner: M 1 F 2 Both 3  16
9. Frequency of sexual intercourse (per two weeks):  
 None 1 One 2 Two 3 Three 4 Four 5  
 Five 6 Six 7 Seven 8 Daily 9 More than 14 10  17-18
10. Prophylactic measures (For the most recent month):  

	Condom <u>1</u>	Douche <u>2</u>	Wash <u>3</u>	Urinate <u>4</u>	Other <u>5</u>	
Always	_____	_____	_____	_____	_____	<input type="checkbox"/> 19
Most of the time	_____	_____	_____	_____	_____	<input type="checkbox"/> 20
Sometimes	_____	_____	_____	_____	_____	<input type="checkbox"/> 21

Number Assignment Card

To assure confidentiality, you have been assigned a number for this study. Your number is:

Please remember your number.

Reminder Card

Your next appointment is:

Time \_\_\_\_\_ Month \_\_\_\_\_ Day \_\_\_\_\_

Please call \_\_\_\_\_ if unable to keep this appointment

Infection Form

Pre-Trial History Form II

History of VD infections (during 12 months prior to participation in study)

DATE	LAB TESTS	LAB RESULTS	CLINIC DIAGNOSIS	TREATMENT	
				DATE	NAME DRUG & QUANT.

11. Total number of positive laboratory results \_\_\_\_\_  22-23
12. Total number of positive clinic diagnosis \_\_\_\_\_  24-25



